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KUWAIT MEDICAL JOURNAL
The Official Journal of The Kuwait Medical Association

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Vol. 58 No. 2 JUNE 2026

KUWAIT MEDICAL JOURNAL

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PUBLISHER: The Kuwait Medical Journal (KU ISSN-0023-5776) is a quarterly publication of THE KUWAIT MEDICAL ASSOCIATION. Address: P.O. Box 1202, 13003 Safat, State of Kuwait; Telephone: 1881181 Fax: 25317972, 25333276. E-mail : kmj@kma.org.kw

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Kuwait Medical Journal

Published by the Kuwait Medical Association
Previously known as The Journal of the Kuwait Medical Association (Est. 1967)

EDITORIAL OFFICE

Editorial Manager : Vineetha Elizabeth Mammen

EDITORIAL ADDRESS

P.O. Box: 1202, 13003-Safat, Kuwait
Telephone: (00-965) 1881181(Ext. 114, 115) - Fax: (00-965) 25317972, 25333276
E-mail: kmj@kma.org.kw
Website: www.kmj.org.kw

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Book: Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 4th ed. St. Louis: Mosby; 2002.

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Review Article

Oral and maxillofacial haemangioendothelioma - a systematic review

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Kuwait Medical Journal 2026; 58 (2): 86 - 101

ABSTRACT

Background: The spectrum of vascular lesions in the head and neck is remarkably diverse, encompassing a wide array of cancers and abnormalities. These conditions range from simple capillary anomalies to complex structures of arteries, veins and lymphatics. Among them, haemangioendothelioma (HE) stands out as a rare vascular tumour that originates from the endothelial cells lining blood vessels, with the potential to manifest in the oral cavity and other anatomical locations. HE resides on a continuum of malignancy, bridging the gap between completely benign haemangiomas and highly aggressive angiosarcomas. Notably, variants of HE are characterized by their tendency to recur locally, yet they exhibit a lower risk of metastasis, highlighting their relatively low degree of malignancy. Understanding the complexities of these conditions is crucial for effective diagnosis and treatment, emphasizing the need for continued research and awareness in the medical community.

Material and Methods: Major databases such as Medline were explored, resulting in a systematic review of oral and maxillofacial HE.

Results: Five original research scientific articles dated between 2020 – 2024 pertaining to the mentioned topic were highlighted.

Conclusions: HE represents a distinctive class of rare endothelial neoplasms that exhibit a biological behaviour intermediate between benign haemangiomas and aggressive angiosarcomas. This nuanced categorization underscores the importance of recognizing HEs as significant entities that demand careful clinical consideration and management.

KEY WORDS: haemangiomas, head and neck, vascular anomalies, vascular malformations, vascular tumours

INTRODUCTION

Any anatomical structure can be affected by vascular abnormalities, which are diseases of the endothelium and surrounding cells that impact the blood vessels. These malformations are often identified in infancy or childhood, with an estimated incidence rate of 4.5%. Many lesions occur in the head and neck region, leading to psychological discomfort due to perceived disfigurement and associated functional problems. Vascular abnormalities can lead to various complications, including general issues such as congestive heart failure, disseminated intravascular coagulation, pulmonary embolism, thrombocytopenia and sepsis. They can also cause local complications, including bleeding, infection, obstruction, pain, thrombosis, ulceration and damage to anatomical structures. In 1818, the London surgeon Wardrop was the first to differentiate between vascular malformations and haemangiomas. However, this distinction did not lead to the development of a therapeutic approach. In 1846, William Green Morton became the first to publicly use ether anesthesia to surgically remove a venous vascular abnormality. For many years, both medical professionals and the public referred to cutaneous vascular nevi using common terms

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associated with food. This misconception, based on the outdated theory of maternal impressions, is the reason why terms like "cherry," "port-wine stain" and "strawberry" were used to describe these vascular conditions. In the mid-nineteenth century, with the emergence of histopathology, these abnormalities were referred to as angiomas. However, the progress of this field was hindered in the following century by the confusing overlap between clinical and histological terminology.

METHODS

"Vascular" AND "tumour" AND "pathology'' were the words used in MEDLINE database using advance search strategy targeting different article categories between 2020 to 2024. Inclusion criteria were case studies and scientific literature between 2020-2024. Exclusion criteria were scientific literature irrelevant to the specific search. This systematic review was conducted to determine importance of oral and maxillofacial haemangioendotheliomas (HEs) following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). PubMed, Lilacs, Embase, Scopus and Web of Science were the source of electronic databases. The search strategy used Boolean operators (AND and OR): [ALL ("vascular") AND (tumour OR oral OR maxillofacial) AND (vascular malformations)]. The following data were collected: first author, year, country of study, type of study and outcome. The quality of studies was assessed using the Strengthening the Reporting of Observational Studies (STROBE) checklist.

LITERATURE REVIEW

Five articles were included in this systematic review based on the selection criteria and PRISMA flow chart. We analysed and mentioned the five articles reviewed. This included only relevant research articles and excluded articles pertaining to non-specific search terms (Table 1).

Vascular lesions are among the most common congenital and neonatal abnormalities. These anomalies can occur throughout the whole body, with 60%, however, being in the head and neck region probably due to its intricate vascular anatomy of region. Vascular lesions are localized structural defects of the vasculature. The clinical presentation of vascular anomalies is confusing because all lesions appear in the colour spectrum of blue, pink and red. Vascular anomalies can be broken down into two major categories: tumours and malformations. There are several different vascular tumours, but infantile haemangiomas are the most common. Other tumours that will be discussed include tuft angiomas, pyogenic granulomas, angiosarcomas and kaposiform HEs (KHEs). Management of vascular tumours depends on their medical history, diagnosis and most importantly, their location[1].

Vascular anomalies are disorders of the endothelium and surrounding cells that can affect the vasculature and involve any anatomical structure. The estimated prevalence is 4.5%, and the anomalies are usually diagnosed during infancy or childhood. The most common problem associated with vascular anomalies is psychological distress related to the disfigurement as well as functional defects because many lesions affect the head and neck. Vascular anomalies lead to local complication and can also cause general complications such as congestive heart failure, disseminated intravascular coagulation, pulmonary embolism, thrombocytopenia, etc[2].

History and Classification

Pathologists, clinicians and radiologists have traditionally confused the diagnosis of vascular anomalies by using medical terminology that was not specific or defined. The word "birthmark" was one of the first ways used to described vascular anomalies, based on the folk belief that a mother's emotions can leave an imprint on her unborn fetus. In the late 1860s, Dugas and Fisher disproved this belief and concluded that birthmarks were malformations resulting from flawed embryologic development[3].

There have been several classifications dating back to a histologically based version by Virchow in 1863. Since then, there have been many others based on the gross appearance, histological appearance, therapeutic treatment, and even flow rates. One of the most well-known is that of Mulliken and Glowacki, who published the first histology-based scheme, which described lesions in the pediatric population, dividing them into two major groups, tumours and malformations. The most used classification today comes from the International Society for the Study of Vascular Anomalies (ISSVA). It is a comprehensive scheme based on Mullikan and Glowacki's seminal work. Overtime, advances in diagnostics, genetics and treatments have led to several iterations of this classification, most recently in 2018. The ISSVA classification divides vascular lesions into two major categories: tumours (true proliferative neoplasms) and malformations (defects in morphogenesis). The basic categories have remained the same. Vascular tumours are separated into benign, locally aggressive/borderline and malignant (Table 2). The vascular malformations are divided into simple, combined, those of named vessels and those associated with other anomalies[4].

Table 1: An overview

Author	Title	Journal	Outcome
Hector Ramos-Fuentes, Cristina Ortiz-Diaz, Salvador Sifuentes-Cervantes, Jaime Castro-Núñez	Pseudomyogenic Hemangioendothelioma: A Rare Vascular Tumor of the Oral Cavity.	Ramos-Fuentes H, Ortiz-Diaz C, Sifuentes-Cervantes S, Castro-Núñez J. Pseudomyogenic hemangioendothelioma: A rare vascular tumor of the oral cavity. Journal of Craniofacial Surgery. 2020 Jun 1;31(4):e333-4. doi: 10.1097/SCS.0000000000006253.	Pseudomyogenic haemangioendothelioma is a vascular neoplasm that presents a borderline biological behaviour, intermediate between entirely benign haemangiomas and highly malignant angiosarcomas.
Ali Rizvi, Tim K. Blackburn, Guy N. J. Betts	Epithelioid haemangioendothelioma of the mandible – A case report and review of the literature	Rizvi A, Blackburn TK, Betts GN. Epithelioid haemangioendothelioma of the mandible–A case report and review of the literature. Oral Surgery. 2022 Aug;15(3):387-92. doi.org/10.1111/ors.12644	It is classified as a tumour of intermediate malignancy as, in contrast to other types of haemangioendothelioma
Apurva Chouksey, Pratiksha Pawar, Satyajit Tekade, Shishir Dubey, Ameya Bihani, Shubhanshi Kangloo, Michael Prakasam	Hemangioendothelioma of the lower lip masquerading as traumatic lesion: a rare case report and review of literature	Chouksey A, Pawar P, Tekade S, Dubey S, Bihani A, Kangloo S, Prakasam M. Hemangioendothelioma of the lower lip masquerading as traumatic lesion: a rare case report and review of literature. https://doi.org/10.18203/issn.2454-5929.ijohns20242052	Haemangioendothelioma (HE) is an uncommon vascular tumor originating from endothelial cells lining blood vessels that can manifest in various anatomical locations, including the oral cavity.
Luis Ortiz-Peces, María Álvaro-Martínez, Marta de Uribe-Viloria, Martín Andura-Correas, Eduardo Vázquez-Salgueiro, José Luis Cebrián-Carretero	Epithelioid Hemangioendothelioma of Mandibular Gingiva: A Challenging Diagnosis	Ortiz-Peces L, Álvaro-Martínez M, de Uribe-Viloria M, Andura-Correas M, Vázquez-Salgueiro E, Cebrián-Carretero JL. Epithelioid hemangioendothelioma of mandibular gingiva: a challenging diagnosis. Journal of Clinical and Experimental Dentistry. 2024 Sep 1;16(9):e1151. doi:10.4317/jced.61925 https://doi.org/10.4317/jced.61925	Epithelioid haemangioendothelioma (EHE) is a rare neoplasm derived from the vascular endothelium.
Ekanayake Mudiyanselage Kanchana Medhavi Kumari Weerakoon, Kapu Gamage Kanchana Dewinda Kapugama, Bogahawatte Samarakoon Mudiyanselage Samadarani Siriwardena,	Primary intraoral epithelioid hemangioendothelioma of the tongue: a case report and review of literature	Weerakoon EM, Kapugama KG, Siriwardena BS. Primary intraoral epithelioid hemangioendothelioma of the tongue: a case report and review of literature. Brazilian Journal of Otorhinolaryngology. 2022 May 13;88(Suppl 4):S192-5. DOI: 10.1016/j.bjorl.2021.04.010	EHE is an intermediate grade vascular neoplasm. Uncertainty in determining malignant risk indicates the need for a standard clinical and histological criterion to predict the behavior of malignant EHE.

Vascular Tumors – Benign

Hemangioma is a benign lesion of a hamartomatous growth of capillaries with a high proliferation index. Hemangiomas are categorized into infantile hemangioma (IH) and congenital hemangioma (CH). IH is subcategorized depending on the site of its occurrence as focal, segmental and indeterminate, and depending on the depth of the lesion from the skin surface as superficial (previously called capillary hemangioma), deep (previously called cavernous hemangioma) and mixed (capillary cavernous hemangioma). CH is further subcategorized into rapidly involuting CH (RICH) and non-involuting CHs (NICHs)[5].

IHs are glucose transporter protein-1 (GLUT-1) positive, while CHs are not. Interestingly, GLUT-1 expression has been linked to poor prognosis in many neoplastic processes. This over expression is thought to be due to increased need for glucose mediated by hypoxia. It is hypothesized that in utero episodes of hypoxia may lead to upregulation of GLUT-1 and angiogenic cytokines contributing to hemangioma formation. In addition to this genetic difference, they have several unique features that can help differentiate them[6]. IHs are usually diagnosed in the first year of life. They follow a pattern of rapid growth in the first few months followed by slower growth and involution phases that are slower and more variable. These lesions can be contrasted with CHs, which are present at birth, and become symptomatic as they increase in size or in response to hormonal changes, infection and trauma[7].

Pathogenesis

Various theories suggest that the pathogenesis of IH is related to an intrinsic defect of hemangioma endothelial cells (HemECs): clonality of HemECs, somatic mutation of single progenitor cell and loss of heterozygosity to chromosome 5q. Other theories suggest that HemECs' response to extrinsic defects is presented in the local environment. A balance between

intrinsic and extrinsic factors and between stimulators and inhibitors of angiogenesis factors might account for the rapid growth and slow involution of IH. A number of stimulator factors that act on ECs include local tissue environment hypoxia or acidity, vascular endothelial growth factor (VEGF), basic fibroblast growth factor, matrix metalloproteinases-9, intercellular adhesion molecule-3, monocytes chemoattractant protein-1, Eselectin and angiogenesis inhibitors that act on ECs that include proteins such as angiostatin, platelet factor-4, thrombospondin-1, interferon-α (IFNα), tissue inhibitor of metalloproteinases and plasminogen activator inhibitors[8].

Clinical features

Initially, the lesion clinically appears as circumscribed area of discoloration or telangiectasia of facial skin. IH may clinically show scaring, wrinkling, telangiectasia or loose fibro-fatty tissue at the site of their clinical appearance. Focal IH is the most common variant, appearing as localized raised tumour-like lesion that tends to occur at the area of embryological fusion. Segmental IH is a flat plaque-like larger lesion that shows a geographic segmental distribution, and indeterminate IH shows the characteristics of both focal and segmental IH. Colour of the IH varies with the depth of the lesion and they can be bright red (superficial), purple, blue or normal skin colour (deep)[9].

Histopathologic features

Histologically, proliferating IH is characterized by nonencapsulated masses and dense cords of mitotically active plump ECs with pericytes, whereas involuting IH is characterized by enlarged vascular lumina with flattened ECs. Involuted phase of IH has more dilated vascular spaces with adipocytes, fibrous deposits and with few remaining vessels[10].

CH, RICH, partially involuting congenital hemangioma or NICH: CHs have been recognized for years. More recently, these lesions have been found to be biologically distinct from the IH. IHs appear more commonly (70%) than CH (30%).

Clinical features

CH clinically presents as fully developed lesions at birth, which either rapidly involutes during the 1st year of life or may never show involution. These lesions do not exhibit a proliferative phase and usually do not grow after birth. RICHs are present at birth either as red-purple colour plaques with coarse telangiectasia, as flat violaceous lesions, or as a greyish tumour surrounded by a pale halo with multiple tiny telangiectasias. RICH undergoes a rapid regression phase and completely disappears by 12-18 months of age. NICHs are present at birth as pink or purple-coloured plaque-like lesions with prominent overlying coarse telangiectasia and peripheral blanching. NICH does not show a regression phase, may grow

Table 2: Vascular tumours and vascular malformation[5]

Vascular tumors	Vascular malformations
Benign	**Simple**
Infantile hemangioma/Hemangioma of infancy Congenital hemangioma Rapidly involuting (RICH) Non-involuting (NICH) Partially involuting (PICH) Tufted angioma Spindle-cell hemangioma Epithelioid hemangioma Pyogenic granuloma (aka lobular capillary hemangioma) Others	• Capillary malformations Cutaneous and/or mucosal CM, Telangiectasia, CMTC, Nevus simplex, Others • Lymphatic malformations Common (cystic) LM, Generalized lymphatic anomaly (GLA), LM in Gorham-Stout disease, Channel type LM, Primary lymphedema, Others • Venous malformations Common VM, Familial VM, cutaneo-mucosal (VMCM), Blue rubber bleb nevus (Bean) syndrome VM, Glomuvenous malformation (GVM), Cerebral cavernous malformation (CCM), Others
Locally aggressive or borderline	**Combined**
Kaposiform hemangioendothelioma Retiform hemangioendothelioma Papillary intralymphatic angioendothelioma (PILA), Dabska tumor Composite hemangioendothelioma Kaposi sarcoma Others	Capillary-venous malformation, capillary-lymphatic malformation, capillary-arteriovenous malformation,lymphatic-venous malformation, capillary-lymphatic-venous malformation, capillary- lymphatic-arteriovenous malformation, capillary-venous-arteriovenous malformation, capillary-lymphatic-venous-arteriovenous malformation.
Malignant	
Angiosarcoma Epithelioid hemangioendothelioma Others	

proportionately with the growth of the child, and can be mistaken for vascular malformations[11].

Histopathologic features: RICH is characterized by small-to-large lobules of capillaries with moderately plump ECs and pericytes. NICH and IH have similar appearances histologically. Tissue-specific immunohistochemical markers such as GLUT-1, merosin, Fc-gamma-RII and Lewis Y antigens are positive for IH and thus aid in differentiating IHs from other vascular tumours or malformations[12].

Epithelioid Hemangioma (EH) (Synonym: Angiolymphoid Hyperplasia with Eosinophilia)

EH is an uncommon benign vascular tumour characterized by epithelioid morphology. The head and neck region are a common site. EH originates in skin, subcutis, soft tissue and bone and may occur multifocally (in up to 50% of cases). There are three histologic subtypes: conventional, cellular and angiolymphoid hyperplasia with eosinophilia. EH is distinguished by a lobular architecture and a zonated pattern with tightly packed epithelioid cells located centrally, and maturating towards the periphery, which shows well-formed vessels. Intracytoplasmic vacuoles are often present. There is typically mild cytologic atypia, with mitotic figures. A fibromyxoid stromal reaction is often present, and vascular invasion may be seen. The latter, as well as multifocality and solid central sheets of tumour cells can simulate a more aggressive lesion, especially when there is involvement of lymph nodes[13].

However, muscle specific actin and smooth muscle actin (SMA) highlight the pericytic cuff, arguing against epithelioid hemangioendothelioma (EHE) and angiosarcoma (AS). Furthermore, the typical strands and cords of tumour cells and myxohyaline stroma of EHE are not present in EH. An inflammatory reaction with eosinophils is variably present. Kimura disease, a systemic disease with prominent inflammation, lymph node involvement and peripheral eosinophilia is a morphological differential diagnosis, but is clinically distinct. Nuclear FOSB reactivity is reported in a variable subset of cases, including all angiolymphoid hyperplasia with eosinophilia cases. Genetically, EH harbours *FOS* and *FOSB* rearrangements, although these findings are very rare in the superficially located head and neck cases and analyses are not very helpful in this respect. Spontaneous regression has been documented, however, circa 30% of cases recur locally. The optimal treatment is complete excision[14].

Tufted angioma

Tufted angioma is a rare vascular tumour that presents with red or violet plaques. Histologically, it is characterized by capillary vessels forming oval or rounded "tufts." These develop usually within the first 5 years of life and can extend into many layers beyond the dermis. There is differing data on the location of these lesions, but they tend to occur in the trunk and extremities in children. In adults, lesions are more likely to present in the head and neck, specifically the oral mucosa. It is important to biopsy these lesions to exclude a malignant neoplasm, namely Kaposi sarcoma or AS. Once pathological diagnosis is obtained, these lesions are usually observed; some of these lesions have known to regress. Treatment is usually symptomatic or cosmetic. Imaging is rarely performed on these lesions. Like KHE, these lesions have also been associated with GNA14[15].

Spindle cell hemangioma can present as a red-brown nodule ranging from a few millimetres to a few centimetres in diameter. They can present as a solitary lesion or cluster of several lesions. These lesions can be painful and have been associated with lymphedema, Mafucci syndrome and Klippel-Trenaunay syndrome. These are mostly superficial lesions limited to the dermal and subcutaneous tissues. On MRI, they have low T1 signal and lobulated high T2 signal, often with phleboliths due to abnormal venous vessels. The most common treatment is surgical excision. While imaging is of limited utility, in select cases, it can be helpful prior to treatment to characterize extent and when extensive reconstruction is expected[16].

Pyogenic granulomas, also known as lobular capillary hemangiomas, are relatively common and commonly present as an angiomatous pedunculated polyp or papule. These lesions commonly occur on the forehead and cheek but can also occur on the mucosal surface including the conjunctiva and oral mucosa. These lesions most often occur secondary to prior trauma, infection, burns and even pregnancy. These lesions are usually first found on clinical examination, often presenting as enlarging lesions over the course of a few weeks, often with bleeding and ulceration. The underlying pathogenesis of these lesions is still unclear; historically, these were thought to be reactive hyperplasia. However, recent genetic studies showing mutations in BRAF, RAS, and GNA14 suggest that this is truly a benign neoplastic process. Sonographic evaluation usually demonstrates hypoechoic nodules in the region of interest with marked internal vascularity. On MRI, these lesions present as T1 iso-intense to muscle with variable T2 signal. As expected, these lesions demonstrate avid enhancement. Imaging can be used to guide biopsy and excision in more extensive cases[17].

Locally aggressive or borderline

The term HE has been applied to name several vascular proliferations, including both benign and malignant neoplasms. Originally, in 1908, Mallory used the term HE to include all proliferations that he

considered arose from endothelial cells of blood vessels, distinguishing between angiomata (i.e., slowly growing neoplasms with evident vessel lumina formation) and endotheliomata (rapidly growing neoplasms composed of solid aggregates of proliferating cells). In 1943, Stout named HEs as a series of malignant vascular neoplasms histopathologically characterized by anastomosing vascular channels lined by atypical endothelial cells[18].

However, some years later, in 1961, Kauffman and Stout in a study of malignant vascular tumors in children and adolescents, distinguished between benign HEs, which included benign juvenile HEs (currently, it would be considered as infantile hemangioma) and Masson vegetant intravascular HEs, and malignant HEs characterized by anastomosing irregular vessels lined by atypical endothelial cells with frequent mitotic figures. Interestingly, Kauffman and Stout described a small group of malignant HEs with low metastatic potential, but with high tendency to persist locally. In 1964, Jones used the term malignant angioendothelioma to encompass all well-differentiated, cutaneous, malignant vascular neoplasms other than AS of the skin. In 1982, Weiss and Enzinger proposed that the term HE should be restricted to those vascular neoplasms showing a borderline biological behaviour, intermediate between entirely benign hemangiomas and highly malignant AS[19].

Kaposiform hemangioendothelioma

It is a rare vascular neoplasm that occurs mostly in children. Although it was originally described in the retroperitoneum, a review of the literature reveals that the skin is the most common location for this neoplasm. When the lesion involves the subcutaneous tissue, the mediastinum or the retroperitoneum, it may cause Kasabach-Merritt syndrome. Moreover, it has recently been found that patients with Kasabach-Merritt syndrome do not have large infantile hemangiomas entrapping platelets, as classically had been considered, but have specific and closely related histopathologic variants of acquired vascular neoplasms, namely tufted hemangioma and KHE. In some instances, KHE is associated with lymphangiomatosis or with congenital lymphedema (Milroy disease). Cutaneous KHE appears as an erythematous-violaceous plaque with firm consistence involving the full thickness of the skin and extending into the subcutaneous tissues. Sometimes, the skin surface shows hemorrhagic areas as the earliest sign of an accompanying Kasabach-Merritt syndrome. Any area of the body may be affected by this neoplasm, but the trunk and the proximal areas of the extremities are the sites of predilection[20].

KHE combines histopathologic features of infantile hemangioma and the nodular stage of Kaposi sarcoma. Characteristically, the lesion is composed of several solid poorly circumscribed nodules separated by connective tissue. Each of these nodules is composed of a mixture of small capillaries and solid lobules of endothelial cells arranged in a glomeruloid pattern. Proliferating cells are round or ovoid and may contain hyaline globules or hemosiderin. Cytoplasmic vacuolization is a frequent sign of primitive vascular differentiation. At the periphery of the nodules, there may be small capillaries that often contain microthrombi. The multilobular or cannon-ball pattern of KHE resembles that of tufted hemangioma, although the nodules of KHE are larger and worse circumscribed than those of tufted hemangioma[21].

Nevertheless, there are several reports describing overlapping histopathologic features of tufted hemangioma and KHE in the same lesion, and currently, many authors consider these two entities as closely related neoplasms. Within the solid nodules, there are spindle-shaped cells intermingled with small lumina with a cleft or crescent shape, which may also contain microthrombi. These spindle cell fascicles closely resemble those of nodular lesions of Kaposi sarcoma, although they are shorter and narrower than those seen in that neoplasm. Cellular atypia is absent, and mitotic figures are infrequent. In rare instances, lesions of KHE may show areas of fibrosis with an amianthoid appearance. A frequent finding consists of the presence of areas of lymphangiomatosis adjacent to the solid nodules. These vessels of the associated lymphangiomatosis are lined by a discontinuous layer of flat endothelial cells. In some instances, the solid and lymphangiomatous areas are sharply separated, whereas in other cases, they are closely intermingled[22].

Immunohistochemical studies in KHE have demonstrated the endothelial nature of proliferating cells because they expressed positivity for vimentin, FLI 1, CD31 and CD34 and resulted negative for LeY, HHV8 and SMA, although a peripheral ring of SMA-positive pericytes is seen surrounding the best-formed vascular spaces of the neoplasm. GLUT-1, the most specific immunohistochemical marker of proliferating endothelial cells in infantile hemangioma, is negative in KHE, whereas VEGFR-3 resulted positive in the 6 investigated cases, which may indicate a lymphatic line of differentiation for this neoplasm. Recently, positivity for podoplanin has been reported in proliferating cells of KHE, further supporting its lymphatic differentiation. Electron microscopy studies have shown that endothelial cells of KHE are closely packed, with poorly formed vascular lumina. Some

cells are surrounded by a discontinuous basement membrane, and there also are some pericytes surrounding the endothelial cells. No Weibel-Palade bodies have been identified[23].

In contrast with IH, lesions of KHE show no tendency for spontaneous regression. Large lesions of subcutaneous tissues, mediastinum and retroperitoneum cannot be completely excised and may cause fatal complications due to the associated Kasabach-Merritt syndrome. In these cases, several medical therapies have been assayed, including systemic corticosteroids; interferon alfa-2a; combined treatments with systemic corticosteroids, alfa interferon, vincristine and radiotherapy; embolization, systemic interferon, cyclophosphamide, epsilon aminocaproic acid and compression therapy; combined chemotherapy with vincristine, cyclophosphamide and actinomycin-D113; vincristine and ticlopidine; only vincristine; and combined with sirolimus. Small lesions and those with superficial location are better managed with surgical excision[24].

Retiform hemangioendothelioma

In 1994, authors described 15 patients with a distinctive low-grade angiosarcoma that they named retiform HE. The lesions were mainly located in the upper and lower extremities, although there were also cases on the head, trunk and penis. The age of the patients ranged between 9 and 78 years. Since this original description, few additional examples of retiform HE have been reported, most of them in young adults, although there also are some examples described in children. From the clinical point of view, lesions present as solitary exo-endophytic masses with slow growth, resulting in a plaque or subcutaneous nodule with firm consistency[25].

It is an infiltrative neoplasm composed of elongated arborizing vessels arranged in anastomosing pattern resembling that of the rete testis. The neoplasm involves the entire thickness of the dermis and often extends to subcutaneous tissue. Neoplastic vessels are lined by a single layer of hobnail-like endothelial cells that protrude within the narrow lumina. The nuclei of the hobnail-like endothelial cells are hyperchromatic, whereas their cytoplasm is scant. Mitotic figures are absent or scant. In some areas, the vascular component may be obscured by a dense lymphocytic infiltrate, which may also be present within the lumina of the vessels, near endothelial cells. Besides this retiform pattern of elongated vessels, there are also solid areas composed of epithelioid and spindle cells and dilated vascular structures with intraluminal papillary structures identical to those of papillary intralymphatic angioendothelioma (PILA), and, as noted earlier, some reports describe overlapping histopathologic features of retiform HE and PILA in the same lesion[26].

Immunohistochemically, the hobnail-like cells lining the elongated vascular spaces express endothelial markers, including von Willebrand factor, CD31 and CD34. Spindle cells of the solid areas express CD31 but result negative for von Willebrand factor and CD34. Cytokeratins and SMA are negative in all neoplastic cells. The lymphocytic infiltrate is composed of a mixture of CD20-positive B-lymphocytes and CD3-positive T-lymphocytes, although intravascular lymphocytes are mostly T-lymphocytes[27].

Retiform HE should be differentiated from hobnail hemangioma, known also as targetoid hemosiderotic hemangioma, which probably represents a superficial lymphatic malformation. This lesion occurs mostly in young adults and presents as a small erythematous papule surrounded by an ecchymotic halo. Hobnail hemangioma is histopathologically characterized by elongated vascular structures lined by hobnail-like endothelial cells, but this is a superficial lesion that does not extend to deep dermis or subcutaneous tissue and is accompanied by abundant deposits of hemosiderin[28].

All patients with retiform HE have been treated by surgical excision of the lesion. From studies with a mean follow-up of 7.25 years in 14 patients, local recurrence is common, but metastatic disease is rare, with only two patients developing regional lymph node metastases and no patients died of their neoplasm. The case described as aggressive retiform HE of the scalp is probably better interpreted as a classic AS with focal retiform pattern[29].

PILA (Dabska tumor)

In 1969, Dabska described, under the name malignant endovascular papillary angioendothelioma, a locally destructive vascular neoplasm involving mostly the head and neck of 6 children, with ages ranging between 4 months and 15 years. Since this original description, few additional cases have been reported. Recently, based on its immunohistochemical findings, the name of PILA has been proposed as the most appropriate for this neoplasm[30].

Clinical features in most described cases: the lesions involved the skin and subcutaneous tissues of the neck and head of children and adolescents, although there are also examples reported in adults, as well as lesions involving the tongue, testis, spleen and bone. Some examples of PILA arose in preexisting vascular anomalies, including a vascular malformation, an intramuscular hemangioma, a chronic lymphedema of the involved limb and a circumscribed lymphangioma[31].

It is characterized by irregular vascular channels lined by hobnail-like endothelial cells and prominent lymphocytic infiltrate. Vascular spaces range in size and shape from narrow elongated vessels to dilated thin-walled structures. The most characteristic finding consists of papillary tufts, with a central hyaline core lined by hobnail-like endothelial cells protruding into the lumina and, in some instances, occluding the vascular spaces. The hyaline central core exhibits periodic acid-Schiff positivity, and immunohistochemical studies have demonstrated that they are composed of basement membrane material. In some areas, intravascular papillary structures result in a glomeruloid pattern. Endothelial cells lining the papillary formations show a round or polygonal shape, with large and hyperchromatic nuclei eccentrically located in the luminal border of the cell[32].

Immunohistochemical studies demonstrate that endothelial cells lining the papillary structures of PILA express reactivity for von Willebrand factor, C 3.1 (another endothelial marker), CD31, CD34 and SMA, but they do not express S-100 protein, cytokeratins, EMA, desmin, Leu-M1, HLA-DR, alpha-1 antichymotrypsin or common leukocyte antigen. Immunoreactivity for VEGFR3 has also been reported in the hobnail endothelial cells of PILA, supporting a lymphatic line of differentiation for this neoplasm. More recently, the lymphatic endothelial marker podoplanin has also been detected in the hobnail endothelial cells of PILA, further supporting its lymphatic nature. Ultrastructural studies have shown that neoplastic cells of PILA exhibit irregular nuclei and ample cytoplasm, with abundant cytoplasmic filaments, which condensate around the nucleus and numerous pinocytotic vesicles. In some cells, Weibel-Palade bodies have been identified. The central cores of the papillary structures are composed of basement membrane material[33].

Histopathologic differential diagnosis of PILA includes intravascular papillary endothelial hyperplasia (Masson pseudoangiosarcoma), glomeruloid hemangioma and atypical vascular proliferations in areas of radiotherapy. In most cases of Masson pseudoangiosarcoma, the process is limited to the lumen of a dilated vein, which shows its lumen filled by a thrombus and papillary structures lined by a single layer of plump endothelial cells, but these cells do not show the hobnail like appearance and hyperchromatic nuclei seen in the papillary structures of PILA. The core of the papillae consists of fibrin or collagenous connective tissue. Glomeruloid hemangioma is an intravascular proliferation seen in patients with polyneuropathy, organomegaly, endocrinopathy, M-protein, skin changes (POEMS) syndrome and Castleman disease. It consists of aggregates of capillaries filling dilated dermal and subcutaneous vascular spaces, resulting in a pattern that resembles renal glomeruli. Atypical vascular proliferations in areas of radiotherapy may also show small intravascular papillary tufts lined by prominent endothelial cells, but this is a focal finding, and the general configuration of the lesion consists of dilated lymphatic structures involving only the superficial dermis[34].

Treatment PILA should be surgically excised with clear margins and excision of the involved lymph nodes. Only two patients have developed metastases to the lymph nodes, and one of them died because of extensive lung metastatic disease[35].

Composite hemangioendothelioma

Composite HE is the term that has been coined to name locally aggressive vascular neoplasms of low-grade malignancy showing varying combinations of benign, low-grade malignant and high-grade malignant vascular components. Fewer than 20 cases have been reported[36].

Except for one congenital case, composite HE presents in young adult patients, with a mean age of 39.5 years. The hands and feet are the sites of predilection, and in most cases, the lesion has been present for several years before the diagnosis was established. A case in the oral cavity has also been reported. Clinical appearance of the lesions is variable, including nodules, plaques and ulcerated tumours. A patient with composite HE had Maffucci syndrome[37].

It is histopathologically characterized by a combination of different patterns of benign and malignant vascular proliferations. The proportion of each component varies from case to case, but retiform HE, epithelioid HE and spindle cell hemangioma are the predominant components in most cases. In some cases, papillary structures like those of PILA are also seen. In rare instances, areas of high-grade AS are also present, with solid aggregates of atypical pleomorphic cells and numerous mitotic figures[38].

Immunohistochemically, neoplastic cells of composite HE express the usual endothelial markers, such as von Willebrand factor and CD31, although CD34 is mostly negative in proliferating cells. Immunoreactivity for SMA has been found in some stromal cells as well as in the muscular layer on non-neoplastic vessels. In one case, the nuclei of neoplastic cells expressed immunoreactivity for Prox-1, supporting a lymphatic line of differentiation for this neoplasm. Composite HE should not be mistaken for polymorphous HE. The latter has been described in soft tissues and lymph nodes and is histopathologically characterized by a combination of undifferentiated solid areas with evident angiomatous pattern and

uniform cytologic elements, whereas composite HE combines different histopathologic patterns in the same lesion[39].

With the exception of one case treated with interferon, all cases of composite HE has been surgically excised. In three cases, the neoplasm persisted locally, and three other patients developed metastases to adjacent soft tissues and regional lymph nodes several years after the original surgical excision. In one of these cases, lymph node metastases showed the histopathologic pattern of epithelioid HE, which seems to indicate that lesions with an epithelioid component have a more aggressive behaviour than those that combine other types of nonepithelioid HE[40].

Pseudomyogenic hemangioendothelioma (epithelioid sarcoma-like hemangioendothelioma)

Recently, a new histopathologic variant of HE has been reported under the name pseudomyogenic HE. Probably, examples of the same neoplasm were previously included in a published series of epithelioid sarcoma and were described under different names, including fibroma-like variant of epithelioid sarcoma, spindle cell variant of epithelioid sarcoma, or epithelioid sarcoma-like HE[41].

The neoplasm seems to be more common in males than in females and has a predilection to develop between the second and fifth decades of life. Clinically, the most common form of presentation is as multiple nodules involving the lower extremities. In some patients, these nodules were painful, whereas other patients were asymptomatic. Although the lower limbs are the most frequently involved sites, there are also examples reported in upper extremities, trunk and head. In most cases, multiple nodules are grouped in an anatomical region. This neoplasm has no distinctive clinical feature, and the most frequent clinical diagnoses include cutaneous cyst, nodular fasciitis or benign tumour[42].

Histopathologic features at scanning magnification: pseudomyogenic HE appears as a poorly circumscribed lesion with architectural features of a malignant neoplasm. The lesion shows infiltrative borders involving the adjacent soft tissues. The neoplasm may be entirely dermal or extend to the subcutaneous fat and underlying skeletal muscle. Dermal lesions may show a variable degree of epidermal hyperplasia similar to dermatofibroma. Most lesions exhibit a fascicular pattern and areas of myxoid stroma, and neutrophils scattered over the neoplastic fascicles are also frequent histopathologic findings. Neoplastic cells show a round or oval shape, with vesicular nuclei and inconspicuous nucleoli, but, characteristically, they show ample homogeneous eosinophilic cytoplasm. In many areas, these ample cytoplasms result in a rhabdomyoblastic appearance of neoplastic cells. Cytologic atypia is scant, and mitotic figures are sparse. In some cases, intravascular invasion by neoplastic fascicles within entrapped blood vessels may be seen[43].

Immunohistochemically, most neoplastic cells express AE1/AE3 and FLI 1, with frequent immunoreactivity also for CD31, CAM 5.2, SMA, EMA and pancytokeratin MNF-116, whereas they do not express CD34, desmin and S-100 protein. In contrast with neoplastic cells of epithelioid sarcoma, neoplastic cells of pseudomyogenic HE keep their expression of INI1 intact, which provides the most helpful immunohistochemical tool for histopathologic differential diagnosis between these two neoplasms. Although Weibel-Palade bodies have not been identified in the cytoplasm of neoplastic cells, the neoplasm is composed of polygonal- or spindle-shaped cells with ample cytoplasm, abundant rough endoplasmic reticulum, and numerous aggregates of intermediate filaments. All these ultrastructural findings, in conjunction with the immunophenotype of the neoplastic cells, supported their endothelial nature. From the cytogenetic point of view, a balanced translocation t(7;19)(q22;q13) has recently been identified as the sole anomaly in three lesions of the same patient and an unbalanced der(7)t(7;19) in another case, which indicates that the translocation between chromosomes 7 and 19 seems to be a recurrent phenomenon and is likely to be of pathogenetic significance in at least a subset of pseudomyogenic HEs[44].

Most patients with pseudomyogenic HE have been treated with simple excision, and only few of these received postsurgical radiotherapy. In patients with follow-up, more than half showed local recurrence of the tumour or appearance of new nodules in adjacent soft tissues. In the largest published series, which included 50 cases, one patient developed metastases to the regional lymph nodes, and another patient died because of widespread metastatic disease[45].

Lastly, there is Kaposi sarcoma (KS), a mesenchymal tumour that arises from lymphatic endothelial cells first described in 1872. KS garnered attention in literature and worldwide in the 1980s for its association with acquired immune deficiency syndrome (AIDS). Kaposi sarcoma herpes virus/human herpes virus 8 was identified in 1994 and plays a key role in the pathogenesis of KS, particularly in the setting of immune dysregulation. KS is divided into four variants: classic, endemic, iatrogenic (most commonly post-transplant) and AIDS related. Classic and endemic KS have a more indolent course and typically do not require imaging evaluation. Iatrogenic and AIDS-related KS are much more aggressive and often present

with disseminated disease. There has been significant decrease in AIDS-related cases since the introduction of highly active antiretroviral therapy[46].

Malignant Vascular Tumors - Angiosarcoma

AS is a rare, aggressive sarcoma; one of its most common sites is the UV-exposed skin of the head and neck. Classically, it occurs on the scalp of older Caucasian men mimicking a bruise or hemangioma. As tumours progress, lesions can become nodular, fungated and ulcerated. Local recurrence rates are high because of multifocality. Survival rates are generally poor, with a 5-year overall and disease specific survival of 26.5% and 48.3%, respectively. The traditional mainstay of AS treatment focuses on wide local excision with adjuvant radiotherapy. Chemotherapy produces partial response in the metastatic setting. Inhibitors of VEGF and VEGFR and broad-spectrum tyrosine kinase inhibitors have been reported to show clinical response with short-term outcomes. Propranolol and immunotherapy may be promising. The histologic spectrum of AS ranges from well to poorly differentiated, and features can vary within a single neoplasm[47].

The anastomosing vascular channels are ill-defined and diffusely dissect the dermal collagen when arising in the skin. A sieve-like architecture is a common feature. The atypical endothelial cells are usually multilayered, with enlarged, hyperchromatic nuclei and often prominent nucleoli. High-grade areas contain solid nests or sheets of tumour cells with spindle cell or epithelioid morphology with occasional intracytoplasmic lumina. Blood-filled spaces, high mitotic rate and necrosis are more often seen in less-differentiated tumours. The most reliable immunohistochemical markers are CD31 and ERG with use in combination, while CD34 is variably present. Expression of keratins, partially observed in epithelioid AS should not be confused with carcinomas. CD31 and ERG can exceptionally be positive in atypical fibroxanthoma, which could be a diagnostic pitfall. Genetically, various abnormalities have been described, including complex karyotypes, amplifications, mutations and fusion genes, underpinning that AS constitutes a heterogeneous group of neoplasms. MYC amplification with expression of the corresponding protein is predominantly seen in cases secondary to radiation or UV-damage in contrast to primary AS being rarely MYC amplified[48].

EHE is an angiocentric vascular tumour with metastatic potential. Previous terminology used to describe this entity includes intravascular bronchioloalveolar tumour, angioglomoid tumour and myoid angioblastomatosis. The term 'epithelioid hemangioendothelioma' was originally described by Weiss and Enzinger (1982) to classify a vascular tumour with borderline biological properties intermediate between hemangioma and AS. This tumour was described by WHO as an intermediate malignant neoplasm. Histologically, this tumour was typically composed of epithelioid endothelial cells arranged in short cords and nests, set in a distinctive fibro-myxoid stroma. Clinically, EHE can arise in soft tissues, viscera, skin and bone. A few cases have been documented in the head and neck region including neck, thyroid gland, larynx and scalp. EHE are extremely rare in the oral cavity[49].

EHE was originally described as a distinctive low-grade angiosarcoma. Usually, the neoplasm presents as a painful and poorly circumscribed mass involving subcutaneous soft tissues of the extremities, although examples involving the skin and the oral cavity have also been reported. In some instances, EHE presents as an ulcerated nodule. The neoplasm may appear at any age, although is rare in children, and affects both sexes with similar frequency. In half the cases, the neoplasm was in connection with a pre-existing vessel, almost always a large vein. In some of these cases, the occluded vessel caused edema and thrombophlebitis of the involved area[50].

Cutaneous EHE presents as a well-circumscribed dermal nodule, which is sometimes covered by hyperplastic epidermis. In some cases, this hyperplasia also involves the adjacent eccrine ducts, resulting in a pattern that resembles eccrine syringofibroadenoma[51].

EHE is composed of cords, strands and solid aggregates of round, oval and polygonal cells, with abundant pale eosinophilic cytoplasm, vesicular nuclei and inconspicuous nucleoli, embedded in a fibromyxoid or sclerotic stroma. Many neoplastic cells exhibit prominent cytoplasmic vacuolization as expression of primitive vascular differentiation. Sometimes, nuclear pleomorphism and mitotic figures are present. In rare instances, vascular channels and well-formed large vessels are seen in the central areas of the lesion. Occasionally, bone metaplasia has been described in the stroma of EHE[52].

Lesions that arise in a preexisting vessel extend centrifugally to adjacent soft tissues, and the architecture of the original vessel is spared. In rare instances, the lumen of the vessel appears occluded by necrotic material and dense collagen bundles. Histopathologic differential diagnosis between EHE and metastatic signet-ring cell adenocarcinoma may be challenging because neoplastic cells of signet-ring cell adenocarcinoma may show cytoplasmic vacuoles containing mucin. In these cases, the presence of erythrocytes within the cytoplasmic vacuoles is a helpful clue for diagnosis of EHE[53].

Immunohistochemistry is also helpful in this differential diagnosis because neoplastic cells of epithelioid haemangioendothelioma express immunoreactivity for endothelial markers, such as von Willebrand factor, CD31, and CD34. They also express positivity for podoplanin, Lyve-1, and Prox-1, supporting a lymphatic line of differentiation. However, caution should be taken with the immunostains for cytokeratins 7 and 18, as well as for SMA, as neoplastic cells of EHE contain abundant intermediate filaments and may express positivity for these markers, leading to a wrong diagnosis. EHE should also be differentiated from epithelioid AS, which is usually composed of sheets and solid aggregates of very atypical neoplastic cells that destroy preexisting structures of the dermis. Neoplastic cells of epithelioid AS show numerous atypical mitotic figures, and both necrosis of individual cells and necrosis en masse are frequent findings[54].

Electron microscopy studies have demonstrated that neoplastic cells of EHE show ultrastructural characteristics of endothelial cells, with well-developed basement membrane, pinocytotic vesicles and occasional Weibel-Palade bodies. These cells differ from normal endothelial cells by the abundant number of intermediate filaments within their cytoplasm. Cytogenetic studies in EHE failed to demonstrate microsatellite instability, although two cases showed a t(1;3)(p36.3;q25) translocation[55].

Although EHE was successfully treated with imiquimod, surgical excision with clear margins is the best treatment for this neoplasm. Regional lymph nodes should be also evaluated, as they are the most frequent sites for metastases. Metastases seem to be more common when the primary neoplasm exhibits cytologic atypia. Less than half the patients with lymph node metastases will die of the neoplasm because surgical excision of the primary neoplasm and the involved lymph nodes is usually curative[56].

VASCULAR MALFORMATIONS

Vascular malformations, as congenital abnormalities, result from abnormal vessel development and morphogenesis. In general, they are present at birth (but may be hidden in a deep location) and grow in proportion to the child's growth, persisting throughout the lifetime.

Capillary malformations

Capillary malformations (CMs), also known as port-wine stains or nevus flammeus, are the most common type of congenital vascular malformations. These lesions are initially flat and bright pink, red, or violaceous and typically affect the face (90%), followed by the neck, trunk, leg, arm and hand. They often seem to lighten significantly over the first few months of life. This is not indicative of spontaneous resolution but is probably due to a decrease in circulating blood hemoglobin concentration. In contrast to other similar birthmarks, most CMs become darker, thicker and more nodular over time. This is particularly true of facial lesions. The incidence rate is reported as 0.3% in newborns, with an equal sex distribution, occurring spontaneously within the population. In most affected individuals, CMs occur as a sporadic unifocal lesion and are not associated with any underlying abnormalities[57].

However, CMs are sometimes associated with other underlying syndromes such as Sturge-Weber syndrome, macrocephaly-capillary malformation syndrome, capillary malformation-arteriovenous malformation syndrome, and overgrowth syndromes such as Klippel-Trenaunay syndrome. The pathogenic mechanism of CM is still unknown. Studies identified a somatic mutation in GNAQ with isolated CMs, disrupting vascular development. Facial CMs initially appear as a faint pink macule; however, some patients may develop soft tissue hypertrophy, bony hypertrophy, and/or nodule formation during adulthood. Depending on the size and location, these changes can cause functional deficits in vision, speaking or eating, and significant psychological distress related to the resulting stigmatization or disfigurement. The gold standard therapy for facial or aesthetically sensitive CM is still the pulsed dye laser treatment. In patients with associated soft tissue or bony hypertrophy, surgical management can be helpful in restoring the normal anatomy and in re-establishing a symmetric contour[58].

Lymphatic malformations

Lymphatic malformation (LM) results from errors in the development of the lymphatic system; lymphatic tissue may form in an abnormal location. LM is divided into three types according to the size of the malformed channels, namely microcystic, macrocystic or combined (microcystic/macrocystic). LM is a soft and compressible lesion that usually appears at birth; however, a small or deep lesion may not become evident until the lesion has grown large enough to cause deformity or symptoms[59].

LM is most located on the head and neck, causing a deformity and psychosocial morbidity. The overlying skin appears in various shapes, which may be normal, have a bluish hue or have pink vesicles like CM. LM is problematic because of its progression, its slow expansion over time and its recurrence. The common complications are bleeding and infection. Intralesional bleeding occurs in up to 35% of LMs, causing pain or swelling. LM is vulnerable to infection because the

malformed lymphatics contribute less to antibody production and protein-rich fluid provides a good environment for bacterial growth. Somatic PIK3CA mutations were found in several malformative or overgrowth syndromes, including LMs as a component. Small or asymptomatic lesions may be observed. Symptomatic lesions causing pain, deformity or threatening vital structures necessitate operative treatment[60].

Venous malformations

Venous malformation (VM) results from errors in vascular morphogenesis. Thin-walled veins with abnormal smooth muscle are dilated, and then the VM expands and the flow stagnates with clotting. VM is present at birth but may not become evident until it has grown large enough to cause a deformity or symptoms. VMs are blue, soft and compressible; sometimes phleboliths may be palpable. VMs may appear from localized skin lesions to diffuse malformations involving multiple tissue and structures. VMs are sporadic and solitary in 90% of patients; 50% of patients have a somatic mutation in the endothelial receptor TIE2, which is involved in angiogenesis[61].

VMs are usually larger than 5 cm (56%) and involve the skin, mucosa or subcutaneous tissue; 50% of VMs also involve muscle, bone and viscera; appear singly (99%); and are located on the head/neck (47%), followed by the extremities (40%) and trunk (13%). Complications related to VMs depend on the extent and location and cause psychosocial morbidity because of their appearance. Common complications are ulceration, bleeding, compression of adjacent structures, and chronic low grade consumptive coagulopathy in large and extensive lesions. Pain and swelling are dependent on position or are secondary to thrombosis and phlebolith formation. In the head and neck, VMs may severely affect compression of adjacent structures. Although nonproblematic lesions can be observed, symptomatic lesions causing pain, deformity or threatening vital structures necessitate sclerotherapy or operative treatment[62].

Arteriovenous malformations

Arteriovenous malformation (AVM) results from errors in vascular development during embryogenesis; absent capillary beds lead to shunting directly from the arterial to venous circulation through a fistula or nidus (abnormal channels between feeding arteries and draining veins). The most common site of extracranial AVM is the head and neck, followed by the limbs, trunk and viscera. AVM is present at birth but may not become evident until childhood. AVM has a pink-red cutaneous stain with a palpable thrill or bruit, and it is important to distinguish AVM from a CM or haemangioma. Arteriovenous shunting reduces capillary oxygen delivery, causing ischemia. Common complications are pain, ulceration, bleeding and congestive heart failure[63].

AVM can cause disfigurement, compression or destruction of adjacent tissues. Although AVM is considered a quiescent lesion, angiogenesis and/or vasculogenesis may be involved in AVM expansion. AVM is not a static malformation, progresses over time and recurs. Genetic abnormalities cause certain types of familial AVMs. Capillary malformation-arteriovenous malformation results from a mutation in RASA1. The goal of treatment usually is to control AVM. For superficial AVMs, patients should prevent desiccation and subsequent ulceration, and compression garments for extremity lesions may reduce pain and swelling. Intervention including embolization, resection or a combination is focused on reducing symptoms, preserving vital functions and improving deformities[64].

Diagnosis of most vascular lesions is made using accurate terminology of lesion, detailed clinical history and physical examination of lesion. Special investigations such as imaging modalities in the form of Color Doppler ultrasound, MRI, computerized tomography (CT), phlebography, nuclear imaging studies, single photon emission CT, and multiplanar computed angiography help diagnose and distinguish vascular lesions. MRI is the investigation of choice as it provides accurate information about the extent of the lesion, better contrast between the lesion and surrounding tissues, and has multiplanar capabilities. It can also help distinguish between the different types of vascular anomalies. It provides anatomic and physiologic information noninvasively with the use of nonionizing radiation from the radiofrequency band of the electromagnetic spectrum. MRI depends on the properties of nucleus. MRI is commonly performed without a gradient echo sequence (GRE) or without the intravenous administration of contrast material[65].

Fat suppressed T2 weighted images are mainly used to evaluate the extent of the abnormality; GRE images are used to identify the hemodynamic nature of the condition (high vs. low flow lesion), and contrast enhanced images are used to determine the extent of the malformation and to distinguish slowflow vascular anomalies (VM vs. LM). Grayscale ultrasound and colour Doppler analysis are useful in defining whether the lesion is solid or cystic and to establish the presence or absence of highflow vessels. Angiography is usually reserved for therapeutic endovascular interventions. Angiography includes arteriography, venography and direct intralesional contrast agent injection. Arteriography is used for the evaluation of highflow

vascular lesions. Arteriography has no diagnostic value in the assessment of lowflow lesions. Nuclear imaging techniques can be used for the study of congenital vascular malformations. This technique provides functional information of the lesion[66].

Treatment of vascular lesions is often very complex, there are various treatment modalities and guidelines for the management of haemangiomas and vascular malformations depending on the stage and type of lesions; each has its pros and cons and is under incessant renewal. Corticosteroids are the first line of treatment for alarming or potentially endangering haemangiomas and may be administered systemically, intralesionally or topically. The response rates may vary and correlate with the proliferative rate of the lesion as well as anatomic site. Normal starting dose begins at 2-3 mg/kg/day of prednisolone followed by the tapering of dose gradually once the adequate response is obtained. If the lesion does not respond to corticosteroids, vincristine or IFNα2b can be used as a second line of treatment. Laser therapies are also effective for treating superficial and deep haemangiomas. These lasers cause vessel wall damage through destruction of hemoglobin while minimizing injury to adjacent structures. Superficial lesions with small and intermediate size vessels can be treated successfully with pulse dye laser whereas larger vessels with deep haemangiomas can be treated with neodymium: yttrium aluminium garnet laser. Tissue necrosis and scarring are often observed by uncritical use of lasers. Surgical excision of lesion should be considered when there is threat to life or function, complicated course, failure of pharmacotherapy, cosmetic revision of scars after lesion involution, atypical growth or emotional burden. Treatment of other vascular lesions such as KHE is treated first by systemic corticosteroids followed by vincristine or IFN. All these therapies are less effective in treating KHE than haemangioma. The treatment of pyogenic granuloma is curettage, shave excision and laser phototherapy or full thickness excision[67].

The current management techniques of CM are cosmetic camouflage, laser therapy followed by excision and grafting, and for VMs, they are elastic compression, sclerotherapy and surgical resection or a combined approach. Sclerotherapy is used to reduce the size of lesion or preoperatively as a support to surgery. There are many types of sclerosing agents used to destroy the vascular endothelium through different mechanisms: chemical agents (iodine or alcohol), osmotic agents (salicylates or hypertonic saline), detergents, and anticancer drugs, which change the surface tension of the cell, producing tissue maceration. Sclerotherapy induces inflammation and thrombosis of the lesion, leading to fibrosis and shrinkage of lesion. Ethanol is recognized as the most effective sclerosing agent in the treatment of VM. Surgery is indicated in well-circumscribed malformations of moderate size, in which possibilities of anatomic and functional restoration are maximal. Surgical treatment of more extensive lesions can often lead to loss of motor function, nerve damage and massive bleeding. Embolization and surgery are the treatment choice for AVMs. Goal of surgery in AVMs is to completely remove the lesion, while maintaining control of hemorrhage and to reconstruct the defect to a functional and aesthetic level[68].

The treatment options for LMs include surgery, sclerotherapy and laser therapy. Surgery remains the mainstay or even the only treatment choice and remains the first choice in the hands of many surgeons. Macrocystic lesions, on the other hand, are more localized and respect tissue planes and are more easily excised compared to microcystic lesion. Diffuse microcystic lesions are more difficult and may require multiple operations. Superficial oral mucosal microcystic LMs can be treated with laser therapy. Sclerotherapy may be an effective treatment for macrocystic lesions. Each vascular lesion case should be managed on its merits after careful discussion and counselling. An individualized treatment protocol should be made based on the condition of the patient and the technical availability. Most often, application of a multidisciplinary approach will achieve the best results when planned well and implemented[69].

CONCLUSION

Abnormal angiogenesis, vasculogenesis or lymphangiogenesis can lead to various vascular lesions. Since different types of vascular lesions require specific treatment approaches, it is essential for both academicians and clinicians to understand the clinical presentation of these lesions, as well as their outdated and often confusing terminologies, to make accurate diagnoses. Despite significant advancements in this field, much work remains to be done to understand the pathophysiology of these lesions and to develop targeted therapies that can improve patients' quality of life. It is important to understand that vascular malformations and tumours are two distinct categories of vascular anomalies found in the head and neck. Vascular malformations refer to abnormalities in the development of blood vessels, while tumours are characterized by the proliferation of abnormal cells. These lesions can occur in various locations within the head and neck. Accurate diagnosis and appropriate treatment of these lesions often rely on imaging techniques.

ACKNOWLEDGMENT

Conflict of interest: Nil

Funding details: Nil

Author's contribution: Karthik Shunmugavelu: study concept and design, manuscript drafting and statistical analysis; Anbumozhi M K: data acquisition, manuscript revision, administrative, technical, and material support; Hemachandiran V: data analysis and interpretation, study supervision

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Original Article

Abnormal uterine bleeding pattern in patients with endometrial cancer and endometrial hyperplasia

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Kuwait Medical Journal 2026; 58 (2): 102 - 106

ABSTRACT

Objective: This study aimed to determine whether the type of abnormal uterine bleeding (AUB) is a risk factor for malignant or premalignant endometrial biopsy results.
Design: A retrospective study was conducted on 1813 women who underwent endometrial biopsy due to AUB.
Settings: Tertiary care center in Riyadh, Saudi Arabia
Subjects: Patients who underwent endometrial biopsy due to AUB
Intervention: Endometrial biopsies
Main Outcome Measure(s): The relation between the pattern of AUB and risk of endometrial cancer and atypical endometrial hyperplasia.
Results: Of the 1813 patients, 3.6% had malignant or premalignant biopsy results. Significant risk factors for malignancy included postmenopausal bleeding, irregular AUB, age over 45 and obesity, while heavy regular AUB was associated with a reduced risk of malignancy. The study also found that the type of AUB is a significant independent risk factor for endometrial cancer and atypical hyperplasia.
Conclusion: Current clinical recommendations for endometrial cancer detection in women with AUB may not align with the underlying risk. This study suggests that the type of AUB should be considered in assessing clinical and epidemiologic risk prediction models for endometrial cancer and atypical endometrial hyperplasia.

KEY WORDS: atypical endometrial biopsy, endometrial hyperplasia, endometrial neoplasms, obesity, postmenopausal bleeding, uterine hemorrhage

INTRODUCTION

The incidence of endometrial cancer (EC) is increasing worldwide, and EC is one of the most common cancers reported in women globally[1]. EC remains the most common gynecologic malignancy. The lifetime risk for uterine malignancy is 1 in 32 women in the USA and 1 in 224 women in Malaysia[2,3], and almost 100 cases per 100,000 woman-years will involve EC in South Korea[4].

Although the majority of EC patients present with stage I disease (80-90%), which has a high 5-year survival rate[5-7], the mortality rate has increased recently[1], and early diagnosis and treatment are key to decreasing mortality and morbidity from EC.

Endometrial hyperplasia (EH) is abnormal proliferation of the endometrial glands, with an increase in the gland-to-stroma ratio compared with the proliferative endothelium and can be the first warning sign of the pathological process, eventually leading to endometrial carcinoma[8]. The latest World Health Organization classification of EH includes two groups based on the presence or absence of cytological atypia, and the terms atypical hyperplasia and hyperplasia without atypia are interchangeable with benign (EH) and premalignant (endometrial intraepithelial neoplasia)[9]. Atypical endometrial hyperplasia (AEH) is a precursor of EC; 31.58% of patients will have EC, and up to 40% of patients operated on for this condition have concurrent EC[10,11].

More than 90% of postmenopausal women with endometrial carcinoma present with abnormal uterine bleeding (AUB)[8,12]. In premenopausal women with AUB, 1-14% will have EC or AEH[11,13]. AEH and EC are uncommon in AUB studies (0.0-1.9%)[14]; however, many factors have been found to increase the risk of

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AEH and EC, such as increasing age (women 45-50), obesity and unopposed estrogen exposure[15-17].

All guidelines recommend endometrial biopsy in women presenting with postmenopausal bleeding; however, in premenopausal women with abnormal uterine bleeding, the guidelines vary in the cutoff age, with some being 40 years and others being 45 years. American College of Obstetricians and Gynecologists guidelines recommend endometrial biopsy in all women aged 45 years and older with any type of AUB and in women less than 45 years if other risk factors are present. The National Institute for Health and Care Excellence (NICE) recommended endometrial biopsy in all perimenopausal women with AUB when conventional medical management has failed[18-20].

AUB affects 52% of women and accounts for 30% of gynecology outpatient visits. The majority of these patients are perimenopausal, and the prevalence of malignant or premalignant pathologies is low if there are no risk factors for EC. The need for endometrial biopsy in such patients should be based on risk factors to avoid unnecessary and painful procedures[21].

There is limited data regarding the type of AUB and the risk of EC and AEH, and our main objective was to determine whether the type of AUB is a risk factor for malignant or premalignant endometrial biopsy results.

MATERIALS AND METHODS

After approval from King Saud University's Institutional Review Board (IRB), a retrospective study was carried out for all women who underwent endometrial biopsy due to AUB at the Gynecology clinics, King Saud University Medical City (KSUMC), Riyadh, KSA, from 2011 to 2017. The data were accessed through the hospital's electronic records. Deidentified data were collected and entered through patient code to maintain privacy and confidentiality. Data included patient demographics, *i.e.*, age, weight (kg), height (cm), body mass index (BMI), histopathology results and type of AUB.

The AUB was classified as either regular heavy, irregular bleeding, postmenopausal bleeding or other (post coital bleeding, continuous spotting). The histopathology results were categorized into non-malignancy, premalignancy (EH without atypia), malignancy (AEH and EC) or sufficient.

Patients that had endometrial samples for reasons other than AUB were excluded. Categorical data were summarized as the mean values with standard deviation. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 23. One-way ANOVA. The chi-square test was used for the analysis of correlation between pathology findings, 45 years was used as a cutoff age and BMI >30 kg/m^2. The association between the study variables and AUB was determined using a t-test. The significance level was set at a *P*-value ≤0.05.

Inclusion criteria

All patients who presented to our gynecology clinic with AUB and underwent an office endometrial biopsy were included in the study.

Exclusion criteria

Patients who underwent endometrial biopsy without a history of AUB were excluded from the study. Additionally, patients with incomplete data and those with pregnancy-related abnormal bleeding were also excluded.

RESULTS

During the study period, we had 1826 endometrial biopsy results; 1813 patients had AUB, and only 13 patients were found to have a thick endometrium by ultrasound and were excluded. All patients were Saudi. Table 1 displays patients' characteristics and results. The majority of AUB complaints were heavy or prolonged bleeding (921, 50.8%), postmenopausal bleeding (420, 23.2%), irregular bleeding or intermenstrual bleeding (326, 18%) and other instances of AUB (146, 8.1%).

The majority of our cohort were aged 45 years or older (1442 (79%)), and 1185 patients (65.4%) were obese. The majority of biopsy results were benign (1430, 78%), and EH was reported in 98 (5.4%) patients.

Only 66 patients (3.6%) had malignant tumors (EC and AEH). Simple and multiple logistic regression analyses were performed to identify the significant

Table 1: Patient characteristics, type of bleeding and pathology results

Characteristics	N (%)
Age	
< 45 years	371 (20.5)
≥ 45 years	1442 (79.5)
BMI	
Obese (BMI ≥30 kg/m^2)	1185 (65.4)
Non-obese (<30 kg/m^2)	628 (34.6)
Pathological result	
No malignancy	1430 (78.9)
Premalignancy	98 (5.4)
Malignancy	66 (3.6)
Insufficient	219 (12.1)
Bleeding type	
Abnormal uterine bleeding (heavy or prolonged)	921 (50.8)
Abnormal uterine bleeding (intermenstrual)	326 (18)
Post-menopausal bleeding	420 (23.2)
Other	146 (8.1)

Table 2: Risk factors for non-benign histopathology results

Characteristics	No malignancy (n = 1430) N (%)	Premalignancy (n = 98) N (%)	Relative risk (95% CI)	Sig.	Malignancy (n = 66) N (%)	Relative risk (95% CI)	Sig.
Age ≤45 year	331 (23.1)	12 (12.2)	1		8 (12.1)	1	
Age >45 year	1099 (76.9)	86 (87.1)	2.1 (1.15, 3.75)	0.016	58 (87.9)	2.1 (1.02, 4.40)	0.0429
Nonobese (BMI <30 kg/m^2)	504 (35.2)	19 (19.4)	1		13 (19.7)	1	
Obese (BMI ≥30 kg/m^2)	926 (64.8)	79 (80.6)	2.2 (1.33, 3.53)	0.002	53 (80.3)	2.2 (1.18, 3.91)	0.012
Post-menopausal bleeding	241 (16.9)	45 (45.9)	3.9 (1.59, 9.60)	0.003	40 (60.6)	5.8 (1.82, 18.35)	0.003
Abnormal uterine bleeding irregular	242 (16.9)	28 (28.6)	2.6 (1.02, 6.50)	0.046	20 (30.3)	3.10 (0.94, 10.25)	0.063
Abnormal uterine bleeding	862 (57.9)	20 (20.4)	0.56 (0.21, 1.47)	0.241	3 (4.5)	0.14 (0.03, 0.69)	0.016
Other cause	119 (8.3)	5 (5.1)	1		3 (4.5)	1	

risk factors for nonbenign biopsy results, as shown in Tables 2 and 3. Figure 1 demonstrates the distribution of histopathology results among different presenting types of abnormal uterine bleeding.

The significant risk factors for nonbenign biopsy results were age 45 and above, BMI >30 kg/m^2, postmenopausal bleeding and irregular AUB. Regular abnormal bleeding significantly lowers the risk of having a premalignant biopsy result, and the highest risk factor was postmenopausal bleeding (relative risk (RR): 4.14), followed by irregular uterine bleeding (RR: 2.63) and obesity (RR: 2.09). Heavy uterine bleeding was found to be associated with a lower risk of nonbenign pathology results (RR: 0.41).

DISCUSSION

Our research objective was to investigate the role of different types of AUB as independent risk factors for malignant or premalignant endometrial biopsy outcomes. In our cohort of 1813 patients, we found a 3.6% risk of malignancy, which encompasses both EC and AEH. This prevalence aligns with similar reported data[3,18].

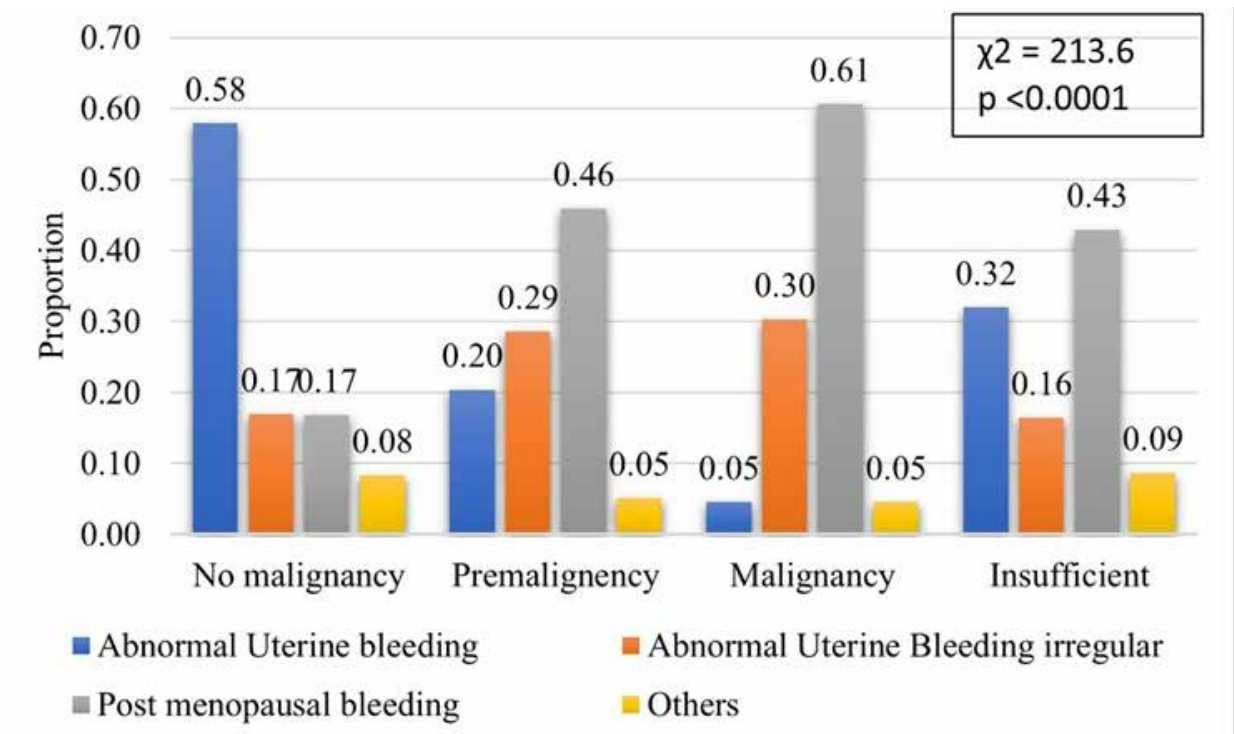

Figure 1: Histopathology results in different types of AUB.

Table 3: Multivariant analysis of the risk factors for non-benign endometrial results

Characteristics	No malignancy (n = 1430) N (%)	Premalignancy and malignancy (n = 164) N (%)	Relative risk (95% CI)	Sig.
Age ≤45 year	331 (23.1)	20 (12.2)	1	
Age >45 year	1099 (76.9)	144 (87.8)	2.03 (1.29, 3.2)	0.002
Non-obese (BMI <30 kg/m^2)	504 (35.2)	32 (19.5)	1	
Obese (BMI ≥30 kg/m^2)	926 (64.8)	132 (80.5)	2.09 (1.44, 3.03)	0.000
Post-menopausal bleeding	241 (16.9)	85 (51.8)	4.14 (2.06, 8.29)	0.000
Abnormal uterine bleeding irregular	242 (16.9)	48 (29.3)	2.63 (1.28, 5.39)	0.008
Abnormal uterine bleeding	862 (57.9)	23 (14)	0.41 (0.19, 0.9)	0.027
Other	119 (8.3)	8 (4.9)	1	

Significant risk factors for malignancy in our study included postmenopausal uterine bleeding, irregular uterine bleeding, age over 45 and obesity. Interestingly, heavy regular bleeding was associated with a reduced risk of malignancy.

The primary goal of performing endometrial biopsies in women with AUB is to identify or rule out EC or AEH for early intervention and treatment. Current clinical practice guidelines universally recommend biopsies for all cases of postmenopausal bleeding. However, there is controversy regarding the need for endometrial biopsy in premenopausal women where the risk is lower[18]. Guidelines vary, with some advocating for a specific age cutoff, the presence of risk factors or failed medical treatment as indications for biopsy[18-20].

While endometrial biopsy is typically performed on an outpatient basis, it can cause anxiety, pain and potential complications for patients, as well as increased health care costs and burdens. Identifying significant risk factors, such as obesity and postmenopausal status, can help avoid unnecessary biopsies. These two factors consistently appear to be risk factors for malignancy in patients with AUB. Other risk factors, such as infertility, diabetes, parity and estrogen exposure have also been reported[13,22,23]. The reported risk of malignancy in women presenting with AUB without risk factors is generally 1% or less. NICE recommends a cancer risk threshold of >3% for screening guidance[15,22]. In our study, we used the age of 45 or older as a cutoff, as most data indicate a low risk of malignancy in women younger than 45[20,24]. Additionally, we considered obesity and postmenopausal status as consistent risk factors for malignancy in patients with AUB[24]. While some studies have suggested intermenstrual bleeding as a risk factor, there are limited data to support this notion[25].

In our research, we identified the type of AUB as an independent risk factor for malignancy. RR of malignancy was higher in cases of postmenopausal bleeding and irregular AUB compared to obesity and age. Conversely, patients with heavy regular AUB exhibited a lower relative risk of malignancy and premalignancy.

CONCLUSION

Current clinical recommendations for endometrial cancer detection in women with abnormal bleeding are not consistent with the underlying risk. The type of abnormal uterine bleeding is a significant risk factor for endometrial cancer and atypical hyperplasia. They should be included in a formal assessment of clinical and epidemiologic risk prediction models.

ACKNOWLEDGMENT

The author of this manuscript has no conflict of interest to disclose.

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Original Article

Investigating the significance of HbA1C, platelet/lymphocyte and neutrophil/lymphocyte on mortality in patients hospitalized with COVID-19

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Kuwait Medical Journal 2026; 58 (2): 107 - 111

ABSTRACT

Objectives: Elderly patients with COVID-19 and patients with COVID-19 who suffered from some comorbidities had worse prognosis.
Design: Demographic information, comorbidities, duration of hospital stay, the values of HbA1c, platelet, leukocyte, neutrophil and lymphocyte count, hemoglobin, C-reactive protein, ferritin, procalcitonin, D-dimer and fibrinogen level, discharge or death status of patients were recorded.
Setting: This study was carried out in Mersin City Training and Research Hospital.
Subjects: This study is to assess the effects of comorbidities on mortality in hospitalized patients with COVID-19. The secondary aim is to determine some possible prognostic markers for mortality.
Intervention: A linear multiple regression model with stepwise backward elimination to find the possible predictors for mortality**.**
Main outcome measures: The percentage of hypertension was significantly higher in exitus-group of patients in which diabetes mellitus and heart failure were found higher in alive group. The values of ferritin level, neutrophil-lymphocyte ratio, platelet/lymphocyte ratio are higher in exitus group. HbA1c levels were found lower in alive group compared to exitus.
Results: HgA1c and ferritin were the significant predictors for mortality. Hypertension was significantly higher in exitus-group.
Conclusion: The present study revealed that the presence of hypertension is a determinant factor of mortality in patients with COVID-19 infection, as well as the values of ferritin level, neutrophil-lymphocyte ratio, platelet/lymphocyte ratio and age may be predictive factors for mortality.

KEY WORDS: COVID-19, hypertension, mortality, prognostic factor

INTRODUCTION

Acute respiratory syndrome coronavirus broke out in Wuhan, China in December 2019. The disease, also called COVID-19 (coronavirus disease), was recognized as a worldwide pandemic in March 2020. Millions of people around the world have been infected since the start of the pandemic, and more than a million people have died due to the disease and disease-related complications[1]. The pathogenesis of coagulation-related alveolar damage in the disease is explained by the migration of inflammatory cells (neutrophils, macrophages and monocytes) from the vessels into the alveolar space those causes, damage to the alveolar capillary membrane structure, elevated coagulation factors and the exudation of fibrinogen-rich plasma proteins[1-3]. It has been reported that elderly patients with COVID-19 and patients with COVID-19 who suffered from comorbidities such as hypertension (HT), chronic obstructive pulmonary disease (COPD), cardiovascular diseases and diabetes mellitus (DM) are more likely to progress to acute respiratory distress syndrome, septic shock, metabolic acidosis and organ failure[3,4].

The primary aim of this study is to assess the effects of comorbidities on mortality in hospitalized patients, whereas the secondary aim is to determine whether

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the levels of HbA1c, neutrophil-lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) and ferritin could be possible prognostic markers for mortality.

SUBJECTS AND METHODS

This study was designed as a cross-sectional retrospective research. The clinical trial was approved by the Clinical Research Ethics Committee of XXX University (Grant number: 2021/523).

Patients over 18 years of age and under 99 years of age who were hospitalized with a diagnosis of COVID-19 in Mersin City Training and Research Hospital between April 2020 and January 2021 were obtained from the hospital information management system. Demographic information, comorbidities, duration of hospital stay and intensive care unit admission, the levels of HbA1c, platelet count, leukocyte count, neutrophil count, lymphocyte count, hemoglobin, C-reactive protein (CRP) level, ferritin level, procalcitonin (PCT) level, D-dimer level, fibrinogen level at 5th and 10th day, discharge or death status of patients with complete file information were recorded. NLR and PLR were calculated for each patient.

Statistical analysis

One-sample Kolmogorov-Smirnov test was used to find the distribution of the variables. Quantitative data had been displayed as means and standard deviation, and qualitative data as frequency and percentage. The comparisons among groups were performed by Mann-Whitney U test. A multivariate linear backward regression analysis was used where all CBC and biochemical outcomes were considered as variables in this method. Statistical analyses had been completed by Statistical Package for Social Sciences (SPSS Inc., Chicago, IL) version 20.0 program. Statistical significance was accepted as P <0.05 in analyses.

RESULTS

After enrolling 2000 patients, a total of 199 patients with complete data were included in this study. The mean age was 64.12±16.95 years, where 89 (44.7%) of the patients were female. The demographic characteristics of patients are presented in Table 1. The percentage of HT was significantly higher in exitus-group patients in which DM and heart failure were found higher in alive group (P=0.02, P=0.046, P=0.002, respectively; Table 1). A linear multiple regression model with stepwise backward elimination to find the possible predictors for mortality where HbA1c, ICU stay, WBC, neutrophile count, lymphocyte count, platelet count, NLR, PLR, ferritin level, CRP level, fibrinogen level and PCT level were assigned as independent variables showed that HbA1c and ferritin were the significant predictors for mortality (OR=0.47, β=0.373, P=0.016, 95% Confidence Interval (CI): 0.016 – 0.144, OR=0.42, β=-0.379, P=0.015, 95% CI: -0.001 – 0.144, respectively; Table 2). The mortality rate of elderly patients was approximately two-fold higher than patients aged below 65 years (P=0.021; Table 3).

Table 1: Demographic characteristics

Parameters	Alive (Mean±SD)	Exitus (Mean±SD)	*P*
Age (years)	62.07±16.51	68.75±17.17	**0.003***
	N (%)	**N (%)**	
Gender (F) Female	56 (40.6)	33 (54.1)	0.077
Comorbidities			
DM	59 (42.8)	17 (27.9)	**0.046***
HT	34 (24.6)	25 (41)	**0.020***
CAD	33 (23.9)	13 (21.3)	0.688
COPD	10 (7.2)	5 (8.2)	0.815
RF	4 (2.9)	2 (3.3)	0.885
HF	5 (33.3)	10 (16.4)	**0.002***
Ward stay (days)	7.85±6.13	4.81±3.68	0.109
ICU stay (days)	9.32±7.74	11.1±9.83	0.345

*P<0.05 Mann-Whitney U
DM: diabetes mellitus; HT: hypertension; CAD: Coronary artery disease; COPD: chronic obstructive pulmonary disease; RF: renal failure; HF: heart failure; ICU: intensive care unit

DISCUSSION

Based on our study results, we could suggest that age, PLR and NLR, ferritin levels and concurrent HT are all determinant factors of mortality among COVID-19 patients. During COVID-19 pandemic period, numerous parameters were studied, and it was revealed that parameters such as older age, female gender, CRP, ferritin, low lymphocyte, NLR and PLR could be recognized as biomarkers in detecting poor clinical status[2,4-9].

Limited numbers of studies have been conducted during the pandemic to investigate the link between HbA1c levels and morbidity and mortality in COVID-19 patients. In addition, studies were undertaken to investigate the association between DM, HbA1c level, surgical infection, morbidity and mortality[3,9,10]. Since it is predicted that vaso-occlusive events and coagulation abnormalities are likely to occur in COVID-19 patients, there have been studies suggesting that this may lead to severe complications and increased mortality[11,12].

The present study showed that HbA1c level was lower in patients who died due to COVID-19 compared to those who were alive. In this respect, Aydinli *et al* studied whether HbA1c was a predictive factor for mortality among patients undergoing coronary bypass

Table 2: Comparison of the CBC and biochemical analysis of the groups

Parameters	Alive (n=138) (Mean±SD)	Exitus (n=61) (Mean±SD)	*P*
HbA1c	7.88±3	6.4±1.74	**0.002***
WBC-Base	15.58±54.71	14.08±12.37	**0.015***
Neutrophil-Base	8.45±5.65	10.73±5.25	**0.001***
Lymphocyte-Base	7.33±64.57	2.46±9.46	**0.003***
Platelet-Base	263.9±132.54	254±128.2	0.758
Neut./Lymp.-Base	8.23±10.37	13.25±13.1	**<0.05***
Plt/Lymp.-Base	234.08±247.71	322.75±322.27	**0.031***
Ferritin-Base	403.5±1027.7	770.56±1191.94	**0.009***
PCT-Base	10.09±60.09	2.63±9.84	0.067
CRP-Base	6.9±7.64	10.47±11.52	0.128
Fibrinogen-Base	470.23±190.22	464.31±193.63	0.875
D-Dimer-Base	3.63±10.56	9.54±20.83	**0.002***
WBC-5th day	11.09±5.47	16.41±19.03	**<0.05***
Neutrophil-5th day	8.96±5.17	12.36±5.42	**<0.05***
Lymphocyte-5th day	1.27±0.81	2.85±14.75	**<0.05***
Platelet-5th day	280.31±130.27	251.22±120.43	0.223
Neut./Lymp.-5th day	12.17±17.95	29.53±51.14	**<0.05***
Plt/Lymp.-Base-5th day	359.5±529.17	559.11±797	**0.031***
Ferritin-5th day	338.99±411.82	1350.45±5113.74	**0.030***
PCT-5th day	5.2±37.7	2.54±11.5	**<0.05***
CRP-5th day	12.9±95.49	8.73±7.42	**<0.05***
Fibrinogen-5th day	413.94±186.51	464.09±161.68	0.077
D-Dimer-5th day	8.78±40.31	3.51±3.42	**0.001***
WBC-10th day	11.61±6.04	14.27±7.83	**0.049***
Neutrophile-10th day	9.3±6.1	12.61±7.1	**0.012***
Lymphocyte-10th day	1.53±1.26	0.97±0.76	**0.012***
Platelet-10th day	269.73±123.78	185.16±120.29	**0.002***
Neut./Lymp.-10th day	10.74±11.42	24.78±38.48	**0.001***
Plt/Lymp.-Base-10th day	295.61±293.89	381.13±791.68	0.743
Ferritin-10th day	565.65±1301.36	745.22±1602.34	0.862
PCT-10th day	0.7±2.29	0.92±1.18	**<0.05***
CRP-10th day	3.63±5.76	11.8±8.54	**<0.05***
Fibrinogen-10th day	399.83±149.94	481.99±214.87	**0.039***
D-Dimer-10th day	4.58±15.98	5.91±9.25	**<0.05***

**P*<0.05 Mann-Whitney U
SD: standard deviation; WBC: white blood cell; PCT: procalcitonin; CRP: C-reactive protein

surgery and concluded that it could not be accepted as an independent predictor apart from other factors[13].

Another study conducted by Merzon *et al* predicting HbA1c as a biomarker for hospitalization in COVID-19 is the first study conducted during pandemic. Authors found that 43.5% of patients hospitalized with COVID-19 had HbA1c <7%, while 56.5% of them had HbA1c >7%. It was also found that 69.3% of non-hospitalized patients had HbA1c <7% and 30.7% of them had HbA1c >7%. Comorbidities were screened in that study, but morbidity and mortality were not[3].

In the present study, ferritin, NLR and PLR values were found to be high in patients who died. This is consistent with the view that these parameters are biomarkers of mortality, as in other studies.

Table 3: Comparison of several biochemical analyses among patients over 65 years and below 65 years of age

Parameters	Age groups		*P*
	Age ≤ 65 years (n=93) N(%)	Age ≥ 65 years (n=106) N(%)	
Alive	75 (52.2)	66 (47.8)	0.021*a
Exitus	21 (34.4)	40 (65.6)	
	Mean±SD	**Mean±SD**	
Ferritin-base	640.54±1508.41	419.16±501.16	0.987b
Neut/Lymp base	13.89±16.08	19.55±40.41	0.195b
Plt/Lymp base	339.46±288.25	476.21±792.22	0.564b

[a]Chi-square test; [b]Mann-Whitney U test

Furthermore, Solmaz *et al* evaluated 1750 patients with COVID-19 and reported that there was an increase in NLR, CRP and a decrease in PLR in which lymphocyte/CRP ratio were prognostic for intensive care unit admission and mortality[8].

In the present study, it was also found that gender differences had no effect on mortality; however, mortality was higher in hypertensive patients. Additionally, the survival rate was higher in patients with DM. Moreover, Akpinar *et al* assessed patients who required intensive care admission where they reported male gender ratio and mean age were higher. In addition, the lymphocyte count was lower in patients who were admitted to intensive care compared to those who did not transfer to intensive care. They also found that asthma-COPD was a comorbidity elevating the length of stay in intensive care unit, whereas DM did not contribute significantly in terms of prognosis[14]. These findings were similar to our study, in which DM had no effect on mortality.

Nevertheless, Khairy *et al* reviewed 1468 articles including 1,281,510 patients, and revealed that HT was observed as a comorbidity in 25% of patients with COVID-19 and increased the severity of the disease and the duration of hospitalization[15]. In addition, Qian *et al* reviewed studies on 13,293 patients and they found that HT increased the need for intensive care, which was also a risk factor for mortality[16]. The results of our study also showed that HT was a determinant factor in mortality.

Studies correlating mortality with age support the results of our study[17-19]. In our study, mortality was higher in the patient group over 65 years of age.

This study has some limitations. First, laboratory parameters that might be associated with the severity of the disease had not been clearly evaluated which was related to the sample size of the study. Second, the previous status of the HbA1c levels of the patients could not be found, where this value can be beneficial to compare and obtain detailed information about the condition of the patients' previous history.

CONCLUSION

In conclusion, it can be speculated that the presence of hypertension is a determinant of mortality in patients with COVID-19 infection, as well as ferritin level and the ratios of NLR, PLR values are predictors for mortality. Further studies with larger sample size could be required to find possible predictors for COVID-19.

ACKNOWLEDGMENT

Financial support: None

Conflicts of interest: None

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Original Article

The impact of inflammatory biomarkers in predicting cancer in indeterminate thyroid nodules: A preliminary report

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Kuwait Medical Journal 2026; 58 (2): 112 - 120

ABSTRACT

Objectives: Cancer exclusion is essential for indeterminate thyroid nodules (ITNs). We aimed to evaluate the platelet-to-lymphocyte (PLR), lymphocyte-to-monocyte (LMR) and neutrophil-to-lymphocyte ratios (NLR) as predictors of ITN malignancy.
Design: Retrospective observational study
Setting: A single tertiary hospital
Subjects: Fifty patients with ITNs who underwent thyroidectomies
Interventions: None
Main Outcome Measures: The association between preoperative PLR, LMR and NLR and the risk of malignancy (ROM), with data stratified by age, sex and nodule size.
Results: Of the 50 participants, 68% were women and 52% had malignant pathology. The hematological indices were not significantly different between the benign and malignant groups; however, NLR and ROM were significantly associated in individuals aged ≥55 years with nodules ≥4 cm (P=0.045). PLR and ROM were significantly correlated in women aged ≥55 years with nodules <4 cm (P=0.001), whereas NLR and ROM were significantly associated in men aged <55 years with nodules ≥4 cm (P=0.010).
Conclusions: According to our findings, NLR and PLR may be useful predictors of ITN malignancy, although their implementation remains to be validated.

KEY WORDS: biopsy, cytology, fine needle, thyroid cancer, papillary

INTRODUCTION

The global prevalence of thyroid cancer (TC), particularly papillary thyroid carcinoma (PTC), has been increasing, which could be related to technological advancements in radiology and the widespread utilization of diagnostic fine-needle aspiration (FNA). PTC, an indolent tumor originating from follicular cells, is the most prevalent type of TC and is more common in women[1,2]. Notably, it represents about 95% of all TCs and 85% of all well differentiated TCs. Furthermore, it has a favorable prognosis in comparison to other TCs. PTC has a 10-year survival rate of 93% and is unlikely to progress or cause mortality[2].

In Saudi Arabia, TC is the predominant endocrine cancer in women and the ninth most predominant in men. Furthermore, the incidence in Saudi Arabia rose significantly for both men and women from 1990 to 2019, with a 22-fold increase for men and a 15-fold increase for women[3]. The etiology of this phenomenon remains uncertain; factors such as insufficient iodine intake, a familial predisposition to TC, previous exposure to radiation, tobacco use, elevated levels of leptin and obesity have all been postulated as potential causative agents[3]. Other contributing factors for the development of PTC include genetic mutations, such as rearrangements involving the RET/PTC oncogene and point mutations in the BRAF and RAS genes, with

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the latter being the most widespread in affected patients[4].

Thyroid nodules (TNs) are a common surgical problem and are typically identified using neck ultrasonography, although 5% of adult patients present with clinically palpable nodules. Most TNs are benign and asymptomatic; nevertheless, there is a 5-15% chance of them becoming cancerous[5]. TNs are typically evaluated clinically, radiologically and cytologically. Neck ultrasonography is the preferred radiological approach to determine the risk of malignancy (ROM) in TNs and defines the diagnostic indication of FNA. With a specificity of 56-100% and sensitivity of 68-98%, FNA of TNs provides a definite preoperative diagnosis[1]. However, 25% of all TNs have an uncertain cytology and are clinically challenging[6]. These are known as indeterminate TNs (ITNs) and comprise the Bethesda III (also called atypia/follicular lesion of undetermined significance [AUS]/[FLUS]) and Bethesda IV categories[7]. Cancer exclusion in ITNs is clinically significant and estimated to be 5-15% in the Bethesda III category and 15-30% in the Bethesda IV category[7]. Furthermore, the ROM in Bethesda III resected nodules ranges between 6% and 48%, whereas in surgically excised Bethesda IV nodules, it ranges between 14% and 34%[5]. These variations can be attributed to the significant difficulties in accurately assessing the ROM due to the small proportion of nodules classified as Bethesda III that actually undergo surgery. The overestimation of ROM arises from selection bias when depending solely on histopathological data for measurement[8].

Given the high incidence of ITNs, early and correct diagnosis allows for prompt planning of surgery and radiometabolic therapy[1]. Therefore, establishing hematological markers that are noninvasive and capable of detecting PTC at an early stage in these problematic nodules is essential. Indeed, ITNs have been extensively studied in terms of cytological subtypes and clinical, radiological, biochemical and molecular properties, with the goal of predicting malignancy in these nodules[1,5,6,8,9]. Identifying such predictive biomarkers will allow for safe, well-tolerated and accepted methods of diagnosis that will help reduce the likelihood of overtreatment[1].

Chronic inflammation is known to increase the risk of several cancers, including PTC[10]. Inflammatory responses and immune system dysregulation are correlated with cancer initiation, progression, metastasis and prognosis[11]. Interestingly, inflammation has the ability to eliminate cancer cells but also contributes to the creation of a tumor microenvironment for the growth and multiplication of cancer cells[12]. The hallmarks of cancer refer to the shared characteristics that regulate the conversion of healthy cells into cancerous ones.

Mediators of the inflammatory response include monocytes, lymphocytes, neutrophils and platelets[1]. Lymphocytes and monocytes are the principal immune cells that act as antitumor mediators[1,12]. A decrease in their levels results in poor prognosis and a low overall survival (OS). Furthermore, monocytes promote the apoptosis of cancer cells to minimize angiogenesis, which reduces cancer invasion and progression[1]. Conversely, neutrophils and platelets play important roles in carcinogenesis. In particular, neutrophils generate vascular endothelial growth factor and interleukins (IL; e.g., IL-10, IL-8, IL-6, and IL-2) and suppress tumor necrosis factor-α; when elevated, they can promote tumor development and invasion[1,2,11]. Platelets can assist tumor cells in evading antitumor immunity by producing platelet-derived and vascular endothelial growth factors[10].

The platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR) and neutrophil-to-lymphocyte ratio (NLR) can easily be measured during routine preoperative laboratory workups. These systemic inflammatory markers have prognostic value in several types of cancer, such as head and neck, urinary, biliary and hepatocellular malignancies[13]. Nevertheless, the specific functions they play in TCs have not been firmly established, with contradictory results regarding their ability to predict TCs. The prognostic significance of these markers remains uncertain and challenging to assess due to the infrequent incidence of cancer recurrence and the high survival rate of TCs. However, some authors have reported systemic inflammatory markers as potential prognostic indicators in PTC[13]. Studies examining the impact of systemic inflammatory indicators on TC primarily focus on their ability to predict the diagnosis of thyroid malignancies. However, their correlation with unfavorable clinicopathological characteristics of TCs, such as lymph node metastasis and extrathyroidal extension, has been insufficiently examined[13]. The differentiation between TC and benign TNs using systemic inflammatory markers is a subject of ongoing controversy[13].

Although there is evidence that these ratios influence the prediction of high-risk differentiated and anaplastic TCs, only two studies have investigated their significance in ITNs[1,2]. Both studies used the Italian cytological classification[14] and focused on the third group comprising indeterminate thyroid lesions (TIR3A [low-risk indeterminate lesions] and TIR3B [high-risk indeterminate lesions])[1,2]. According to Gambardella *et al*[2], the NLR is a simple inflammatory biomarker that has been proven to increase the reliability of preoperative cancer prognosis, particularly in Thyr 3B patients. They concluded that combining biochemical and cytological techniques could offer more personalized therapy while avoiding

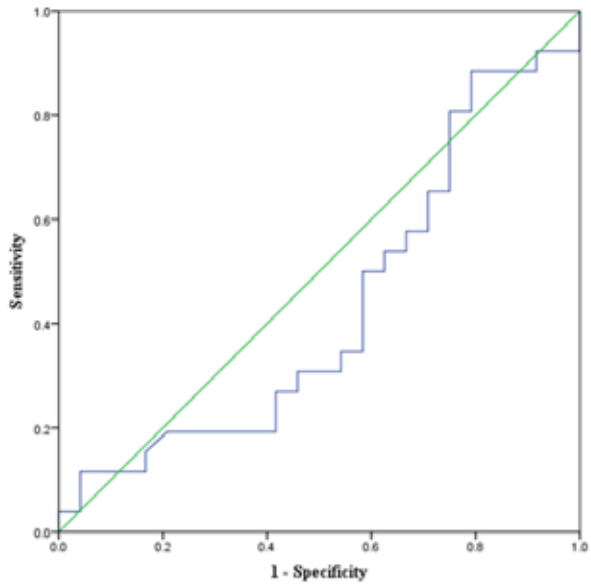

Fig 1: Receiver operating characteristic curve for the lymphocyte-to-monocyte ratio.

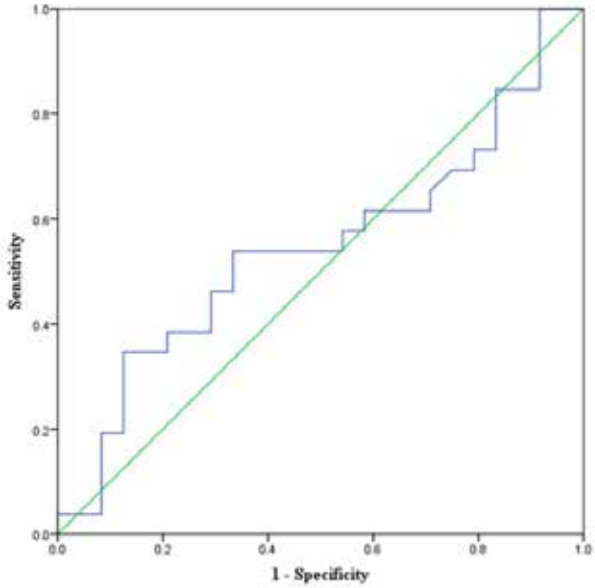

Fig 2: Receiver operating characteristic curve for the neutrophil-to-lymphocyte ratio.

diagnostic thyroidectomy[2]. In contrast, Offi *et al*[1] found that the LMR was more likely to detect TC in patients with ITNs. As a result of these conflicting reports, the current study explored the roles of PLR, LMR and NLR as indicators of ITN malignancy.

SUBJECTS AND METHODS

A retrospective analysis was performed to explore the efficacy of preoperative inflammatory biomarkers (PLR, LMR and NLR) as noninvasive predictors of malignancy in patients with ITNs. We used data from our earlier report[9], and a cohort of 115 adult participants from over a four-year period were initially reviewed. The cohort included patients who underwent thyroidectomies at our hospital, with a cytological diagnosis of AUS/FLUS according to the 2009 Bethesda System for Reporting Thyroid Cytopathology[7]. An electronic database was used to acquire clinical, demographic and pathological features, as well as laboratory data. This data included the age, gender, body mass index, type of surgery, final pathology (benign vs. PTC), preoperative white blood cell (WBC) counts and their differentials and platelet counts. A total of 65 patients were excluded because of missing data; consequently, the final sample size was 50 patients.

The postoperative histopathologic diagnosis was performed by the Department of Pathology and Laboratory Medicine in our hospital and was reported based on the World Health Organization classification of thyroid tumors. Based on the final pathological results, participants were categorized into two distinct groups: benign and PTC. Before surgery, all included patients were evaluated clinically at the endocrine surgery clinic and underwent preoperative complete blood counts (CBC), WBC differentials, thyroid function tests, FNA and neck ultrasound. Neutrophils, monocytes and lymphocytes were among the WBC differentials. The PLR, LMR and NLR were determined using absolute counts as follows: PLR = platelet count/absolute lymphocyte count, LMR = absolute lymphocyte count/absolute monocyte count, and NLR = absolute neutrophil count/absolute lymphocyte count.

To enable the analysis of WBC and platelet counts, tubes containing ethylenediamine tetraacetic acid were used for routine preoperative bloodwork. A SYSMEX Digital Imaging Machine (Dl-60, S/N:61126; SYSMEX Corp., Kobe, Japan) was used for CBC and WBC differentials. The normal ranges of laboratory data in our hospital were as follows; WBC: 3.9–11.0 × 10^9 /L; absolute monocytes: 0.25–1.0 × 10^9 /L; absolute lymphocytes: 1.5–4.3 × 10^9 /L; absolute neutrophils: 1.35–7.5 × 10^9 /L; and platelets: 155–435 × 10^9 /L. In addition, the normal range of hematological ratios are as follows; NLR: 0.9–1.74; LMR: 4.3–6; and PLR: 101.2–103.3.

The age was categorized as <55 and ≥55 years according to the age at diagnosis using the Updated American Joint Committee on cancer/tumor-node-metastasis staging system for differentiated and anaplastic TC (8^{th} edition)[15]. Additionally, the preoperative nodule size was categorized as <4 and ≥4 cm. Notably, the nodule size was not available for

Table 1: The comparison of WBC, neutrophils, lymphocytes, monocytes, platelets, NLR, LMR and PLR between the benign and malignant groups.

Variables	Benign (n = 24)		Malignant (n = 26)		95% CI		*P*
	Mean	SD	Mean	SD			
WBC	8.3	4.19	7.9	3.08	-1.65	2.50	0.684
Neutrophils	5.6	4.13	5.1	3.33	-1.65	2.61	0.652
Lymphocytes	2.0	0.85	2.1	0.98	-0.61	0.43	0.734
Monocytes	0.5	0.27	0.5	0.22	-0.09	0.19	0.513
Platelets	270.1	71.39	271.1	84.23	-45.54	43.64	0.966
NLR	4.1	5.25	3.7	3.97	-2.3	3.0	0.781
LMR	4.3	2.50	4.7	2.61	-1.9	1.0	0.512
PLR	179.8	135.98	165.9	97.10	-52.9	80.7	0.678

*P<0.05 was considered statistically significant.
SD: standard deviation; CI: confidence interval; WBC: white blood cells; NLR: neutrophil-to-lymphocyte ratio; LMR: lymphocyte-to-monocyte ratio; PLR: platelet-to-lymphocyte ratio.

one male patient with a benign pathology. All individuals underwent hemithyroidectomy or total thyroidectomy.

The main outcome of the study involved assessing the predictive capacity of PLR, LMR and NLR in ITNs (AUS/FLUS) for determining malignancy based on the final pathology after surgery.

Ethical approval was obtained by the appropriate Ethics Committee at King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia (publication number: 2235234) and conducted in compliance with the Declaration of Helsinki. As there was no direct contact with patients, informed consent was not required.

All gathered data were coded into MS Office Excel software (Microsoft, Redmont, WA, USA) and subsequently transferred to the Statistical Package for Social Sciences software (SPSS version 20.0; IBM Corp., Armonk, NY, USA) for statistical analysis. Quantitative variables such as platelet count, WBC count, PLR, LMR and NLR are described as mean and standard deviation (SD). Qualitative variables such as sex, categories of age and categories of nodule size are summarized using appropriate descriptive statistics such as frequency and percentage. An independent t-test was utilized to compare categorical and quantitative variables, and chi-squared or Fisher's exact tests were conducted to compare categorical variables, as appropriate. The association between inflammatory biomarkers and ROM was analyzed for all data stratified by age and nodule size, with a subgroup analysis based on sex. A *P*-value <0.05 was considered significant.

RESULTS

A total of 50 participants were enrolled for this analysis: 34 women (68%) and 16 men (32%); of these, 26 (52%) had malignancy reported on the final pathology. More than half of the nodules were right-sided (n=27, 54%), 22 (44%) were left-sided, and only one nodule was at the isthmus. Age ranged from 15-71 years, with a mean ± SD of 44±13.11 years. Compared with patients with malignant pathology, the mean age of those with benign nodules was higher (42.3±13.05 vs. 45.9±13.20 years, respectively), without statistical significance (*P*=0.342). Of the patients with benign nodules, six were diagnosed with Hashimoto's thyroiditis, eight had nodular hyperplasia, four had follicular adenoma, five had multinodular goiter, and one had an adenomatous nodule. In contrast, the malignant nodules were the following subtypes of PTC: 20 follicular variants, two classic, two tall cell variants, one mixed classic and solid, and one

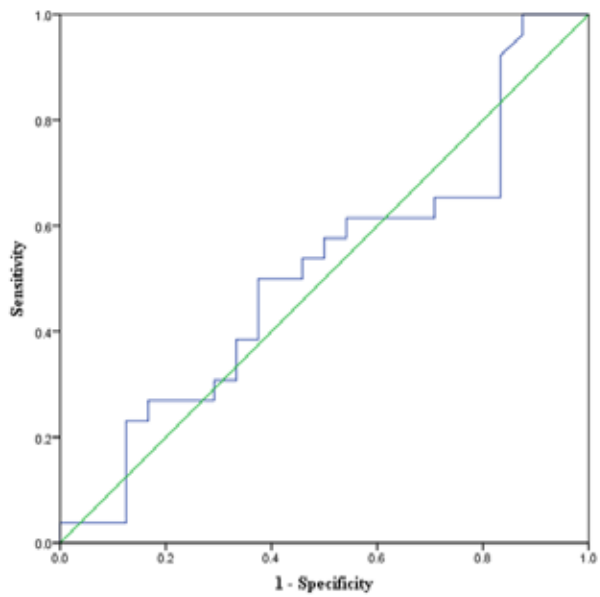

Fig 2: Receiver operating characteristic curve for the platelet-to-lymphocyte ratio.

Table 2: The correlation between inflammatory markers and risk of malignancy in all participants, stratified by age and nodule size.

Age	Marker	Benign		Malignant		95% CI		*P*
		Mean	SD	Mean	SD			
< 4 cm		**n = 13**		**n = 15**				
< 55 years	NLR	4.9	6.80	3.8	4.74	-3.37	5.64	0.608
	LMR	3.6	1.82	4.0	2.03	-1.86	1.16	0.639
	PLR	207.3	157.11	177.5	97.99	-70.48	130.01	0.547
< 4 cm		**n = 3**		**n = 2**				
≥ 55 years	NLR	2.8	1.88	2.9	0.52	-4.60	4.49	0.971
	LMR	4.6	1.43	3.0	1.00	-2.23	5.34	0.282
	PLR	105.1	8.54	291.1	179.12	-1785.12	1413.00	0.380
≥ 4 cm		**n = 5**		**n = 6**				
< 55 years	NLR	3.2	2.64	2.4	2.39	-2.61	4.25	0.603
	LMR	3.4	1.60	5.8	2.83	-5.66	0.81	0.124
	PLR	180.8	152.18	107.9	43.24	-72.92	218.72	0.287
≥ 4 cm		**n = 2**		**n = 3**				
≥ 55 years	NLR	1.4	1.05	6.8	2.07	-10.68	-0.25	0.045*
	LMR	7.2	5.01	7.7	3.53	-12.36	11.35	0.901
	PLR	110.9	14.15	140.6	46.31	-142.11	82.68	0.462

*P<0.05 was considered statistically significant.
SD: standard deviation; CI: confidence interval; NLR: neutrophil-to-lymphocyte ratio; LMR: lymphocyte-to-monocyte ratio; PLR: platelet-to-lymphocyte ratio.
N.B. One male patient with benign pathology has no available nodule size.

encapsulated oncocytic variant. Body mass index was comparable, with no significant difference (29.4±6.47 vs. 28.9±6.60 kg/m^2 for the benign and malignant groups, respectively, *P*=0.808). Malignant nodules were larger in size than benign nodules (3.2±2.21 vs. 2.8±2.40 cm, respectively), but not significantly different (*P*=0.634). Of the 50 patients, 33 (66%) underwent hemithyroidectomy and 17 (34%)

Table 3: The correlation between inflammatory markers and risk of malignancy in women, stratified by age and nodule size.

Age	Marker	Benign		Malignant		95% CI		*P*
		Mean	SD	Mean	SD			
< 4 cm		**n = 11**		**n = 9**				
< 55 years	NLR	5.4	7.34	3.9	3.87	-4.23	7.19	0.593
	LMR	3.8	1.92	4.1	2.19	-2.25	1.61	0.731
	PLR	216.2	170.44	196.3	99.36	-115.42	155.16	0.761
< 4 cm		**n = 3**		**n = 1**				
≥ 55 years	NLR	2.8	1.88	2.5	--	-9.03	9.65	0.898
	LMR	4.6	1.43	3.8	--	-6.26	7.96	0.658
	PLR	105.1	8.54	417.8	--	-355.16	-270.28	0.001*
≥ 4cm		**n = 4**		**n = 3**				
< 55 years	NLR	2.1	0.52	3.1	3.56	-5.50	3.48	0.588
	LMR	3.6	1.75	7.3	3.49	-8.85	1.33	0.116
	PLR	201.5	167.40	128.5	57.65	-191.44	337.45	0.510
≥ 4cm		**n = 1**		**n = 2**				
≥ 55 years	NLR	2.1	--	7.9	1.37	-27.13	15.57	0.180
	LMR	3.6	--	8.9	3.98	-67.23	56.68	0.475
	PLR	120.9	--	154.3	56.22	-908.34	841.49	0.712

*P<0.05 was considered statistically significant.
SD: standard deviation; CI: confidence interval; NLR: neutrophil-to-lymphocyte ratio; LMR: lymphocyte-to-monocyte ratio; PLR: platelet-to-lymphocyte ratio.

Table 4: The correlation between inflammatory markers and risk of malignancy in men, stratified by age and nodule size.

Age	Marker	Benign		Malignant		95% CI		*P*
		Mean	SD	Mean	SD			
< 4 cm		**n = 2**		**n = 6**				
< 55 years	NLR	2.4	0.49	3.6	6.24	-12.62	10.16	0.800
	LMR	2.5	0.57	3.7	1.93	-4.74	2.37	0.447
	PLR	158.6	9.16	149.4	97.52	-168.85	187.17	0.904
< 4 cm		**n = 0**		**n = 1**				
≥ 55 years	NLR	--	--	3.3	--	Cannot be calculated		
	LMR	--	--	2.3	--	------		
	PLR	--	--	164.5	--			
≥ 4 cm		**n = 1**		**n = 3**				
< 55 years	NLR	7.9	--	1.7	.53	3.53	8.75	0.010*
	LMR	2.5	--	4.2	.71	-5.26	1.77	0.166
	PLR	97.9	--	87.3	8.83	-33.17	54.54	0.405
≥ 4 cm		**n = 1**		**n = 1**				
≥ 55 years	NLR	0.6	--	4.7	--	Cannot be calculated		
	LMR	10.7	--	5.2	--			
	PLR	100.9	--	113.2	--	------		

*P<0.05 was considered statistically significant.
SD: standard deviation; CI: confidence interval; NLR: neutrophil-to-lymphocyte ratio; LMR: lymphocyte-to-monocyte ratio; PLR: platelet-to-lymphocyte ratio.
N.B. One male patient with benign pathology has no available nodule size.

underwent total thyroidectomy. Individuals who underwent hemithyroidectomy and received a diagnosis of malignancy in their final pathology report underwent completion thyroidectomy.

The comparison of WBC, lymphocytes, monocytes, neutrophils, platelets, PLR, LMR and NLR between the malignant and benign groups is shown in Table 1, with no statistical significance detected. There were no significant associations between the ROM and other measured variables, including age (categorized as <55 and ≥55 years), sex and size (categorized as <4 and ≥4 cm) (*P*=0.887, 0.104, and 0.755, respectively).

The correlations between inflammatory biomarkers and ROM in all patients, stratified by age and nodule size, are displayed in Table 2. The mean NLR for patients with malignant pathology was greater than that for those with benign nodules in patients aged ≥55 years with nodules ≥4 cm (6.8±2.07 vs. 1.4±1.05, respectively, *P*=0.045).

Tables 3 and 4 show the associations between inflammatory biomarkers and ROM, stratified by age and nodule size, for women and men, respectively. Notably, a significant correlation was observed between PLR and ROM in women who were aged ≥55 years and had nodules <4 cm (*P*=0.001, Table 3). Conversely, a significant association was detected between NLR and ROM in men aged <55 years who had nodules ≥4 cm (*P*=0.010, Table 4).

DISCUSSION

The anti-tumor function of immune cells, including natural killer and activated T cells, can be hindered by systemic inflammatory responses. Although the precise mechanisms are not clearly understood, some indicators such as platelet, neutrophil and lymphocyte counts, either individually or when represented as ratios, have been associated with the prognosis of many types of malignancies[13]. However, only two studies have investigated the role of PLR, LMR and NLR as indicators of malignancy in ITNs[1,2]. Thus, this study explored their effects as predictors of ITN malignancy in our population.

TC is experiencing the most rapid growth among all types of malignancies, with a significant increase in new cases worldwide. While the majority of cases have a good prognosis, TC necessitates a significant amount of ongoing medical attention[3]. Despite the fact that the vast majority of ITNs (70-80%) have benign histopathology following surgical intervention, they remain a clinical issue for endocrine surgeons and endocrinologists. Furthermore, because they are heterogeneous entities, choosing between surgery and a conservative strategy with long-term surveillance remains challenging[16,17]. Given these facts, personalized approaches have been recommended in recent years. According to the updated guidelines, repeat FNA, molecular testing or diagnostic lobectomy

are the recommended therapeutic strategies for ITNs[8]. However, repeat FNA is usually not a well-accepted option for patients, and surgery is unnecessary in 70% of cases[1]. Moreover, surgery is associated with possible complications such as hypocalcemia, nerve injury, hypothyroidism, neck hematoma, infection and keloids[1]. In addition, although molecular testing is an effective management tool, its unavailability in most centers limits its application. Consequently, continuing research is being conducted to develop noninvasive, safe, low-cost and well-tolerated tests aimed at the screening, diagnosis and follow-up of ITNs. Such tests may include inflammatory biomarkers (LMR, NLR and PLR), which can be determined using routine preoperative laboratory work at no additional expense and with minimal patient discomfort[1].

Of note, inflammation may have a significant impact on the development and advancement of cancer. The relationship between inflammation and cancer is believed to be intricate and dependent on various physiological processes, including diverse inflammatory cells, mediators and signaling pathways within cancerous tissue[18]. Additionally, cancer-related inflammatory responses lead to cancer growth, survival of tumor cells and angiogenesis, ultimately contributing to cancer progression.

The correlation between tumors and inflammation is often regarded as a significant mechanism in the progression of cancer. Alterations in the proportions of certain cells have a direct or indirect impact on the prognosis of tumors[10]. Various inflammation-related processes have been discovered in the carcinogenic process: genomic instability, stimulation of cell growth and survival, immunomodulation of the tumor microenvironment and enhancement of metastatic spread. Most cancer cells exhibit genomic instability, which arises from elevated levels of DNA damage and from modified DNA repair pathways. Inflammation likely plays a significant role in causing genomic instability by triggering somatic mutations[11]. Furthermore, the elevation of pro-inflammatory cytokine levels is considered to be a reliable indicator of the prognosis of disease and the patient's response to the tumor. Therefore, systemic indicators of inflammation such as C-reactive protein, concentration of albumin, NLR and PLR could potentially serve as predictive biomarkers[18].

The simplicity of the calculations of LMR, NLR and PLR from leukocyte fractions and the ability to collect these data from routine blood tests offer a significant advantage in clinical practice. These ratios are independent predictive markers of various solid tumors[1,2], and they have been found to be involved in TC development and metastasis[10]. Both LMR and NLR have been observed to forecast long-term results. Nonetheless, the clinical significance of these inflammatory markers in differentiated TC remains to be elucidated[19].

LMR refers to the presence of tumor-infiltrating lymphocytes, circulating myeloid-derived suppressor cells, and precursor mononuclear cells of tumor-associated macrophages[19]. Low LMR is correlated with poor prognosis, lower OS and lower PTC-free survival[12]. Moreover, low LMR enhanced the incidence of recurrence in both differentiated and anaplastic TCs[1,11,12] and has been recognized as a risk factor for radioactive iodine-refractory status and mortality[12]. Similarly, a study involving 570 patients with PTC revealed a significant correlation between low preoperative LMR and recurrence, particularly in individuals with advanced PTC[19]. In contrast, high LMR indicated no risk of cancer[1,11].

Compared with other inflammatory biomarkers, NLR is recognized for its greater predictive value in comparison to the other individual leukocyte counts. In addition, NLR is a reliable and substantial predictor in head and neck malignancies[20], but its usefulness in TC prediction is still unknown[2,13]. A high NLR correlates with extrathyroidal extension and tumor size, indicating that NLR is a straightforward and useful diagnostic marker for understanding the clinical behavior of patients with PTC[18]. Cheong *et al*[13] discovered that the NLR had a noteworthy predictive capacity for TC in nodules larger than 2 cm when patients were stratified by tumor size. When adjusting for the disparity in size between TC and benign TNs, NLR was a robust predictor of TC[13]. Furthermore, an increased NLR was associated with incidental papillary thyroid microcarcinoma and TC[21]; in stage III and IV PTC, an elevated NLR was correlated with lower disease-free survival[22]. The preoperative NLR in PTC was assessed by Lang *et al*[23]; their results indicated that while a high NLR may suggest a more unfavorable tumor profile, it is not significantly linked to a poorer disease-free survival or an increased likelihood of occult central nodal metastases in PTC.

According to Ozmen *et al*[24], the PLR and NLR surpass C-reactive protein in detecting the development of well-differentiated TC. A study by Ari and Gunver[25] showed that the NLR and PLR yielded comparable findings for both thyroid inflammation and malignancy. Notably, obtaining distinct outcomes to distinguish cancer from inflammatory episodes using these markers appears to be challenging. In the same study, the authors recommended utilizing them as adjunctive indicators for PTC or inflammation[25].

Only two studies have examined the impact of inflammatory biomarkers in detecting malignancy in ITNs[1,2]. According to Offi *et al*[1], the LMR was found to serve as an additional tool in predicting

malignancy in ITNs and in optimizing personalized therapy. Furthermore, these authors found that the mean PLR was significantly different when comparing the benign and malignant groups. However, this notable difference was absent in the univariate analysis[1]. Gambardella *et al*[2] validated the utility of the NLR as a non-invasive biomarker that may be readily acquired and demonstrated that it had an advantage in prognosticating malignancy in ITNs, specifically in TIR3B patients. Our findings showed that the NLR was significantly correlated with ROM in individuals aged ≥55 years with nodules ≥4 cm. Furthermore, a significant association was observed between PLR and ROM in women aged ≥55 years with nodules <4 cm and between NLR and ROM in men aged <55 years with nodules ≥4 cm.

The strength of our study is that it is the third to examine the impact of inflammatory biomarkers on cancer prediction in ITNs, with promising findings. In contrast to these two previous studies[1,2], our study analyzed all data stratified by age and nodule size and explored the association in subgroups based on sex. Nevertheless, acknowledging the underlying limitations is imperative, particularly the small sample size collected from a single institution and the retrospective design of the study. These constraints may have contributed to a Type II statistical error. Moreover, the inclusion of resected nodules may have overestimated the ROM and did not represent all AUS/FLUS TNs, leading to a selection bias. Furthermore, the analysis did not include other pathological features such as Hashimoto's thyroiditis, lymph node metastasis, extrathyroidal extension and the stage of PTC. Therefore, a comprehensive, prospective, controlled study with a significant sample size is imperative to address these constraints.

CONCLUSIONS

In summary, our findings showed that the NLR and PLR may be useful markers of malignancy in ITNs, with potential application in the appropriate management of ITNs and in avoiding over- or under-treatment. Furthermore, these markers could offer a practical recommendation for identification of preoperative risk factors in the setting of ITNs. Large longitudinal multi-institutional studies are required to confirm these findings.

ACKNOWLEDGMENTS

The authors would like to thank the Deanship of Postgraduate Studies and Scientific Research at Majmaah University for supporting this work under project number R-2025-1757.

Author Contributions: All authors worked on software, validation and investigation. Saad M Alqahtani and Saif S Al-Sobhi: conceptualization, methodology, data curation, formal analysis, writing- review and editing, and supervision. Saad M Alqahtani: resources, writing-original draft, visualization, project administration and funding acquisition. Kashif Shaikh: conceptualization, data curation and visualization. Hamed I Albalawi: resources and data curation; Yousef S Alalawi: resources. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: This study was approved by the Ethics Committee of King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia (publication number: 2235234) and conducted in compliance with the Declaration of Helsinki.

Informed Consent Statement: Patient consent was waived as there was no direct contact with patients.

Data Availability Statement: The authors confirm that the data supporting the findings of this study are available within the article.

Conflict of Interest: The authors declare no conflicts of interest.

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Original Article

The association of serum iron parameters with histopathological grade and mast cell density in prostatic adenocarcinoma: A single-center retrospective study

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Kuwait Medical Journal 2026; 58 (2): 121 - 126

ABSTRACT

Objective: To investigate the association between mast cell density, histopathological grades and prediagnostic serum iron parameters in prostate cancer
Design: A retrospective design
Settings: Paraffin-embedded tissue blocks were retrieved from the archives of the Department of Pathology at Bilecik Training and Research Hospital, Turkey.
Subjects: The study included twenty-four cases of prostate cancer with measured serum iron parameters within a one-year prediagnostic period.
Interventions: Serum iron and ferritin levels within one year before biopsies were recorded. Gleason scoring was performed using histochemistry. Mast cells were counted in the intratumoral area of histological sections stained with toluidine blue.
Main outcome measures: Statistical analysis of serum iron or ferritin levels and mast cell density was conducted to evaluate their association with grade in terms of prognosis.
Results: Among the cases, 62.5% were classified as low grade, while 37.5% were categorized as high grade. Age correlated with grade (P <0.05). High-grade cases exhibited significantly lower serum iron levels and higher serum ferritin levels (P <0.05). A strong negative correlation was observed between serum iron and grade (r=-0.763, P=0.001), while a robust positive correlation existed between serum ferritin levels and grade (r=0.705, P<0.001). However, mast cell density did not significantly differ between groups and did not correlate with age, grade or serum iron parameters (P >0.05).
Conclusion: There is no significant association between intratumoral mast cell density and serum iron parameters or prostate cancer grade. However, prediagnostic serum iron parameters, showing a high correlation with grade, could serve as potential prognostic factors in prostate cancer.

KEY WORDS: ferritins, iron, mast cells, neoplasm grading, neoplasm

INTRODUCTION

Prostate cancer ranks as the second most prevalent solid tumor among men globally and stands as the fifth leading cause of cancer-related deaths[1]. Predominantly, prostatic adenocarcinoma constitutes the primary malignancy of the prostate gland, typically diagnosed through non-targeted needle biopsies prompted by elevated serum prostate-specific antigen (PSA) levels[2]. The Gleason score is the leading histopathological scoring system for prostate cancer and provides crucial prognostic information[3]. In 2014, the International Society of Urological Pathology and the World Health Organization adopted this simplified grading system composed of 5 prognostic grade groups[4].

Mast cells exhibit distinct associations within the tumor microenvironment, differing when assessed in peritumoral versus intratumoral contexts[5]. Extensive research has consistently linked higher intratumoral mast cell counts to a more favorable prognosis, while conversely indicating an inverse trend with extratumoral mast cell numbers, suggesting a less

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favorable outcome[6-8]. Additionally, the relationship between iron status and mast cells reveals that iron deficiency affects these cells in allergic reactions, and intradermal administration of iron binders can lead to mast cell activation and histamine release[9]. A study in 2018 also suggested that mast cells release ferritin from secretory granules[10]. Despite this knowledge, the literature lacks elucidation on the correlation between mast cell counts and serum iron parameters in prostate cancer. Therefore, this study aims to investigate the association of serum iron parameters with Gleason score and intratumoral mast cell density.

Iron plays a crucial role in various cancer cell reactions, including DNA synthesis, mitochondrial metabolism, tumor proliferation and metastasis. Similar to other cancers, iron is significant for tumor proliferation and survival in prostate cancer[11]. However, conflicting results exist in the literature regarding iron parameters in prostate cancer[11-14]. In our study, we analyzed both serum iron and serum ferritin levels as iron parameters according to the Gleason score system.

MATERIALS AND METHODS

We conducted a retrospective examination of patients diagnosed with prostate cancer from prostate needle biopsy samples at Bilecik Training and Research Hospital between 2014 and 2023, focusing on serum iron parameters and Gleason scores. Cases with measured serum iron or ferritin levels within one year before biopsy were included in the study (n=24). To ensure that the analysis results were not influenced by independent factors, cases of atypical acinar proliferation and intraepithelial neoplasia were excluded. Ethical approval for the study was obtained from the Ethics Committee of Bilecik University (approval number: 2023/5-5), ensuring full compliance with the ethical guidelines outlined in the Declaration of Helsinki.

Histopathological examination

After endoscopic biopsy, tissues were fixed in 10% neutral buffered formaldehyde and underwent standard tissue follow-up procedures, including dehydration, clearing and paraffin impregnation. Subsequently, the tissues were sectioned into 5-micrometer sections, which were then mounted on glass slides. These sections underwent deparaffinization and dehydration using a series of ethanol grades, followed by rinsing with water. The rehydrated sections were stained with hematoxylin-eosin or 1% toluidine blue. Stained sections were examined under a brightfield microscope (Olympus CX23), and relevant histological features were captured using an attached Olympus camera (Olympus EP50).

Histopathological classification

Prostate needle biopsy samples were examined using hematoxylin-eosin staining, and Gleason scoring was performed. Gleason grade groups were classified as follows:

Gleason grade 1: 3+3=6
Gleason grade 2: 3+4=7
Gleason grade 3: 4+3=7
Gleason grade 4: 8 (4+4=8, 3+5=8, 5+3=8)
Gleason grade 5: ≥ 9 (4+5=9, 5+4=9, 5+5=10)[4]

Gleason grade 1 and 2 groups were categorized as low grade, while those with 3 and above were classified as high grade group[15].

Mast cell quantification

Mast cells were quantified using toluidine blue staining on sections from paraffin blocks. Areas with the highest mast cell concentration within each sample were identified at x100 magnification, considering the non-uniform distribution of mast cell infiltration. For mast cell density analysis, three intratumoral regions were randomly selected from these identified areas at x400 magnification. The field of view of the microscope was calculated in mm^2, and mast cells per mm^2 served as the basis for statistical comparisons between the groups[16,17].

Statistical analysis

Statistical analysis was performed using a statistical package program. A *P*-value of less than 0.05 was considered statistically significant in all analyses. The normal distribution of the data was assessed using the Shapiro-Wilk test. For the comparison of demographic and clinical parameters between low and high-grade groups, the Student's t-test was employed for parametric data, while the Mann-Whitney U test was used for nonparametric data. Spearman's test was utilized to assess the correlation between nonparametric variables, whereas Pearson's test was applied for the correlation analysis of parametric variables. A correlation coefficient greater than 0.7 was considered indicative of a high correlation.

RESULTS

Histomorphological results

Following histological examination, in the low Gleason grade group (Grade <3), small glandular structures consisting of round, monomorphic nucleus cells, with occasional merging tendencies and minimal stroma in between, were observed (Fig 1A). In the high Gleason grade group (Grade ≥3), tumor cells with large, hyperchromatic nuclei, occasionally vacuolated cytoplasm, and dispersed distribution within the stroma were noted (Fig 1B).

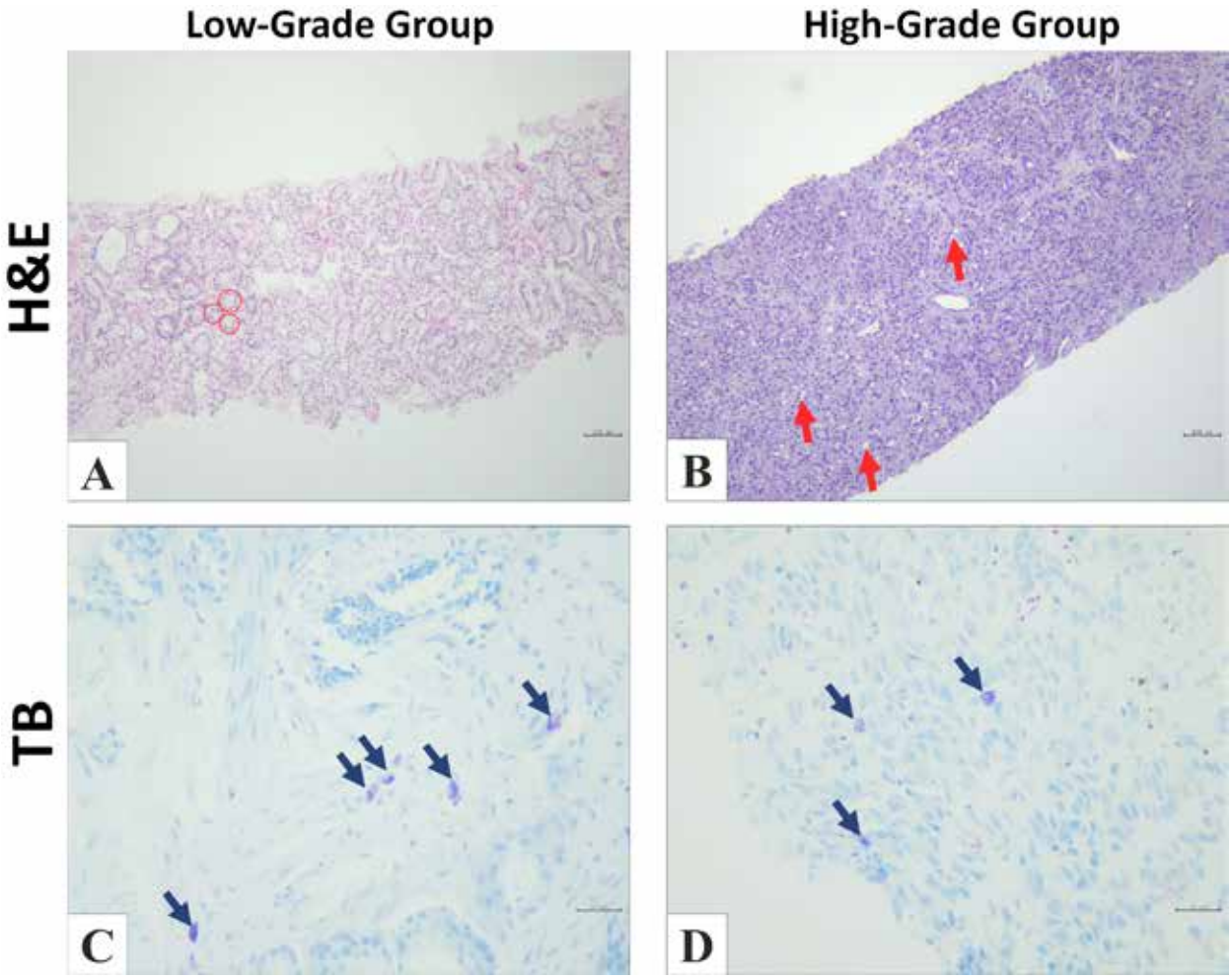

Figure 1: Prostate cancer low-grade (Gleason <3) and high-grade (Gleason ≥3) groups stained with hematoxylin-eosin (H&E) and toluidine blue (TB). **A)** Low-grade group; small glandular structures with round, monomorphic nucleus cells and occasional merging tendencies (red circles); **B)** High-grade group; dispersed distributed tumor cells with large, hyperchromatic nuclei show occasionally vacuolated cytoplasm (red arrow); **C)** Mast cells in low-grade group (black arrow); **D)** Mast cells in high-grade group (black arrow). Scale bars: A,B 100 μm, C,D 30 μm

Toluidine blue staining was performed for mast cell quantification. No significant difference in mast cell count was observed between the groups (Fig 1C-D).

Demographic and clinical parameters: comparison between high and low grade groups

In the study, 62.5% of cases were classified as low grade (Grade < 3), while 37.5% were categorized as high grade (Grade ≥3). The average age of all patients was 73.1 (9) years, with a significant increase observed in the high-grade group (78.2 (7.7) years) compared to the low-grade group (70 (8.5) years; P <0.05). When examining the average iron parameters of all prostate cancer cases, the serum iron level was 59.8 (29.7) ug/dL, and the serum ferritin level was 136.3 (194.6) mg/dL. In the high-grade group, a significant decrease was noted in serum iron levels [29.4 (17.4) ug/dL] compared to the low-grade group [68.2 (22.6) ug/dL], while serum ferritin levels [347.2 (68.5) mg/dL] showed an increase compared to the low-grade group [58.3 (12) mg/dL] (P <0.05). The total intratumoral mast cell density was 157.7 (48.6) per mm^2. When comparing low [148.5 (51)] and high grade [161.1 (55.6)] groups, no significant difference was observed in mast cell density (P >0.05) (Table 1).

Correlation among prostate cancer grade, serum iron parameters, mast cell density and age

A negative linear correlation was observed between serum iron parameters (serum iron and serum ferritin) (r=-0.58, P <0.05). Regarding the correlation of these parameters with grade, a strong negative relationship was found with serum iron (r=-0.763, P=0.001), while a strong positive correlation was observed with serum ferritin levels (r=0.705, P <0.001). Age showed a negative correlation with serum iron (r=-0.558, P <0.05)

Table 1: Comparison of demographic and clinical parameters between low and high-grade groups.

Grade	Low Grade (<3)	High Grade (≥3)	Total	*P* value
Percentage (%)	62.5%	37.5%	100%	
Age, Mean (SD)	70 (8.53)	78.22 (7.73)	73.08 (9.03)	0.027*
Serum iron, µg/dL, Mean (SD)	68.2 (22.6)	29.4 (17.4)	59.8 (29.7)	0.008*
Serum ferritin, mg/dL, Mean (SEM)	58.32 (12)	347.2 (68.5)	136.3 (56.2)	0.0001*
Mast cell density, per mm^2, Mean (SD)	148.5 (51)	161.1 (55.6)	157.7 (48.6)	0.689

Student's t-test/Mann-Whitney U test, SD: Standard deviation, SEM: Standard error, *P <0.05

and a positive correlation with grade (r=0.435, P <0.05). No statistically significant relationship was found in pairwise comparisons of intratumoral mast density with other parameters (P >0.05; Table 2).

DISCUSSION

The literature presents conflicting findings regarding serum iron parameters in prostate cancer[11-14]. In our study, we aimed to elucidate the relationship between serum iron parameters, Gleason grade and intratumoral mast cell density.

Muralidhar *et al* observed an age-related increase in the percentage of Gleason scores 8-10 across different age ranges, with percentages of 8.9%, 16.2% and 28.5% for ages 50 to 54, 70 to 74, and 80 to 84, respectively[18]. In our study, with a mean age of 73.1 (9) years, the percentage of Gleason score 7 (4+3) and above was 37.5%. Consistent with existing literature, we found that the average age was higher in the high-grade group (78.2 (7.7) years; P <0.05).

Saleh *et al* observed an elevated serum iron level of 2 (0.6) ug/mL in newly diagnosed prostate cancer patients, indicating an increase compared to the control group with an average serum iron level of 1.2 (0.2) ug/mL[12]. Similarly, Wenhao *et al* reported high iron levels (31.8 µmol/mL) in prostate cancer compared to benign prostate hyperplasia[15]. In contrast, our study found the average serum iron level to be below the reference range (60-150 ug/dL) at 59.8 (29.7) ug/dL. Our findings align with Kaba *et al*'s study, which reported low serum iron levels in prostate cancer[13]. Additionally, we utilized average iron parameters within the prediagnostic period of one year, differing from the literature. Ying *et al*'s meta-analysis did not find a significant difference in serum iron levels between prostate cancer cases and controls, but reported a decrease in serum ferritin levels[14]. The average ferritin level in our study was within the normal reference range (21.8-274.7 mg/dL) at 136.3 (194.6) mg/dL. Wenhao *et al* reported ferritin levels at 98 ng/mL in prostate cancer[15]. In the current study, rather than comparing with controls, a comparison was made between high and low Gleason grade groups among cancer cases, and the correlation with grade was examined. Wenhao *et al* reported an increase in both ferritin (109.1 ng/mL) and iron levels (33.4 µmol/mL) in the high-grade group. However, the preoperative total iron level in prostate cancer was already high at 31.8 µmol/mL[15]. The average iron level during the one-year prediagnostic period in our study's prostate cancer group was below the reference range. In our study, compared to the low-grade group [serum iron levels 68.2 (22.6) ug/dL, serum ferritin 58.3 (12) mg/dL], the high-grade group showed a decrease in prediagnostic serum iron levels [29.4 (17.4) ug/dL]

Table 2: Correlation analysis of demographic and clinical parameters.

Parameters	Age	Grade	Serum iron	Serum ferritin	Mast density
Age					
r		0.435	-0.558	0.038	-0.112
P		0.034*	0.031	0.871	0.628
Grade					
r	0.435	-0.763	-0.763	0.705	0.076
P	0.034*	0.001*	0.001*	0.0004*	0.742
Serum iron					
r	-0.558	0.705		-0.580	-0.216
P	0.031	0.0004*		0.048*	0.439
Serum ferritin					
r	0.038	0.076	-0.580		0.010
P	0.871	0.742	0.048*		0.967
Mast density					
r	-0.112		-0.216	0.010	
P	0.628		0.439	0.967	

Spearman/Pearson correlation test, r: Correlation coefficient, *P <0.05

and an increase in prediagnostic serum ferritin levels [347.2 (68.5) mg/dL] (P <0.05). Moreover, Wang *et al* categorized prostate cancer into high and low severity based on serum PSA levels, Gleason score and TNM classification. They found a correlation between serum ferritin levels and the severity of the clinical presentation (r=0.81, P=0.001)[19]. Similarly, Tian *et al* also reported a positive relationship between ferritin levels and grade (r:0.326, P <0.001)[20]. In our study, we found a strong positive correlation between prediagnostic ferritin levels and Gleason grade (r=0.705, P <0.001), as well as a strong negative correlation between prediagnostic serum iron levels and Gleason grade (r=-0.763, P=0.001). Banas *et al* identified a positive correlation between Gleason grade and iron levels at the tissue level in prostate cancer[21]. Considering that iron sequestration occurs in cancerous tissue, it is inferred that this sequestration correlates with iron parameters according to malignancy grade[11].

Mast cells exhibit a different association with the tumor microenvironment when evaluated separately as peritumoral and intratumoral[5]. Hempel *et al* reported that the minimum intratumoral mast cell density is lower in prostate cancer with Gleason grade ≥3[22]. Johansson *et al* stated that intratumoral mast cells exhibit a protective role in terms of angiogenesis, metastasis and tumor proliferation. However, they reported a low correlation with a Spearman correlation coefficient <0.3, and the correlation coefficient between Gleason score and intratumoral mast cells was -0.113[23]. In our study, no correlation was found between intratumoral mast cell density and Gleason grade. Due to the study's single-center nature and low patient count, this low correlation may not have been detected. Ward *et al* showed that mast cells contain ferritin in their secretory granules[10]. However, our study did not demonstrate a correlation between intratumoral mast cell density and serum iron parameters. It is worth noting that extratumoral mast cells may serve as a significant source contributing to elevated ferritin levels in cancerous tissue.

CONCLUSION

Various studies in the literature have utilized different units for serum iron parameters, and many of them have not specified reference ranges. Additionally, it is worth noting that studies have typically focused on preoperative samples, overlooking the effect of anemia treatment during the prediagnostic period. Given the controversial relationship between serum iron parameters and prostate cancer, attention should be paid to these aspects in future studies. In conclusion, our findings suggest that intratumoral mast cell density may not directly correlate with serum iron parameters or prostate cancer grade. However, prediagnostic serum iron parameters, showing a high correlation with grade, could serve as potential prognostic factors in prostate cancer.

ACKNOWLEDGMENT

Conflict of interest: None

Author contributions: Damla Gul Findik: conceptualization, methodology, formal analysis and investigation; writing - original draft preparation, writing - review and editing; Erhan Sahin: formal analysis and investigation, writing - original draft preparation; Ozlem Turelik: methodology, writing - original draft preparation; Tugba Celik Samanci: methodology, formal analysis and investigation

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Case Report

Maxillary brown tumor as initial presentation of parathyroid adenoma: A case report

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Kuwait Medical Journal 2026; 58 (2): 127 - 131

ABSTRACT

Background: The brown tumor is one of the pathognomonic findings of primary hyperparathyroidism and is a focal, tumor-like bone lesion caused by the osteoclastic transformation of bone.
Case presentation: We present a case of a brown tumor located in the left maxilla of a 44-year-old male patient. The detected brown tumor was the first clinical manifestation of primary hyperparathyroidism. In this way, the underlying long-term primary hyperparathyroidism caused by a large parathyroid adenoma was finally diagnosed.
Conclusions: Primary hyperparathyroidism can be recognized by the presence of an osteolytic lesion called a brown tumor. It should be kept in mind that the first clinical manifestation of primary hyperparathyroidism, accompanied by increased parathyroid hormone and hypercalcemia, may be a brown tumor.

KEY WORDS: brown tumor, parathyroid adenoma, primary hyperparathyroidism

INTRODUCTION

Hyperparathyroidism (HPT) is defined as a disease with complex biochemical, anatomical and clinical abnormalities[1]. Primary hyperparathyroidism (PHPT) results from the secretion of high amounts of parathyroid hormone from the parathyroid gland. Although the most common cause is parathyroid adenoma, it may be due to many etiologies[2]. PHPT usually occurs with an incidental diagnosis of hypercalcemia, but less frequently, the clinical presentation includes kidney stones, osteoporosis, neuropsychiatric symptoms, and rarely peptic ulcer disease or pancreatitis[3]. Bone findings due to prolonged HPT result in the formation of osteitis fibrosa cystica, or brown tumor, characterized by increased osteoclastic activity and bone resorption and are usually located in the pelvis, ribs, clavicles and extremities[4]. Radiographic changes in the jaws are less common, including the osteoporotic appearance of the mandible or rarely maxilla (salt and pepper appearance), loosening of teeth, overall cortical plate thinning and partial loss of lamina dura[1]. Brown tumors histopathology is identical to central giant cell granuloma and derives its name from its color, which is usually dark red-brown due to abundant hemorrhage and hemosiderin deposits within the tumor. However, it is not a true neoplasia, so the word "tumor" is a misnomer[5].

We report a rare case of previously undiagnosed PHPT due to a parathyroid adenoma with the initial presentation as Brown's tumor of the anterior maxilla.

CASE REPORT

A 44-year-old male patient applied to the oral and maxillofacial surgery department with a complaint of swelling in the left maxillary vestibule region. In the anamnesis, it was learned that the patient did not have any known systemic disease, he had felt swelling in the maxilla and had lost weight for the last 1 month. In the clinical examination, a solid mass on palpation, with a

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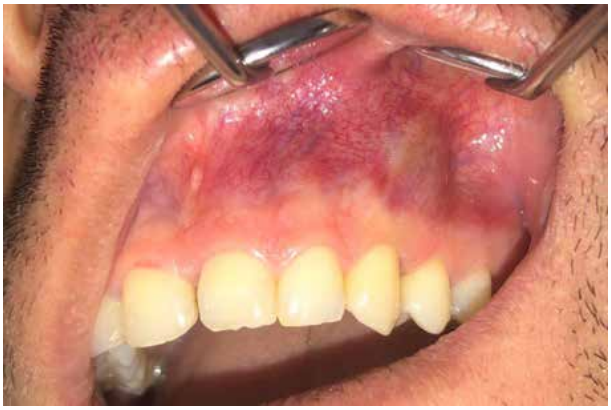

Figure 1: Intraoral view of the lesion

brown reflection under the gingiva and with a normal epithelial appearance was detected in the relevant region (Fig. 1). In the radiographic examinations, a radiolucent lesion was detected between the left upper canine and the first premolar teeth in the panoramic and periapical images (Fig. 2). In cone beam computed tomography images, an irregular border radiolucent lesion with a size of 12x4x4 mm with triangular bone destruction was observed. There was limited root resorption in the left maxillary first premolar due to the lesion that affected the roots of the left canine and first premolar (Fig. 3). The involved teeth responded positively to the vitality test. At the end of the clinical and radiographic examination, excision of the lesion under local anesthesia was planned. The flap was raised using sulcular and vertical incisions between the left upper central and first molar teeth (Fig. 4). The lesion was excised in one piece and the flap was closed primarily (Fig. 5). Then the sample was taken for histopathological evaluation. The result of the pathology report stated that the relevant lesion should be differentially diagnosed in terms of cherubism, central-peripheral giant cell fibroma, brown tumor, and giant cell fibroma. The patient was referred to perform the relevant laboratory tests. Detailed biochemical data observed before and after parathyroidectomy are shown in Table 1. In addition, the scintigraphic examination revealed involvement in the right parathyroid lobe. The patient underwent total parathyroidectomy with the preliminary diagnosis of parathyroid adenoma, and the result was confirmed by pathology reports. During the 6-month follow-up of the patient, no new formations were encountered in the jaws, and normalization was observed in the patient's laboratory test results. In our case, as a result of careful clinical observation and an appropriate treatment plan, the patient was diagnosed with a delayed parathyroid adenoma and received its treatment.

DISCUSSION

There are 3 different types of HPT: primary, secondary and tertiary[1]. The most common cause of PHPT is a parathyroid adenoma, characterized by excessive PTH production and hypercalcemia[6].

Table 1: Detailed biochemical data observed before and after parathyroidectomy

Biochemical data	Preoperative Results	Postoperative results	Normal Value
PTH (ng/L)	789.9	19.3	12-88
Calcium (mg/dL)	12.6	9.2	8.8-10.6
Phosphorus (mg/dL)	1.5	1.9	2.5-4.5

PTH: parathyroıd hormone

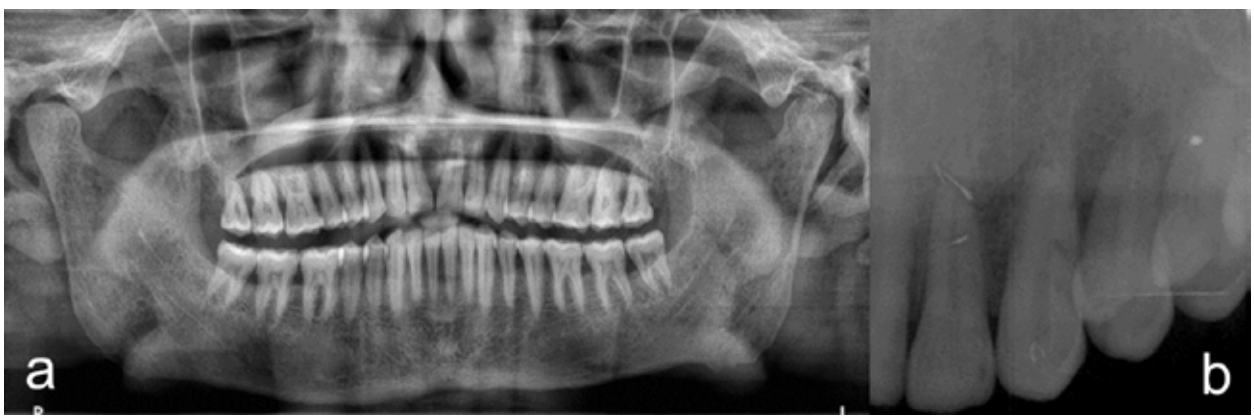

Figure 2: Irregular border radiolucent lesion in the left maxillary canine and first premolar region is seen in the panoramic (a) and periapical (b) radiography of the patient.

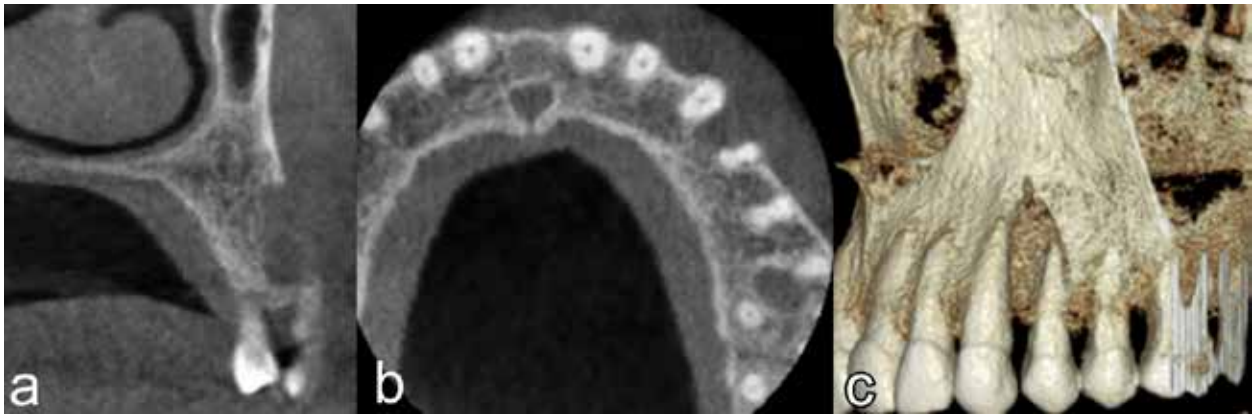

Figure 3: Buccal cortical bone resorption and irregular border radiolucent lesion on the left maxillary premolar region is seen on the coronal (a), axial (b) and 3D reconstriction (c) images of cone beam computed tomography.

Secondary HPT usually results from vitamin D deficiency, malabsorption or hypercalciuria. Low serum calcium levels from primary diseases cause excess PTH secretion. Tertiary HPT develops from secondary HPT in most cases and is a more serious condition[7].

PHPT is the third most common endocrine disease after diabetes and thyroid disorder. Its incidence varies between 0.025-0.065% and is frequently seen in postmenopausal women[8]. Increased PTH often affects calcium levels, phosphate levels and bone metabolism. This condition usually causes kidney and skeletal findings. However, PHPT is usually detected at an early stage, thanks to routine blood calcium and phosphorus tests. Therefore, most of the patients are asymptomatic[9].

Brown tumor is one of the pathognomonic findings of PHPT and is a focal, tumor-like bone lesion caused by the osteoclastic transformation of bone[8]. While the incidence of musculoskeletal findings in PHPT patients is 54.7%, the incidence of brown tumors ranges from 1.5% to 4.5%[7]. It is named for its dark, reddish-brown coloration caused by prominent intralesional hemorrhage and hemosiderin deposition[1]. These bone-resorbing lesions are rarely the first manifestation of HPT. After surgical resection of the parathyroid gland, regression is often seen[7]. Brown tumors are uncommon in the maxillofacial region; they typically develop on the ribs, clavicle and pelvis. When they occur in the maxillofacial region, the most affected bone is the mandible and rarely the maxilla[1]. In this case, a brown tumor was detected in the maxillary

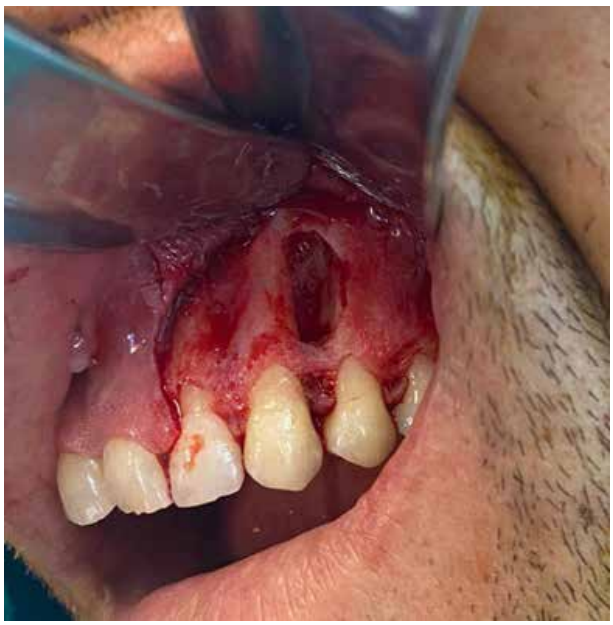

Figure 4: Intraoral image after the operation.

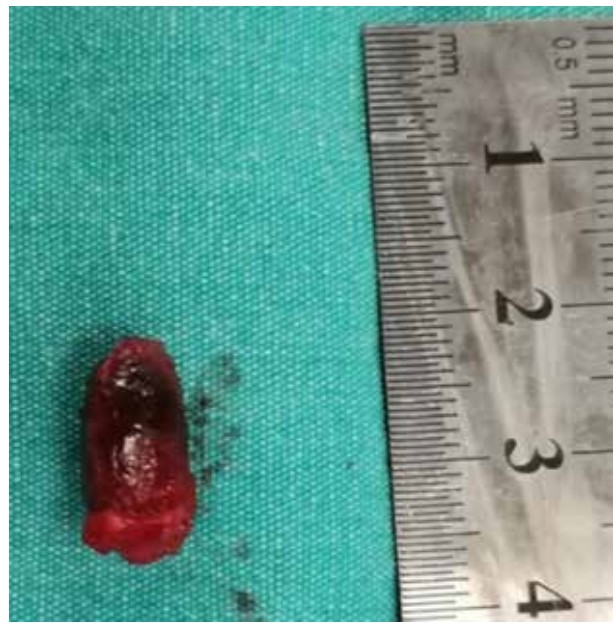

Figure 5: Image of the excised lesion.

premolar region. Moreover, it is rare to have a brown tumor in the maxillofacial region as the first sign of PHPT before the onset of systemic symptoms[10].

The pathological findings of brown tumors are similar to other bone diseases such as central giant cell tumors, and metastatic tumors, and their differential diagnosis can be difficult[8]. Therefore, in addition to pathological findings, radiological findings including bone scintigraphy and laboratory results may be helpful as adjunctive tests in the diagnosis of brown tumors. In addition, serum calcium and PTH measurements are also important diagnostic tools[11]. The increase in PTH and blood calcium levels is diagnostic for brown tumor caused by PHPT[5].

Parathyroidectomy is the first choice in the treatment of brown tumors caused by primary HPT[12]. Opinions are divided about the treatment process of bone lesions after parathyroidectomy surgery[5,6,8]. There are publications stating that most bone lesions will regress spontaneously over time after parathyroidectomy. Therefore, surgical removal of the brown tumor may not be necessary. In one of these studies, it was reported that all 20 maxillofacial brown tumor cases followed for 2 years showed spontaneous regression after parathyroidectomy. Complete clinical regression occurred in 90% of cases, mostly within 4-20 months[13]. In another study, a time period ranging from 6 months to 5 years was mentioned in the observation of spontaneous regression after parathyroidectomy[14]. In individuals over 60 years of age and those with bone lesions located in the cancellous bone, regression may take longer due to differences in bone turnover[5,15].

In cases where advanced bone resorption has occurred, remodeling may not be seen even with normalization of serum calcium levels. After parathyroidectomy, brown tumors may continue to grow even though the patient is normocalcemic[14]. Therefore, surgical intervention is recommended in such cases where resolution is slow or growth continues.

The highlight of this case was the discovery of a brown tumor in the maxilla, the first manifestation of an atypical parathyroid adenoma.

CONCLUSION

Brown tumors in the maxillofacial region, especially in the maxilla, are extremely rare. Although the diagnosis of PHPT is often asymptomatic, manifested by the detection of hypercalcemia in routine biochemical analyzes, there is still the possibility of first-time patients presenting with advanced bone lesions of PHPT. Evaluation of the patients' medical history, radiological findings, blood test results and biopsy results are essential for an accurate and complete diagnosis and correct treatment. The treatment of choice is parathyroidectomy, which removes the cause of PHPT. In addition, there is no consensus in the literature on allowing spontaneous healing of bone lesions or surgical intervention of bone lesions after parathyroidectomy. However, in our opinion, curettage or enucleation may be beneficial for large lesions that cause dysfunction.

ACKNOWLEDGMENT

Authors' contributions: Eda Izgi and Tugba Turel Yucel made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; drafting the work or revising it critically for important intellectual content. All authors gave final approval of the version to be published; and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of interest: The authors have no conflict of interest.

Financial disclosure: The authors declared no financial support.

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Case Report

A rare case of proximal femur insufficiency fracture - Case report and review of the literature

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Kuwait Medical Journal 2026; 58 (2): 132 - 140

ABSTRACT

Insufficiency fractures (IF) of the femur in spastic paraplegic patients pose unique challenges as there is no established optimal treatment approach for such fractures. This article combined a case report of a severely displaced proximal fracture of the left femur in a 33-year-old male with spastic paraplegia with the review of IF. This article aimed to bridge the gap in existing knowledge of IF with a rare case report. Relevant studies were obtained using appropriate keywords. Furthermore, we presented the case report detailing clinical courses, diagnosis and management strategies followed.

Our review reveals a scarcity of studies that evaluated the IF of the femur in spastic paraplegic patients. The interconnected characteristics of muscular weakness, spasticity and decreased bone mass enhance the likelihood of fractures in patients during rehabilitation sessions. Surgical management was the preferred intervention in most of the IF cases. This fracture is characterized by its unique location, significant displacement and the challenges involved in surgical management.

Prevention and management of IF of the femur is the role of a multidisciplinary approach, including orthopedic surgeons and a rehabilitation team. Further research is needed to determine the optimal treatment approach for managing the IF of the proximal femur.

KEY WORDS: femur fracture, osteoporosis, spastic paraplegia, spinal cord injury, vitamin D deficiency

INTRODUCTION

Insufficiency fractures (IF) are a subtype of stress fracture that may occur on the already weakened bone due to repetitive normal pressure over a period of time. This fracture occurs without any traumatic event or underlying pathology in individuals, especially with the patients suffering from osteoporosis and vitamin D deficiency[1-3]. Spasticity is a disorder characterized by a velocity-dependent increase in muscle tone or tonic stretch reflexes with hypertonia[4,5]. It is common and frequently underdiagnosed among patients with upper motor neuron lesions such as spinal cord injuries (SCI). Several authors reported that more than two-thirds of the SCI patients exhibit spasticity[6,7]. A recent study by Sangari S *et al* in 2022 reported that irrespective of injury severity, spasticity is prevalent in most of the patients with chronic SCI[8]. Globally, between 250,000 and 500,000 people suffer from SCI annually, as stated by the World Health Organization[9]. Traumatic events, including falls, motor vehicle and acts of violence, are the most common reasons for SCI, resulting in neurological impairments and various associated conditions. Motor vehicle accidents are a leading cause of SCI, accounting for 38.4% of all SCI cases[7,9-11]. The first six months following the injury are critical, as they have the highest percentage of bone loss; after 12-16 months, it starts to stabilize after a 30% decrease in bone mass. However, the loss does not stop, and a gradual decline continues over time, reaching a 50% loss after ten years. As a long-term result of SCI, motor impairment, particularly in the lower limbs, is related to a reduction in bone mineral density, predisposing to IF[12-14].

These interconnected characteristics of muscular weakness, spasticity and decreased bone mass enhance the likelihood of fractures in SCI patients, particularly

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in weight-bearing bones. The distal femur and tibia, followed by the proximal femur and spine, are the sites most significantly affected by osteoporosis in individuals with SCI due to decreased bone density and increased fracture vulnerability[3,15,16]. In general, the IF in the femur can be diagnosed by clinical assessment, X-rays and MRI studies. X-rays are an initial imaging modality to assess fracture patterns and bone density. However, MRIs are particularly useful to detect occult fractures and soft tissue involvement[17,18]. Despite the fact that IF is not frequent in the general community, the risk of IF arising in SCI patients with spasticity provides unique issues that must be addressed. Considering these facts, the present study aimed to explore the IF comprehensively, with a special focus on patients with SCI and spastic paraplegia, through the literature review and a rare case report. The presented case report provides an overview of our experience in managing a fragile, severely displaced proximal femoral fracture in a spastic paraplegic patient using a static intramedullary nail. The patient involved in this case was informed about the data being submitted for publication and provided consent for its inclusion.

Search strategies

The present study retrieved the necessary studies from the relevant databases to integrate and complement the case report with essential review findings: Web of Science, Scopus, Medline, Embase, Saudi Digital Library and Google Scholar. Only the English works of literature of the past ten years were considered while summarizing the literature findings. The keywords used alone or in combination to search relevant articles were "Insufficiency fracture," "Spastic paraplegia," "Femur fracture," "Fragile fracture," "Risk factors," "Vitamin D deficiency," "Diagnosis," "Management," and "Prevention."

Main text

The present manuscript highlights and discusses the relevant aspects in two categories: Case report and discussion related to the case report and review findings.

CASE REPORT

A 33-year-old male with previous surgeries presented to our ER department with complaints of left lower limb pain and deformity after experiencing a sudden audible click while repositioning in bed. Swelling, ecchymosis, crepitus and a significant apparent left thigh deformity (acquired left posterior hip dislocation) were observed upon examination. Additionally, the patient exhibited signs of sweating, muscle spasticity, mid-plantar flexion of the feet, flexion adduction and internal rotation of the hips and knees. The patient also experienced increased difficulty with pivoting and transfers and was unable to sit down.

A history of spastic paraplegia 15 years prior was revealed due to a motor vehicle accident which resulted in bilateral posterior hip fracture dislocation that was treated conservatively. In addition, the patient suffered a thoracic vertebral fracture of 7-8-9-10 and subsequently underwent surgery.

Despite treatment, due to severe degenerative osteoarthritic hips, the patient did not experience a significant improvement in his neurological conditions, and he experienced severe muscle spasticity in his lower limbs. It led to muscle contractures that significantly impaired his mobility over the next 14 years. Thus, he requires assistance from family members for regular tasks because of his inability to use his fine motor abilities. As a result, frequent physical therapy and rehabilitation sessions were performed, and there were no associated fractures in their upper and lower limbs. However, perineal hygiene was compromised. Approximately one year prior, the patient was admitted to another hospital with a diagnosis of bilateral severe ischial decubiti. Over the last year, their condition improved, resulting in large, deep dimples bilaterally present on the posterior surface of the upper thighs.

He had a bed sore on the left side, and the dressings were changed every day. The suprapubic catheter was changed one month ago. The patient presented with pronounced vitamin D insufficiency, low hemoglobin and decreased ferritin levels of 10 ng/ml, 8.5 g/dl and 15 mcg/L respectively, and normocytic normochromic anemia. In addition, prealbumin level, blood culture, total lymphocyte count and inflammatory markers, known as nutritional evaluations, were conducted. Extremity radiography films indicated a closed, severely displaced comminuted subtrochanteric left femur fracture (Figures 1A-1D).

At the time of hospitalization, he was taking oral vitamin D, vitamin B12 supplement, a baclofen tablet, an IV iron infusion and clexane 40 mg subcutaneous OD.

Open reduction and static intramedullary nail internal fixation were performed on the patient. However, setting up the patient on the traction table was the most challenging step due to the patient's inability to fully extend his hip and knee joints. Hence, the patient was positioned with slight hip adduction and mid-flexion of the hip and knee. The patient received a dose of prophylactic antibiotics during general anesthesia. After preparing and draping, the proximal femur was exposed using a lateral approach. Nonetheless, the intraoperative reduction of the

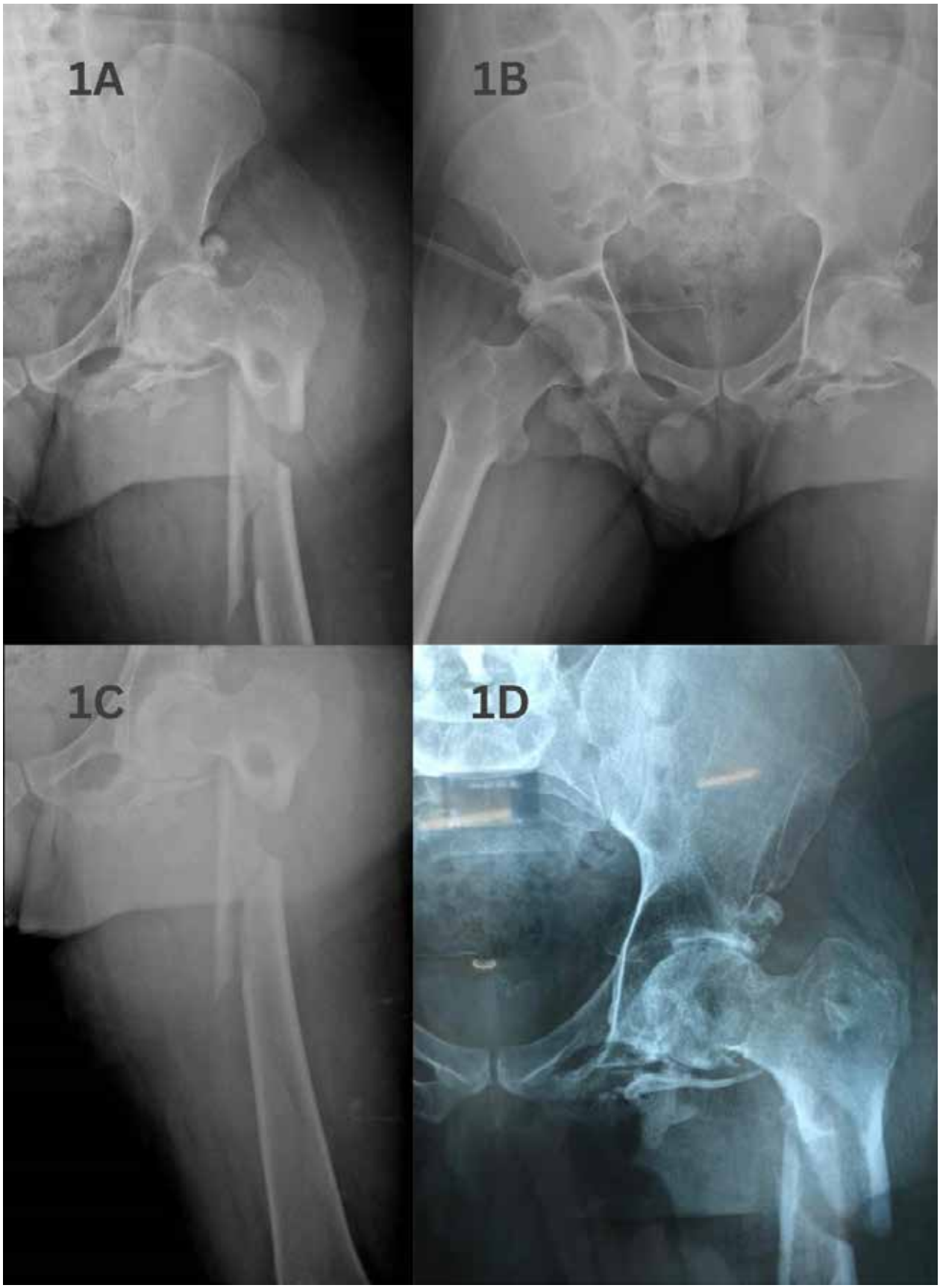

Figure 1 (A-D): Radiological findings of the patient.

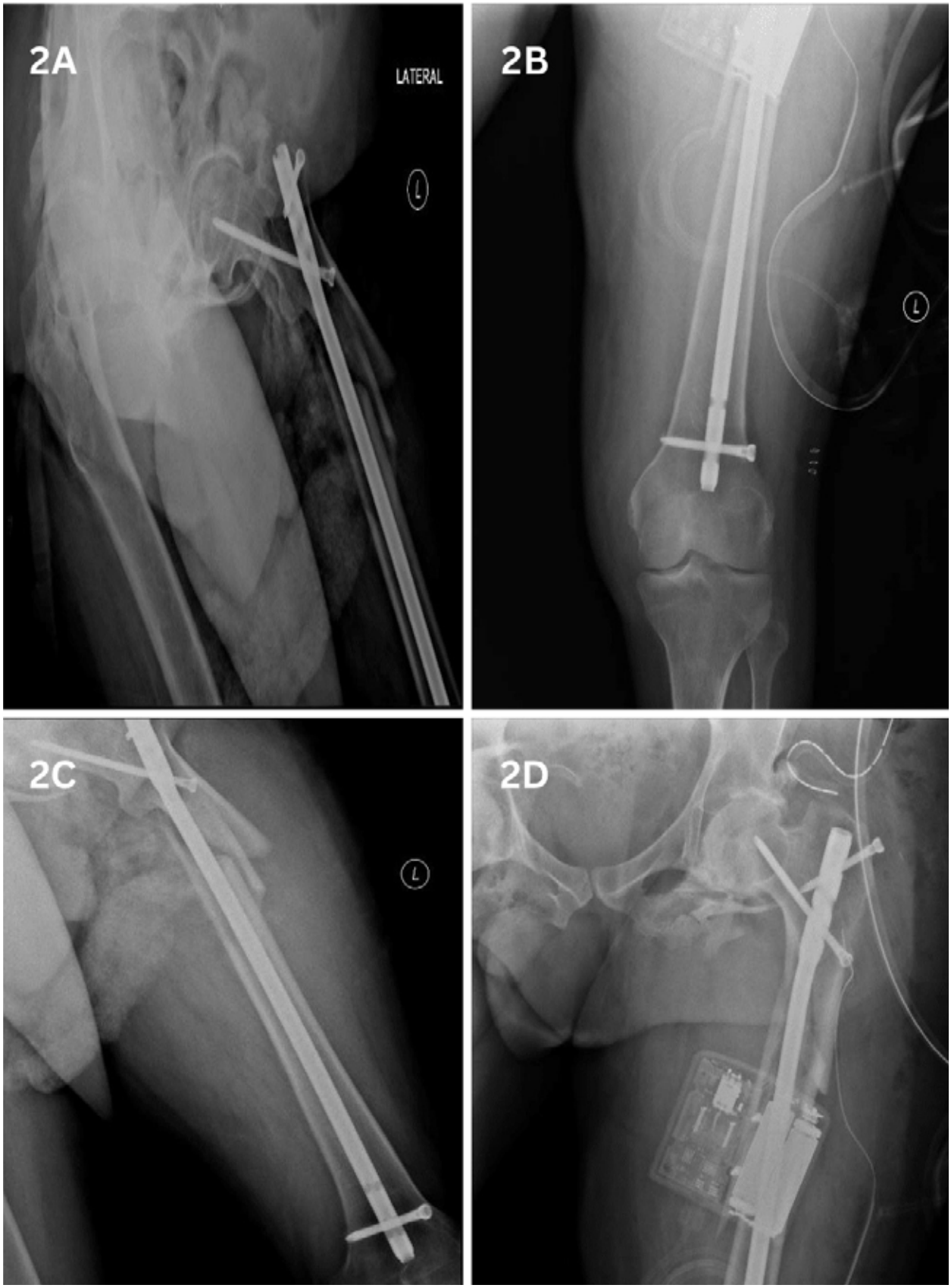

Figure 2 (A-D): Immediate postoperative x-ray

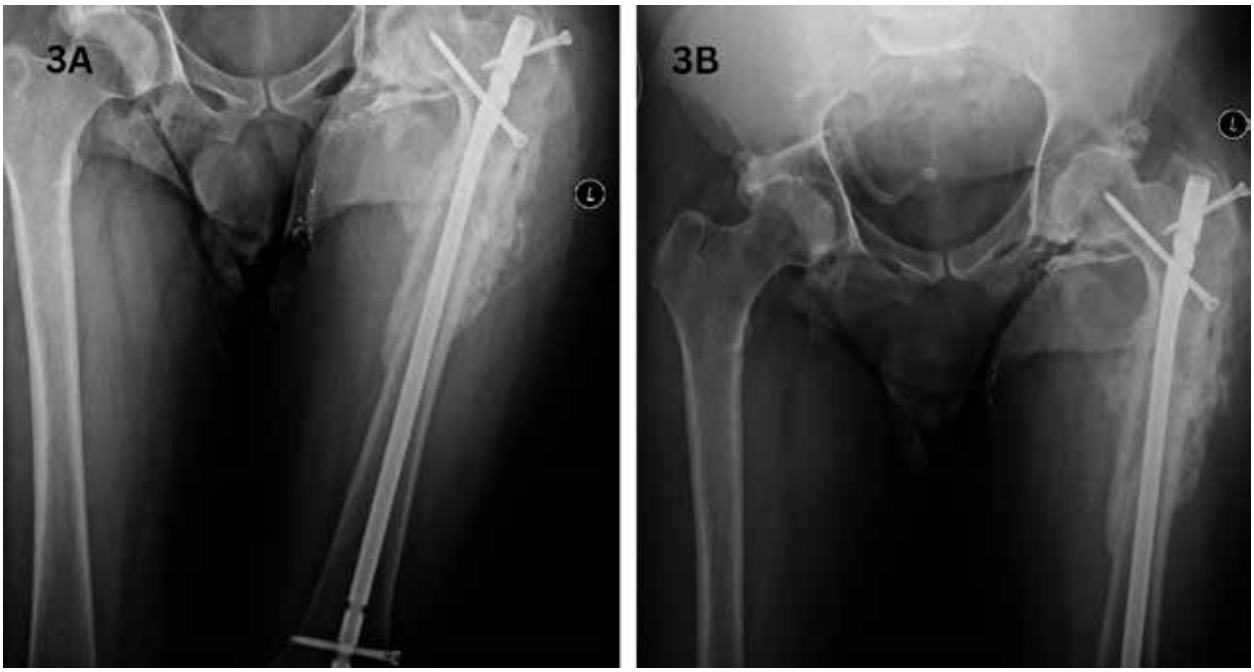

Figure 3 (A-B): Follow-up radiological findings.

fracture and insertion of the guide wire was accompanied by some difficulty due to different factors, such as the proximal fragment's 90-degree flexion, muscular contracture and degenerative osteoarthritis of the hip and knee joints, which was considered the second challenging step.

After freeing the tensor fascia, we were able to achieve reduction and inserted a cephalic reconstructive nail using conventional methods. Because of the significant muscle spasm, adjusting the reconstructive screws proved challenging. During insertion, minimal proximal migration of the inferior screw in the neck was observed, so we placed a short superior screw through the greater trochanter.

After irrigating the wound, the tensor fascia latae muscle was restored, and the surgical incision was stitched over the drain. Throughout the procedure, the patient remained hemodynamically stable. Immediate postoperative plain Xray had been taken (Figure 2A-2D).

The patient was monitored closely in the postoperative phase, during which physical therapy was initiated. He was started on vancomycin intravenously, which was monitored by vancomycin level every other day, intravenous iron, subcutaneous teriparatide and vitamin D supplementation. It was essential to regularly change the patient's position every two hours. Upon discharge, the patient was prescribed vitamin D, clexane and ciprofloxacin 500 mg bid. No complications were observed, and the patient remained clinically stable except for a small raw area of skin incision and increased sweating and muscle spasms, especially near the wound. The stitches were removed, and after two weeks, the left side bed sore healed. Within 4 months, the patient had successfully recovered to his preinjury state. Follow-up plain X-ray showed complete recovery from the fracture (Figure 3A-3B).

DISCUSSION

Approximately 54 cases per 1 million persons have spinal cord injuries in the USA resulting from different traumatic events, such as motor vehicle accidents[19]. Those patients are at significant risk of experiencing fractures even with low-energy mechanisms such as transferring or repositioning the patient because of several factors, including decreased bone quality, reduced muscle mass and a thin insensate soft-tissue layer. Hence, even minor trauma or actions that seem harmless, such as routine transfers, can lead to fractures that pose challenges with treatment, as seen in our specific case[19,20]. Diagnosis of IF in SCI patients is associated with numerous challenges due to atypical clinical presentation, overlapping symptoms, radiographic challenges and under-recognized differential diagnosis[21,22]. Nonetheless, imaging studies such as X-rays, CT scans, MRIs and DEXA scans are considered crucial in the diagnosis of IF of the femur for further management. The choice of imaging studies depends upon the patient's clinical features, the severity of the fracture, the necessity for surgical interventions and available resources[23-25]. The

present case report patient's extremity radiography films indicated a closed, severely displaced comminuted subtrochanteric left femur fracture (Figures 1A–1D). In our case report, a 33-year-old male with a history of a thoracic vertebral fracture of 7-8-9-10 due to a motor vehicle accident and spastic paraplegia for 15 years was admitted to the hospital upon experiencing a sudden audible click while repositioning in bed, leading to left lower limb pain and deformity, and was diagnosed with proximal femur insufficiency fracture. These fractures could result in significant complications for the patient[20,26,27].

Frotzler A *et al* evaluated the pattern of long-bone fractures among SCI patients from a single center in Switzerland. This retrospective hospital-based study conducted by Frotzler A *et al* revealed that only lower limb bones were affected among SCI patients, and the femur was the most commonly associated with the fracture, about 60%. Furthermore, they reported that the distal part of the femur was more frequently affected than the proximal part[28]. Kumar P *et al* reported an interesting case of a fragility fracture of the femur in a young patient (31 years old) obtained during a physiotherapy session. This patient is a person with paraplegia with a history of a lumbar vertebra (L1) fracture a couple of years ago before the incident of a fragility fracture of the femur. Additionally, the patient was evaluated to confirm osteopenia. Hence, IF in paraplegic patients can occur incidentally during physiotherapy sessions, and to avoid serious consequences, proper care is required during rehabilitation[29].

The treatment goal for the IF fracture of the femur is to decrease morbidity and mortality, achieve a stable femur with the lowest complications, and bring the patient's health to the best pre-fracture level[28,30]. The IF of the femur can be managed by surgery or conservatively. However, the choice between surgery and conservative management is case by case, depending on several factors. Furthermore, orthopedic surgeons must carefully consider the patient's and caretaker's opinions after explaining the risks and benefits of the treatment plan[31,32]. Traditionally, orthopedic surgeons avoid surgical intervention in most IF of femur cases due to SCI to prevent complications, osteoporosis condition and the presence of immobility due to paraplegia[33]. The conservative treatment of IF among SCI patients includes non-steroidal anti-inflammatory drugs, sufficient rest, limited weight bearing, tractions, casts, splints, physiotherapy and external fixation[28,33]. Nonetheless, conservative methods were associated with a longer time of healing and immobilization, a higher chance of non or delayed union, and the potential for recurrent fractures. Hence, the trend has changed over the past couple of decades to prefer surgical management over conservative management, unless the patient's general health condition is deplorable, associated with poor and unstable cardiovascular status, very low bone density and lack of social support that hinders the patient attending regular rehabilitation sessions[29,34].

Surgical management includes intramedullary nails, hemiarthroplasty and total hip arthroplasty, cannulated screws and sliding hip screws[35]. However, early interventions using skeletal and skin traction have shown unfavorable outcomes and increased complication rates. It was found in previous studies that patients with higher baseline function, such as wheelchair athletes, were more likely to undergo surgery. Following open treatment, all patients in this group were able to return to their previous employment, regain their previous level of activity and participate in competitive events. The goal of treatment is to promote healing while preserving the patient's functional ability. However, without proper care, the complication rate can be high and the outcomes can be devastating. Consequently, our patient was treated surgically to reduce the risk of skin breakdown[36,37].

Our case report highlights the successful treatment of non-ambulatory individuals with severe paraplegic spasticity by using intramedullary nail repair for a proximal femoral fragility fracture. The patient's perineal hygiene was compromised, and this method of treatment was found to be more hygienic. It is more effective and provides better perineal care. Difficulties in sitting and muscle contractures are frequently encountered in adults with severe spastic paraplegia. The procedure was successful as well in improving the patient's ability to sit, despite the challenge faced in fixation of this type of fracture in a patient with long-standing degenerative changes of the hip joint. Moreover, the significantly dislocated fracture had been anatomically reduced when followed up, as shown by radiographs (Figures 2A-2D).

In SCI patients, the most frequent secondary causes to be ruled out are vitamin D deficiency and long-term corticosteroids. Vitamin D improves intestinal absorption of calcium and phosphate. Hence, reduced levels of vitamin D are linked to decreased calcium absorption. This negative calcium balance subsequently increases parathyroid hormones, resulting in increased bone resorption[38,39]. In our case report, the patient's examination and laboratory tests resulted in vitamin D deficiency with a level of 10 ng/ml and severe degenerative osteoarthritis hips that negatively impacted his neurological conditions. As a result, the patient was unable to fully extend his hip and knee

joints, which caused different challenges while sitting up on the traction table, as well as the intraoperative reduction of the fracture and insertion of the guide wire (Figure 4). This is attributed to several reasons highlighting the disruption of the parathyroid hormone-vitamin D axis, which often results in lower levels of parathyroid hormone and vitamin D in SCI patients. Approximately 61% of SCI patients suffer from secondary osteoporosis as a result of SCI[39]. Vit D supplementation was included as an essential part of the patient's medication regimen during his hospitalization period and continued after discharge as well. According to Hashimoto *et al*, osteoporosis management and prevention of fragility fractures in these patients necessitate medical intervention, and vitamin D is one of the approaches that can enhance bone mineral density by 10% after an 18-month therapy period[40].

Bacteriuria and ulcer infections are common in SCI patients[41,42]. In our case, the patient's suprapubic catheter was recently replaced, marking a significant update after 14 years, and he was diagnosed with bilateral severe ischial decubiti before, which made him more susceptible to infection. Individuals with SCI are frequently colonized with antibiotic-resistant bacteria, including methicillin-resistant *Staphylococcus aureus*. This colonization is common and can pose challenges for infection management and treatment[42]. Hence, intravenous vancomycin was added to his medication list during the postoperative period, and its level was monitored every other day. In patients with objective findings of infection, certain tests can be helpful. These include a complete blood count, urine and blood cultures, as well as inflammatory markers, such as the erythrocyte sedimentation rate and C-reactive protein level. These tests provide valuable information to diagnose and monitor infections in patients[19].

Prevention of IF of femur among spastic paraplegic patients is a role of multidisciplinary approach including orthopedic surgeons, nutritionists and rehabilitation team. This includes control of proper management of systemic diseases, appropriate nutritional supplementation, fracture risk assessment and rehabilitation[43,44]. Hence, evaluating the patient's health status through a multidisciplinary team is critical before initiating the physiotherapy session. It is noteworthy to mention that negative consequences that occur during rehabilitation sessions are under-reported[45]. Physical therapy started for the patient after the surgery had been performed to improve the range of motion of the hip and lower extremities. Despite the fracture risk during simple activities, the early intervention of physiotherapy using mobilization in patients with SCI using standing training or tilt table exercises showed bone mineral density improvement. Physical therapy aims to use Wolff's law principles, which state that bones respond to mechanical stress to stimulate bone growth. However, it does not necessarily translate the increased bone density to increased strength and reduced fracture risk[19,46]. According to Eser *et al*, spastic paralysis causes less bone loss than flaccid paralysis. Subsequently, physical therapy is an essential part of the life of SCI patients with spastic paraplegia. Nonetheless, it is important to avoid any vigorous movements and prioritize gentle and controlled movements during physical activities to minimize the potential for fracture[47].

With rates ranging from 12% to 36%, hip fractures carry a high risk of mortality within the first year. Additionally, only one-third of patients are able to regain their pre-fracture level of functioning, while another one-third require ongoing nursing home care[48,49]. The present case showed complete recovery from the fracture (Figure 3A-3B).

CONCLUSION

An insufficient subtrochanteric femoral fracture, especially in patients with spastic paraplegia, is a rare and often unrecognized case. Nevertheless, it is a well-known surgical emergency. This fracture occurs without any traumatic event or underlying pathology in individuals with spastic paraplegia. This fracture is characterized by its unique location in the subtrochanteric region of the femur, significant displacement and the challenges involved in surgical reduction. The decreased bone mineral density associated with long-term muscle disuse because of spinal cord injury, particularly in the lower limbs, contributes to the occurrence of such fractures. Therefore, it is crucial for medical professionals, physiotherapists and caregivers to understand the crucial role of physiotherapy sessions and to handle patients with care, avoiding any forceful movements. Further research is needed to determine the optimal treatment approach, including the need for soft tissue release in managing subtrochanteric insufficiency fractures.

ACKNOWLEDGMENT

Funding: This research received no external funding.
Informed consent statement: The patient involved in this case was informed about the data being submitted for publication and provided consent for its inclusion.
Data availability statement: The review article did not use any data for analysis.
Conflicts of interest: The authors declare no conflicts of interest.

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Case Report

Pregnancy related recurrent spontaneous pneumothorax: a rare case report and literature review

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Kuwait Medical Journal 2026; 58 (2): 141 - 143

ABSTRACT

Spontaneous pneumothorax is a potentially life-threatening condition. Its occurrence during pregnancy is exceedingly rare, with fewer than 100 cases reported. Early diagnosis is crucial in preventing respiratory compromise that could affect both the mother and fetus.

We present a case of recurrent spontaneous pneumothorax in a 28-year-old patient at 6-week gestation and again in the second trimester. The patient's presentation includes dyspnea and chest pain. Plain chest radiograph revealed large right-sided pneumothorax in both instances and was managed by chest tube insertion.

KEY WORDS: pregnancy complication, recurrent pneumothorax, spontaneous pneumothorax

INTRODUCTION

Spontaneous pneumothorax is described by the manifestation of air in the pleural cavity resulting from the rupture of small apical bullae. It is considered a potentially life-threatening condition[1]. Primary spontaneous pneumothorax is a rare occurrence in pregnancy with fewer than 100 cases reported[2]. Early and prompt diagnosis of pneumothorax in pregnancy is critical as the condition can lead to respiratory compromise affecting both maternal and fetal well-being[3].

In this study, we present a rare case of recurrent spontaneous pneumothorax in a pregnant patient during the same pregnancy and its management.

CASE REPORT

A 28-year-old, gravida 6 para 0 at her 6th gestational week, presented with a 1-day history of chest pain associated with dyspnea. Upon physical examination, she was hemodynamically stable and her breath sounds were decreased on the right side. A chest X-ray was acquired using an abdominal shield and revealed a large right-sided pneumothorax (Figure 1). A chest tube was therefore inserted under local anesthesia and kept on suction for 17 days due to the persistent pneumothorax. Due to persistent air-leak, a Heimlich valve was connected and kept for a further 10 days. A repeat chest X-ray showed a fully inflated lung after 24-hours of clamping, the tube thoracostomy was removed and she was discharged home with follow up.

Five months later, in her second trimester, she presented again with a 3-day history of chest pain and dyspnea. A chest radiograph demonstrated a recurrence of the right-sided pneumothorax (Figure 2). A chest tube was inserted under local anesthesia. Repeat chest X-ray showed persistent lung collapse despite functioning system and was kept on suction. The lung was fully inflated on day 4 and patient was discharged home following tube removal on day 9 with a fully inflated lung. In total during this admission, the patient underwent six chest X-rays.

During follow-up, the patient was doing well and was asymptomatic. She completed her pregnancy with no further complications and gave birth to a healthy full-term child.

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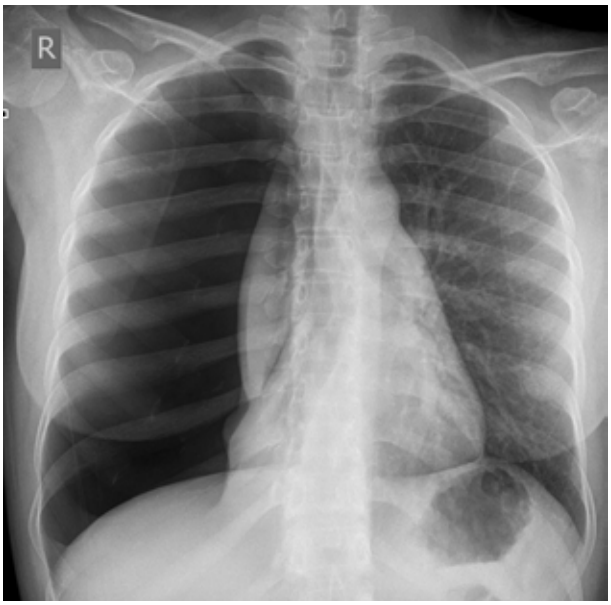

Figure 1: Large right-side pneumothorax.

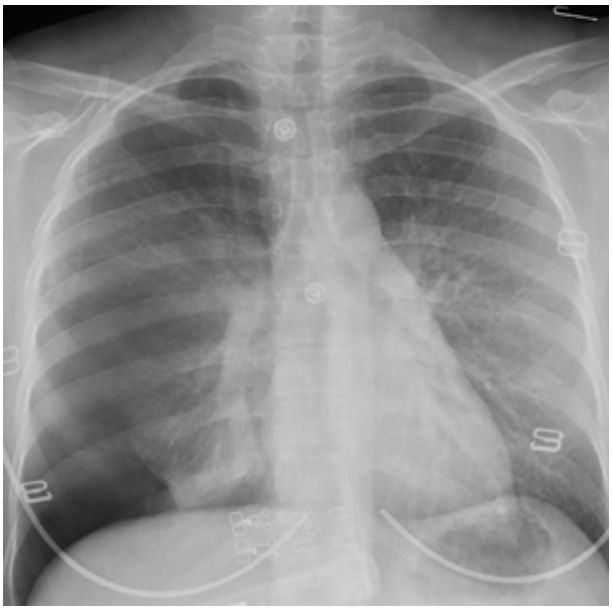

Figure 2: Recurrent large right-side pneumothorax.

She was offered surgical intervention and was scheduled to undergo video-assisted thoracoscopic surgery (VATS); however, the patient became pregnant again.

DISCUSSION

Primary spontaneous pneumothorax frequently occurs in young adults and is correlated with subpleural blebs. In contrast, secondary spontaneous pneumothorax is associated with various lung pathologies including and not limited to tuberculosis, cystic fibrosis, chronic obstructive disease, etc[2].

Primary spontaneous pneumothorax during pregnancy is a rare condition necessitating prompt diagnosis and careful management. The importance of this condition can be attributed to both the respiratory physiological changes during pregnancy and the diagnostic challenges due to the overlapping of normal symptoms seen in pregnancy and the limitation of the diagnostic tests such as chest X-rays and CT scans[4].

Generally, primary spontaneous pneumothorax reoccurs in approximately 30% of patients. However, recurrence in pregnant patients has been reported more commonly at a rate of 44%, with the predominance of recurrence occurring during the first pregnancy[3,5]. This was seen in our case report. The following condition can lead to life-threatening complications to both the patient and the fetus. During pregnancy, functional residual capacity and total lung capacity decrease; however, oxygen consumption by the placenta, fetus and maternal organs is increased[6]. The resulting reduction in lung volume is caused by the displacement of the diaphragm by the uterus, leading to a decrease in gas exchange and exacerbating symptoms than in non-pregnant patients[7]. Additionally, there is a 20% increase in oxygen demand and a further increase to 50% during labor; this increase is attributed to a complex physiological change[8]. This increased ventilatory demand results in a strain to the alveolar-capillary membrane, prompting the rupture of subpleural blebs, ultimately resulting in spontaneous pneumothorax[9]. Progesterone directly stimulates the respiratory center, resulting in an increase in minute ventilation by a rate of 30-50%, which corresponds to the increase in tidal volume[4,10]. Studies have also shown that progesterone can affect connective tissues. It is hypothesized that this can also affect pleural and alveolar tissue, increasing the likelihood of blebs rupture[11]. Any disturbance or impairment in the following physiological process can lead to hypoxia faster than in nonpregnant women, resulting in unsought effects on the fetus[12].

Spontaneous pneumothorax in pregnancy represents a diagnostic challenge. Typically, it presents with chest pain and dyspnea; which are common symptoms in pregnancy and are often misdiagnosed as pregnancy related dyspnea; affecting 75% of pregnant women[13]. Conclusive diagnosis can be determined by a plain chest radiograph. The permitted dose of ionizing radiation in pregnancy is 5 rads (50 mGy) and a single plain chest radiograph delivers approximately 0.00007 rad (0.0007 mGy) to the fetus. The cumulative fetal exposure with multiple radiographs typically remains less than 5 rads. Therefore, once a pneumothorax is suspected in a pregnant patient with chest pain and dyspnea, it is safe

to proceed with a plain chest radiograph with an abdominal shield confirming the suspicion[1].

Risk factors in this population include asthma, cocacine use, hypermesis gravidarum, previous pneumothorax or an underlying infection[4]. These risk factors however were not present in the patient reported in our case series. Furthermore, the condition has been reported to occur at any point of pregnancy, during labour or postpartum[2].

Despite the lack of guidelines addressing management of pneumothorax in pregnancy, current evidence suggests it does not differ than in nonpregnant women[2]. Initially, observation is offered to mothers that are asymptomatic, have no signs of fetal distress and when pneumothorax is less than 2 centimeters. In those with larger pneumothoraces or symptomatic, aspiration with or without tube thoracostomy is preferred[1]. Surgical intervention is best offered in the second trimester due to the completion of organogenesis[8]. In instances where the pneumothorax occurs in the first trimester or in late pregnancy and lung re-expansion is not achieved after simple tube thoracostomy, prolonged drainage is recommended until second trimester or after labor, where definitive management with VATS can be offered[14].

CONCLUSION

In conclusion, spontaneous pneumothorax during pregnancy can present with chest pain and dyspnea, which are common symptoms during pregnancy. These symptoms should be handled with a high index of suspicion of pneumothorax. Imaging is considered safe with abdominal shields. Management of these patients does not differ from the general population, and surgical management is the definitive treatment best offered during the second trimester or postpartum.

ACKNOWLEDGMENTS

Conflict of Interest: No conflict of interest to declare.
Funding: No funding was required for this study.
Author Contribution: All authors have contributed to the following study including study design, literature review and the writing up of the manuscript.
Consent: Informed consent was obtained from the patient.

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Case Report

Treatment with daptomycin of an unusual case of left-sided infective endocarditis due to *Corynebacterium jeikeium*

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Kuwait Medical Journal 2026; 58 (2): 144 - 147

ABSTRACT

Corynebacterium jeikeium is a gram positive, aerobic rod that constitutes a major component of the bacterial flora of the human skin and mucosal membrane. Skin flora is an important source of microorganisms that cause infective endocarditis. Vancomycin is commonly used in the treatment of gram positive infections. Daptomycin is used in the treatment of infections caused by resistant gram positive microorganisms. It is a lipopeptide new drug and has been successfully used in the treatment of complicated skin infections and right-sided infective endocarditis. We report an unusual case of left-sided infective endocarditis due to *Corynebacterium jeikeium* which was initially unresponsive to vancomycin therapy, and then successfully treated with high-dose (12mg/kg/day) daptomycin. She was still doing well clinically.

KEY WORDS: *Corynebacterium jeikeium*, daptomycin, infective endocarditis, vancomycin

INTRODUCTION

Corynebacterium is a commensal microorganism that rarely poses as a pathogen. Skin flora is an important source of microorganisms that cause infective endocarditis (IE). *Corynebacterium* species rarely produce endocardial infection. One species of *Corynebacterium* has received the most attention, *Corynebacterium jeikeium*. This bacterium, a gram positive rod that is strict aerobe, is a rare cause of endocarditis and it more commonly infects prosthetic valves. Vancomycin is generally used for treatment of this multidrug-resistant microorganism[1-3].

We present an unusual case of left-sided endocarditis due to *C. jeikeium* which was not initially responsive to usually recommended vancomycin treatment and then successfully treated with high dose (12mg/kg/day) daptomycin.

CASE REPORT

A 36-year-old woman was admitted with complaints of fever (about 40 °C), fatigue and weakness for a week. She had undergone mitral valve ring annuloplasti due to myxomateous mitral valve degeneration six months ago at the other center. She had been complaining of weakness and fatigue for three months. The transthoracic echocardiographic (TTE) examination had detected 10x5 mm vegetation at the other center. In our unit, transesophageal echocardiography had been performed and revealed 10x5 mm vegetation, papilla muscle rupture and advanced mitral regurgitation. Ejection fraction was 60% and early IE was diagnosed (Duke criteria; Figure 1)[4,5]. An electrocardiography showed sinus rhythm. Laboratory test results showed hemoglobin of 6.4 g/dl, leukocytes $7.3x10^9$/l, platelet count $321x3x10^9$/l, C reactive protein 177 mg/l, sedimentation rate 89 mm (one hour). Three separate sets of blood cultures were taken in one hour. Gram positive rod grew in all bottles in the 24 hours. This bacterium was identified by the BD Phoenix automated identification system (Beckton Dickinson, USA) as a *C. jeikeium* and susceptibility testing was performed by E-test

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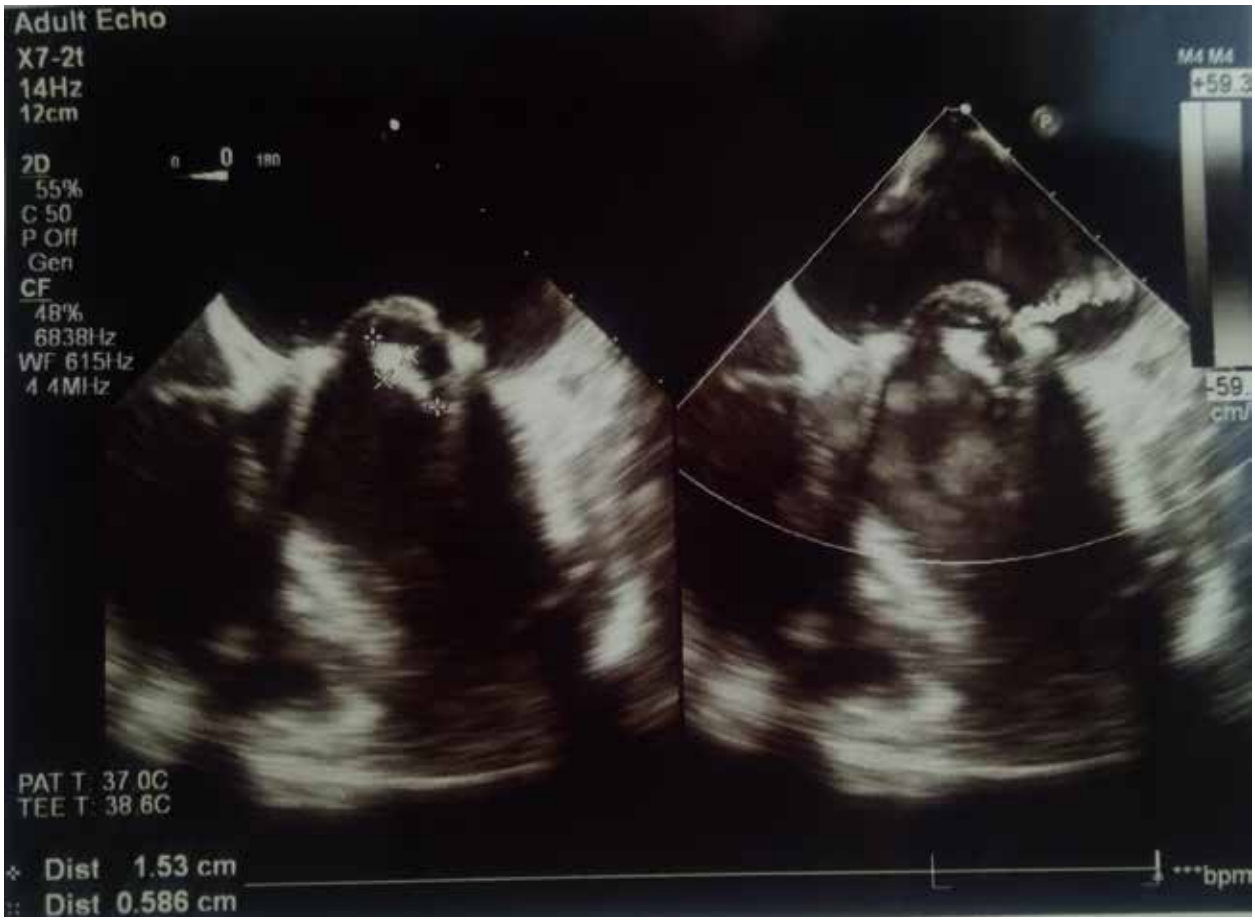

Fig 1: Transesophageal echocardiography (TEE) and 10x5 mm vegetation

method. *C. jeikeium* was susceptible to vancomycin, gentamicin, tetracycline, doxycycline, clindamycin, rifampicin, linezolid and erythromycin and also was resistant to penicilin, ampicillin, azithromycin, cefuroxime and ciprofloxacin. Immediately antibiotic therapy was started; gentamicin 80 mg intravenous (IV) twice daily, vancomycin 1 g IV twice daily and rifampicin 300 mg oral three times daily[5]. Unfortunately, we could not detect procalcitonine values due to laboratory problems. After three days, because C-reactive protein increased to 282 mg/l, vancomycin and rifampicin was stopped and added high-dose daptomycin (IV) (12 mg/kg/day). The patient was administered this treatment regimen for four weeks since there was no reproduction in subsequent blood cultures. Later, the patient was operated, all infective tissues were removed and prosthetic valve (No: 31 medtronic) replacement was performed. Postoperative antibiotic treatment with high-dose (12 mg/kg/day) daptomycin and gentamycin 80 mg intravenous (IV) twice daily was continued for three weeks with no recurrence of fever and persistently negative blood cultures. Physical examination, control TTE and surveillance blood cultures were negative at the post-surgical follow-up. Since the patient had no complaints, she was discharged safely. She comes to routine clinic follow-ups regularly and was doing well clinically.

DISCUSSION

Corynebacterium group JK was first recognized as a distinct species in 1976 and was later designated as *C. jeikeium* in 1987. It is part of the normal skin flora and is commonly found in inguinal, axillary and perirectal sites. In rare instances, it can become an opportunistic pathogen in immunosuppressed patients and patients with prosthetic material such as catheters and cardiac valves[2]. *C. jeikeium* is a gram positive and strict aerobe bacterium, requiring enriched culture medium for its growth in vitro, associated with a wide range of serious infections including native and prosthetic valve endocarditis. It may present an important hospital reservoir of drug resistant genes, which can be easily transferred to other gram positive pathogen microorganisms[1-2]. The studies have shown that mortality rate of *C. jeikeium* endocarditis is about 33%

in patients who did and did not undergo valve replacement[1-2].

In this case report, we diagnosed early left-sided IE due to *C. jeikeium* and chose vancomycin, rifampicin and gentamicin for treatment. However, the patient's C reactive protein increased to 282 mg/l, after three days. We stopped vancomycin and rifampicin and added high-dose (12 mg/kg/day) daptomycin.

Daptomycin is a novel cyclic lipopeptide obtained from *Streptomyces roseosporus* as a fermentation product. Daptomycin was discovered by Eli Lilly in the early 1980s. Rapid bactericidal activity of daptomycin is dependent on the presence of calcium ions against gram positive pathogen microorganisms including multiple antibiotic resistant and susceptible strains. Daptomycin includes rapid bactericidal activity against methicillin resistant and susceptible *Staphylococcus aureus*, glycopeptide-intermediate *S. aureus*, methicillin resistant coagulase negative *Staphylococci*, penicilin resistant *Streptococcus pneumoniae*, and ampicillin and vancomycin resistant *Enterococci*. Also, daptomycin is effective against a variety of *Streptococci* species such as the beta-haemolytic streptococci including *S. pyogenes* and *S. agalactiae* as well as other *Streptococcus* species. Daptomycin is also potent against *C. jeikeium* and a variety of anaerobic species including *Peptostreptococcus* spp., *Clostridium perfringens* and *Clostridium difficile*. Drug synergy with daptomycin has been described in vitro with aminoglycosides and rifampicin[3-6,7]. The European Medicine Agency and the United States Food and Drug Administration approved daptomycin only for the treatment of complicated skin-structure infections and right-sided IE attributable to Gram-positive microorganisms[3,6]. IE is a microbial infection of the endocardial surfaces of heart. Infections of the left side of the heart, involving the aortic or mitral valves, have greater therapeutic failure rates compared with those of the right side, and sometimes necessitate more intensive antibacterial therapy, and more often require surgical intervention. IE of left-sided cardiac valves is characterized by high morbidity and mortality[8,9]. Daptomycin is a therapeutic option for gram positive infections in patients with IE. High-dose (>6 and upto 12 mg/kg/day) daptomycin is recommended in difficult-to-treat infections by national and international guidelines owing to its concentration-dependent pharmacokinetics[10]. Goldstein *et al*[11] reported that daptomycin is more effective against *C. jeikeium* strains than vancomycin and teichoplanin. Bookani *et al*[12] found 10 cases of *C. jeikeium* endocarditis in the English literature review and only one of these cases had been treated with daptomycin (high-dose).

Daptomycin is approved only for right-sided endocarditis[3,7], but we administrated high-dose (12 mg/kg/day) daptomycin in the patient with active IE involving left-sided valve endocarditis due to *C. jeikeium*. In this case, we got successful results in patient treatment and follow-up.

Also, we found only one case in English literature treated with high-dose daptomycin for *C. jeikeium* left-sided prosthetic valve endocarditis[3].

High-risk patients should be educated according to guidelines to prevent IE. Patients with IE should be taught about the precautions they should take regarding their disease after being discharged. The patient should be informed about the symtoms of recurrent IE, endocarditis prophylaxis, dental care and eradication of oral infection foci. The patient should be educated about the need to apply to the hospital in case of any febrile illness and to obtain at least three sets of blood cultures before starting antibiotics[5].

CONCLUSION

Daptomycin can be used in critical cases that do not respond to vancomycin therapy. An appropriate antimicrobial therapy is very important for a successful outcome of IE. We successfully treated with high-dose daptomycin and surgical intervention a case of left-sided endocarditis due to *C. jeikeium* which did not initially respond to usually recomended vancomycin treatment. Our patient has been treated successfully and comes for regular check-ups.

ACKNOWLEDGMENTS

Authors' contributions: Emine Kucukates: concept and design, performed laboratory study and wrote the case report. Murat Mert performed the patient's operation. Lutfiye Oksuz made the advanced identification of the bacterium. All authors have read and approved the final version of the case report.
Conflict of interests: None declared
Ethical approval: None required
Funding: No support for this study

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Selected Abstracts of Articles Published Elsewhere by Authors in Kuwait

Kuwait Medical Journal 2026; 58 (2): 148 - 150

Treatment outcomes of high-efficacy disease-modifying therapies in patients with relapsing-remitting multiple sclerosis: A longitudinal observational study

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Mult Scler Relat Disord. 2026 Apr:108:107024. doi: 10.1016/j.msard.2026.107024. Epub 2026 Jan 19.

BACKGROUND
The evolution of high-efficacy disease-modifying therapies (HE-DMTs) has significantly shifted the management of relapsing-remitting multiple sclerosis (RRMS). Real-world evidence highlighted the role of HE-DMTs in improving disability and controlling disease activity.

OBJECTIVES
To assess the real-world effectiveness, treatment patterns, and discontinuation patterns of HE-DMTs, including cladribine, natalizumab, ocrelizumab, alemtuzumab, fingolimod, and rituximab in RRMS patients.

METHODS
This is a retrospective, observational, longitudinal, multicenter study that included 1,408 RRMS patients treated with HE-DMTs. Data were extracted from the Kuwaiti national MS registry. The primary objective of this study was to assess the proportion of patients with relapse-free status at 12 months. Secondary objectives included confirmed disability progression (CDP), confirmed disability improvement (CDI), Expanded Disability Status Scale (EDSS) changes, proportion of patients with no evidence of disease activity (NEDA-3), and treatment discontinuation patterns. Statistical analysis included descriptive analysis, paired-sample tests, and McNemar's tests.

RESULTS
After 12 months of treatment, first-line HE-DMTs resulted in high relapse-free (≥80%) and NEDA-3 (≥75%) rates, especially with ocrelizumab (90.6%, 82.7%, respectively) and natalizumab (88.4%, 81.9%, respectively). Significant EDSS reductions were achieved with natalizumab (-0.80), ocrelizumab (-0.46), and rituximab (-0.66) in patients receiving first-line HE-DMTs ($p < 0.001$). CDI rates were the highest with alemtuzumab (40.6%) and rituximab (22.1%) in the first-line setting. Discontinuation rates were highest for alemtuzumab due to scheduled stopping (86.9%), fingolimod due to adverse events (17.3%), and natalizumab due to JC virus sero-positivity (65.7%). Ocrelizumab had the lowest discontinuation rate (5.4%), mainly due to pregnancy confirmation or planning (56.5%).

CONCLUSION
Early initiation of HE-DMTs in RRMS patients had a significant clinical impact on disease activity and disability. Treatment effectiveness parameters were lower with later lines of therapy, highlighting the importance of early therapeutic intervention. High tolerability varied among DMTs, demonstrating the need for individualized treatment decisions.

Clinical characteristics and risk factors for intubation of critically ill children with respiratory syncytial virus (RSV) infection: A descriptive analysis from the Kuwait PICUs registry

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J Infect Public Health. 2026 May 3;19(6):103246. doi: 10.1016/j.jiph.2026.103246. Online ahead of print.

BACKGROUND

Respiratory syncytial virus (RSV) is a major cause of pediatric lower respiratory tract critical infection. Using a national pediatric intensive care units (PICUs) registry, we aimed to describe the clinical and management characteristics of RSV-positive PICU admissions, and identify factors associated with the need for invasive mechanical ventilation.

METHODS

We conducted a national-level retrospective study of all children aged 0-14 years admitted to a PICU with laboratory-confirmed RSV infection between September 2023 and June 2025. Data extracted from the Kuwait PICUs Registry included demographics, comorbidities, respiratory support, length of stay, antimicrobial use, and viral coinfections. Descriptive analysis and multivariate logistic regression were performed to identify factors associated with intubation.

RESULTS

Among 1144 RSV-positive admissions representing 19.8% of all PICU admissions, the median age was 91.5 days (IQR 41-304), with 49.4% aged < 3 months, 59.3% were male, and nine died (0.8%). Most patients (86.5%) were previously healthy. Overall, 22.4% required intubation, with genetic disorders (aOR 9.31, 95%CI 4.61-18.79), chronic respiratory disease (aOR 2.93, 95%CI 1.24-6.92), other comorbidities (aOR 4.97, 95%CI 2.45-10.10), viral coinfection (aOR 2.15, 95%CI 1.45-3.17), and younger age independently associated with intubation. The 2024/2025 season had higher admission and intubation rates compared to the 2023/2024 season. Antimicrobial use was frequent despite low bacterial coinfection rates.

CONCLUSION

Severe RSV infection predominantly affects previously healthy young infants, with a substantial proportion requiring intubation. Younger age, comorbidities, and viral coinfection are key risk factors. These findings highlight the significant burden of RSV-disease in PICUs.

Spectrum and management of rare *Candida*/yeast infections in Kuwait in the Middle East

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Ther Adv Infect Dis. 2024 Jul 24:11:20499361241263733. doi: 10.1177/20499361241263733. eCollection 2024 Jan-Dec.

Invasive fungal infections (IFIs) are associated with high mortality rates and mostly affect patients with compromised immunity. The incidence of IFIs is increasing worldwide with the expanding population of susceptible patients. *Candida* and other yeast infections represent a major component of IFIs. Rare *Candida*/yeast infections have also increased in recent years and pose considerable diagnostic and management challenges as they are not easily recognized by routine phenotypic characteristic-based diagnostic methods and/or by the automated yeast identification systems. Rare *Candida*/yeasts also exhibit reduced susceptibility to antifungal drugs making proper management of invasive infections challenging. Here, we review the diagnosis and management of 60 cases of rare *Candida*/yeast IFIs described so far in Kuwait, an Arabian Gulf country in the Middle East. Interestingly, majority (34 of 60, 56.7%) of these rare *Candida*/yeast invasive infections occurred among neonates or premature, very-low-birth-weight neonates, usually following prior bacteremia episodes. The clinical details, treatment given, and outcome were available for 28 of 34 neonates. The crude mortality rate among these neonates was 32.2% as 19 of 28 (67.8%) survived the infection and were discharged in healthy condition, likely due to accurate diagnosis and frequent use of combination therapy. Physicians treating patients with extended stay under intensive care, on mechanical ventilation, receiving broad spectrum antibiotics and with gastrointestinal surgery/complications should proactively investigate IFIs. Timely diagnosis and early antifungal treatment are essential to decrease mortality. Understanding the epidemiology and spectrum of rare *Candida*/yeast invasive infections in different geographical regions, their susceptibility profiles and management will help to devise novel diagnostic and treatment approaches and formulate guidelines for improved patient outcome.

Forthcoming Conferences and Meetings

Compiled and edited by
Vineetha Elizabeth Mammen

Kuwait Medical Journal 2026; 58 (2): 151 - 159

International Conference on Advances in **Medical Science and Health care**
United Arab Emirates, Dubai
Jun 1, 2026
Organized by: Academicsera
Email: info@academicsera.com

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United States, New York
Jun 1, 2026
Organized by: ISSRD
Email: papers.issrd@gmail.com

International Conference on **Medical & Health Science**
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Email: contact.wrfer@gmail.com

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International Conference on **Medical and Health Sciences**
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International **Cancer** Conference
Spain, Jerez De La Frontera
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Email: info.sciencefora@gmail.com

International Conference on **Medical and Health Sciences**
Australia, Melbourne
Jun 6, 2026
Organized by: ISERD
Email: info@iserd.co

International **Cancer** Conference
United States, El Paso, Texas
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Organized by: Biofora
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Organized by: IRF conference
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Greece, Chania
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Email: info@globalsciencesociety.com

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Organized by: ISER
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June 20, 2026
Organized by: Kuwait Heart Foundation

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International **Cancer** Conference
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Jun 26, 2026
Organized by: Biofora
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International Conference on Recent Advances in **Medical and Health Sciences**
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Jun 27, 2026
Organized by: Academics world
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Jun 28, 2026
Organized by: IASTEM
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WHO-Facts Sheet

1. Botulism
2. Hantavirus
3. Japanese encephalitis
4. Kidney disease
5. Marburg virus disease

Compiled and edited by
Vineetha E Mammen

Kuwait Medical Journal 2026; 58 (2): 160 - 170

1. Botulism

KEY FACTS

- Clostridium botulinum is a bacterium that produces dangerous toxins (botulinum toxins) under low-oxygen conditions.
- Botulinum toxins are one of the most lethal substances known.
- Botulinum toxins block nerve functions and can lead to respiratory and muscular paralysis.
- Human botulism may refer to foodborne botulism, infant botulism, wound botulism, and inhalation botulism or other types of intoxication.
- Foodborne botulism, caused by consumption of improperly processed food, is a rare but potentially fatal disease if not diagnosed rapidly and treated with antitoxin.
- Homemade canned, preserved or fermented foodstuffs are a common source of foodborne botulism and their preparation requires extra caution.

Overview

Foodborne botulism is a serious, potentially fatal disease. However, it is relatively rare. It is an intoxication usually caused by ingestion of potent neurotoxins, the botulinum toxins, formed in contaminated foods. Person to person transmission of botulism does not occur.

Spores produced by the bacteria Clostridium botulinum are heat-resistant and exist widely in the environment, and in the absence of oxygen they germinate, grow and then excrete toxins. There are 7 distinct forms of botulinum toxin, types A–G. Four of these (types A, B, E and rarely F) cause human botulism. Types C, D and E cause illness in other mammals, birds and fish.

Botulinum toxins are ingested through improperly processed food in which the bacteria or the spores survive, then grow and produce the toxins. Though mainly a foodborne intoxication, human botulism can also be caused by intestinal infection with C. botulinum in infants, wound infections, and by inhalation.

Symptoms of foodborne botulism

Botulinum toxins are neurotoxic and therefore affect the nervous system. Foodborne botulism is characterized by descending, flaccid paralysis that can cause respiratory failure. Early symptoms include marked fatigue, weakness and vertigo, usually followed by blurred vision, dry mouth and difficulty in swallowing and speaking. Vomiting, diarrhoea, constipation and abdominal swelling may also occur. The disease can progress to weakness in the neck and arms, after which the respiratory muscles and muscles of the lower body are affected. There is no fever and no loss of consciousness.

The symptoms are not caused by the bacterium itself, but by the toxin produced by the bacterium. Symptoms usually appear within 12 to 36 hours (within a minimum and maximum range of 4 hours to 8 days) after exposure. Incidence of botulism is low, but the mortality rate is high if prompt diagnosis and appropriate, immediate treatment (early administration of antitoxin and intensive respiratory care) are not given. The disease can be fatal in 5 to 10% of cases.

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Exposure and transmission

Foodborne botulism

C. botulinum is an anaerobic bacterium, meaning it can only grow in the absence of oxygen. Foodborne botulism occurs when C. botulinum grows and produces toxins in food prior to consumption. C. botulinum produces spores and they exist widely in the environment including soil, river and sea water.

The growth of the bacteria and the formation of toxin occur in products with low oxygen content and certain combinations of storage temperature and preservative parameters. This happens most often in lightly preserved foods and in inadequately processed, home-canned or home-bottled foods.

C. botulinum will not grow in acidic conditions (pH less than 4.6), and therefore the toxin will not be formed in acidic foods (however, a low pH will not degrade any pre-formed toxin). Combinations of low storage temperature and salt contents and/or pH are also used to prevent the growth of the bacteria or the formation of the toxin.

The botulinum toxin has been found in a variety of foods, including low-acid preserved vegetables, such as green beans, spinach, mushrooms, and beets; fish, including canned tuna, fermented, salted and smoked fish; and meat products, such as ham and sausage. The food implicated differs between countries and reflects local eating habits and food preservation procedures. Occasionally, commercially prepared foods are involved.

Though spores of C. botulinum are heat-resistant, the toxin produced by bacteria growing out of the spores under anaerobic conditions is destroyed by boiling (for example, at internal temperature greater than 85 °C for 5 minutes or longer). Therefore, ready-to-eat foods in low oxygen-packaging are more frequently involved in cases of foodborne botulism.

Food samples associated with suspect cases must be obtained immediately, stored in properly sealed containers, and sent to laboratories in order to identify the cause and to prevent further cases.

Infant botulism

Infant botulism occurs mostly in infants under 6 months of age. Different from foodborne botulism caused by ingestion of pre-formed toxins in food, it occurs when infants ingest C. botulinum spores, which germinate into bacteria that colonize in the gut and release toxins. In most adults and children older than about 6 months, this would not happen because natural defences in intestines that develop over time prevent germination and growth of the bacterium.

C. botulinum in infants include constipation, loss of appetite, weakness, an altered cry and a striking loss of head control. Although there are several possible sources of infection for infant botulism, spore-contaminated honey has been associated with a number of cases. Parents and caregivers are therefore warned not to feed honey to the infants before the age of 1 year.

Wound botulism

Wound botulism is rare and occurs when the spores get into an open wound and are able to reproduce in an anaerobic environment. The symptoms are similar to the foodborne botulism, but may take up to 2 weeks to appear. This form of the disease has been associated with substance abuse, particularly when injecting black tar heroin.

Inhalation botulism

Inhalation botulism is rare and does not occur naturally, for example it is associated with accidental or intentional events (such as bioterrorism) which result in release of the toxins in aerosols. Inhalation botulism exhibits a similar clinical footprint to foodborne botulism. The median lethal dose for humans has been estimated at 2 nanograms of botulinum toxin per kilogram of bodyweight, which is approximately 3 times greater than in foodborne cases.

Following inhalation of the toxin, symptoms become visible between 1–3 days, with longer onset times for lower levels of intoxication. Symptoms proceed in a similar manner to ingestion of botulinum toxin and culminate in muscular paralysis and respiratory failure.

If exposure to the toxin via aerosol inhalation is suspected, additional exposure to the patient and others must be prevented. The patient's clothing must be removed and stored in plastic bags until it can be washed thoroughly with soap and water. The patient should shower and be decontaminated immediately.

Other types of intoxication

Waterborne botulism could theoretically result from the ingestion of the pre-formed toxin. However, as common water treatment processes (such as boiling, disinfection with 0.1% hypochlorite bleach solution) destroy the toxin, the risk is considered low.

Botulism of undetermined origin usually involves adult cases where no food or wound source can be identified. These cases are comparable to infant botulism and may occur when the normal gut flora has been altered as a result of surgical procedures or antibiotic therapy.

Adverse effects of the pure toxin have been reported as a result of its medical and/or cosmetic use in patients, see more on 'Botox' below.

Botox

The bacterium C. botulinum is the same bacterium that is used to produce Botox, a pharmaceutical product predominantly injected for clinical and cosmetic use. Botox treatments employ the purified and heavily diluted botulinum neurotoxin type A. Treatment is administered in the medical setting, tailored according to the needs of the patient and is usually well tolerated although occasional side effects are observed.

Diagnosis and treatment

Diagnosis is usually based on clinical history and clinical examination followed by laboratory confirmation including demonstrating the presence of botulinum toxin in serum, stool or food, or a culture of C. botulinum from stool, wound or food. Misdiagnosis of botulism sometimes occurs as it is often confused with stroke, Guillain-Barré syndrome, or myasthenia gravis.

Antitoxin should be administered as soon as possible after a clinical diagnosis. Early administration is effective in reducing mortality rates. Severe botulism cases require supportive treatment, especially mechanical ventilation, which may be required for weeks or even months. Antibiotics are not required (except in the case of wound botulism). A vaccine against botulism exists but it is rarely used as its effectiveness has not been fully evaluated and it has demonstrated negative side effects.

Prevention

Prevention of foodborne botulism is based on good practice in food preparation particularly during heating/sterilization and hygiene. Foodborne botulism may be prevented by the inactivation of the bacterium and its spores in heat-sterilized (for example, retorted) or canned products or by inhibiting bacterial growth and toxin production in other products. The vegetative forms of bacteria can be destroyed by boiling but the spores can remain viable after boiling even for several hours. However, the spores can be killed by very high temperature treatments such as commercial canning.

Commercial heat pasteurization (including vacuum packed pasteurized products and hot smoked products) may not be sufficient to kill all spores and therefore the safety of these products must be based on preventing bacterial growth and toxin production. Refrigeration temperatures combined with salt content and/or acidic conditions will prevent the growth of the bacteria and formation of toxin.

The WHO Five Keys to Safer Food serve as the basis for educational programmes to train food handlers and educate the consumers. They are especially important in preventing food poisoning.

The Five Keys are:

- keep clean
- separate raw and cooked
- cook thoroughly
- keep food at safe temperatures
- use safe water and raw materials.

WHO's response

Botulism outbreaks are rare but are public health emergencies that require rapid recognition to identify the disease source, distinguish outbreak types (between natural, accidental or potentially deliberate), prevent additional cases and effectively administer treatment to affected patients.

Successful treatment depends significantly on early diagnosis and the rapid administration of the botulinum antitoxin.

WHO's role in responding to outbreaks of botulism that may be of international concern is as follows.

Surveillance and detection: WHO supports the strengthening of national surveillance and international alert systems to ensure rapid local outbreak detection and an efficient international response. WHO's main tool for these activities of surveillance, coordination and response is the use of the International Network of Food Safety Authorities (INFOSAN) which links national authorities in Member States in charge of managing food safety events. This network is managed jointly by FAO and WHO.

Risk assessment: WHO response is based on a risk assessment methodology that includes consideration of whether the outbreak is natural, accidental, or, possibly, intentional. WHO also provides scientific assessments as basis for international food safety standards, guidelines and recommendations developed by the Codex Alimentarius Commission.

Containment at the disease source: WHO coordinates with national and local authorities in order to contain outbreaks at their source.

Delivery of assistance: WHO coordinates between international agencies, experts, national laboratories, airlines and commercial organizations to mobilize response equipment, materials and supplies, including the provision and administration of botulinum antitoxin.

2. Hantavirus

KEY FACTS

- Hantaviruses are a group of viruses carried by rodents that can cause severe disease in humans.
- People usually get infected through contact with infected rodents or their urine, droppings or saliva.
- Infection with hantaviruses can cause a range of illnesses, including severe disease and death.
- In the Americas, hantaviruses can cause hantavirus cardiopulmonary syndrome (HCPS), a severe respiratory illness, with a case fatality rate up to 50%.
- *Andes* virus, found in South America, is a currently known hantavirus for which limited humantohuman transmission among contacts has been documented.
- In Europe and Asia, hantaviruses cause haemorrhagic fever with renal syndrome (HFRS).

Overview

Hantaviruses are zoonotic viruses that naturally infect rodents and are occasionally transmitted to humans. Infection in people can result in severe illness and often death, although the diseases vary by type of virus and geographical location. In the Americas, infection has been known to lead to hantavirus cardiopulmonary syndrome (HCPS), a rapidly progressive condition affecting the lungs and heart, while in Europe and Asia hantaviruses has been known to haemorrhagic fever with renal syndrome (HFRS), which primarily affects the kidneys and blood vessels.

While there is no specific treatment that cures hantavirus diseases, early supportive medical care is key to improve survival and focuses on close clinical monitoring and management of respiratory, cardiac and kidney complications. Prevention depends largely on reducing contacts between people and infected rodents.

Viral family and classification

Hantaviruses belong to the family *Hantaviridae*, within the order *Bunyavirales*. Each hantavirus is typically associated with a specific rodent reservoir species, in which the virus causes longterm infection without apparent illness.

Although many hantavirus species have been identified worldwide, only a limited number are known to cause human disease.

- Hantaviruses present in North, Central and South America are known to cause HCPS. The *Andes* virus is part of this family and is known to cause limited human-to-human transmission among close and prolonged contacts, primarily in Argentina and Chile.
- Hantaviruses found in Europe and Asia are known to cause haemorrhagic fever with HFRS. Human-to-human transmission has not been documented in this part of the world.

Burden of disease

Hantavirus infections are relatively uncommon globally but are associated with a case fatality rate of <1–15% in Asia and Europe and up to 50% in the Americas. Worldwide, it is estimated that from 10 000 to over 100 000 infections occur each year *(1, 2, 3)*, with the largest burden in Asia and Europe.

- In East Asia, particularly China and the Republic of Korea, HFRS continues to account for many thousands of cases annually, although incidence has declined in recent decades.
- In Europe, several thousand cases are reported each year, mainly from northern and central regions where *Puumala* virus circulates. In the Americas, HCPS is much rarer, with hundreds of cases reported each year across the continent. The United States of America has reported fewer than 1000 cases, while South American countries such as Argentina, Brazil Chile, and Paraguay report small numbers of cases annually. Despite the lower incidence, HCPS has a high case fatality rate, commonly between 20% and 40%, making it a disease of major public health concern.

Transmission

Transmission of hantaviruses to humans occurs from contact with contaminated urine, droppings or saliva of infected rodents. Infection may also occur, although less commonly, through rodent bites. Activities that involve contact with rodents such as cleaning enclosed or poorly ventilated spaces, farming, forestry work and sleeping in rodent-infested dwellings increase exposure risk.

To date, human-to-human transmission has been documented only for *Andes* virus in the Americas and remains uncommon. When it occurs, transmission between people has been associated with close and prolonged contact, particularly among household members or intimate partners, and appears most likely during the early phase of illness, when the virus is more transmissible.

Symptoms and clinical presentation

In humans, symptoms usually begin between one and eight weeks after exposure, and typically include fever, headache, muscle aches and gastrointestinal symptoms such as abdominal pain, nausea or vomiting.

- In HCPS, the disease may progress rapidly to cough, shortness of breath, accumulation of fluid in the lungs and shock.

- In HFRS, later stages may include low blood pressure, bleeding disorders and kidney failure.

Diagnosis

Early diagnosis of hantavirus infection can be challenging because early symptoms are common with other febrile or respiratory illnesses, such as influenza, COVID-19, viral pneumonia, leptospirosis, dengue or sepsis. A careful patient history is therefore essential, with particular attention to possible rodent exposure, occupational and environmental risks, travel history, and contact with known cases in areas where hantaviruses are present.

Laboratory confirmation relies on serological testing to detect hantavirus-specific IgM antibodies or rising IgG titres, as well as molecular methods such as reverse transcription polymerase chain reaction (RT-PCR) during the acute phase of illness, when viral RNA may be detectable in blood.

Samples collected from patients are a biohazard risk; laboratory testing on non-inactivated samples should be conducted under maximum biological containment conditions. All non-inactivated biological specimens should be packaged using the triple packaging system when transported nationally and internationally.

Treatment

There is no licenced specific antiviral treatment or vaccine for hantavirus infection. Care is supportive and focuses on close clinical monitoring and management of respiratory, cardiac and kidney complications. Early access to intensive care, when clinically indicated, improves outcomes, particularly for patients with hantavirus cardiopulmonary syndrome.

Prevention and control

Preventing hantavirus infection depends primarily on reducing contacts between people and rodents. Effective measures include:

- keeping homes and workplaces clean
- sealing openings that allow rodents to enter buildings
- storing food securely
- using safe cleaning practices in areas contaminated by rodents
- avoiding dry sweeping or vacuuming rodent droppings
- dampening of contaminated areas before cleaning
- strengthening hand hygiene practices.

During outbreaks or when cases are suspected, early identification and isolation of cases, monitoring of close contacts, and application of standard infection prevention measures are important to limit further spread.

Infection prevention and control in health-care settings

Available evidence indicates that the risk of health-care associated transmission of hantavirus, including *Andes* virus, is very low when appropriate infection prevention and control measures are applied. In health-care environments, standard precautions should be applied for all patients, including hand hygiene and safe handling of blood and body fluids.

For suspected or confirmed hantavirus infection, standard precautions combined with droplet precautions during close contact are considered sufficient. Routine airborne precautions are not typically required, except during aerosol-generating procedures. Early recognition of suspected cases, prompt isolation, and consistent adherence to recommended infection prevention and control measures remain essential to protect health-care personnel.

WHO response

WHO works with countries and partners to strengthen surveillance, laboratory capacity, risk communication and community engagement, early detection, patient care and outbreak response for hantavirus infections. This includes developing and updating evidence-based guidance on diagnosis, case management, infection prevention and control, and contact tracing.

WHO promotes integrated One Health approaches that address the links between human health, rodent reservoirs and the environment, and supports countries in reviewing emerging evidence to ensure recommendations remain up to date.

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3. Japanese encephalitis

KEY FACTS

- Japanese encephalitis virus (JEV) is a flavivirus related to dengue, yellow fever and West Nile viruses, and is spread by mosquitoes (especially *Culex tritaeniorhynchus*).

- JEV is the main cause of viral encephalitis in many countries of Asia with an estimated 100 000 clinical cases every year *(1)*.
- Although symptomatic Japanese encephalitis (JE) is rare, the case-fatality rate among those with encephalitis can be as high as 30%. Permanent neurologic, cognitive and behavioural sequelae occur in 30–50% of those with encephalitis.
- The majority of cases occur in children below 15 years of age.
- Twenty-four countries in the WHO South-East Asia and Western Pacific Regions have endemic JEV transmission, exposing more than 3 billion people to risks of infection.
- There is no cure for the disease. Treatment is focused on relieving severe clinical signs and supporting the patient to overcome the infection.
- Safe and effective vaccines are available to prevent JE. WHO recommends that JE vaccination be integrated into national immunization schedules in all areas where JE disease is recognized as a public health issue.

Overview

Japanese encephalitis virus (JEV) is an important cause of viral encephalitis in Asia. It is a mosquito-borne flavivirus and belongs to the same genus as dengue, Zika, yellow fever and West Nile viruses. The first case of Japanese encephalitis viral disease (JE) was documented in 1871 in Japan. The annual incidence of clinical disease varies both across and within endemic countries, ranging from 10 per 100 000 population or higher during outbreaks. A literature review and modelling study estimates about 100 000 clinical cases (95% CI: 61 720–157 522) of JE globally each year, with approximately 25 000 deaths (95% CI: 14 550–46 031). JE primarily affects children. Most adults in endemic countries have natural immunity after childhood infection, but individuals of any age may be affected.

Signs and symptoms

Most JEV infections are mild (fever and headache) or without apparent symptoms, but approximately 1 in 250 infections results in severe clinical illness. The incubation period is 4–14 days. In children, gastrointestinal pain and vomiting may be the dominant initial symptoms. Severe disease is characterized by rapid onset of high fever, headache, neck stiffness, disorientation, coma, seizures, spastic paralysis and ultimately death. The case fatality rate can be as high as 30% among those with disease symptoms. Of those who survive, 20–30% suffer permanent cognitive, behavioural or neurological sequelae such as seizures, hearing or vision loss, speech, language, memory, and communication problems or weakness of the limbs.

Transmission

Twenty-four countries in the WHO South-East Asia and Western Pacific Regions have JEV transmission risk, which includes more than 3 billion people. JEV is transmitted to humans through bites from infected mosquitoes of the *Culex* species (mainly *Culex tritaeniorhynchus*). Humans, once infected, do not develop sufficient viraemia to infect feeding mosquitoes. The virus exists in a transmission cycle between mosquitoes, pigs and/or water birds (enzootic cycle). The disease is predominantly found in rural and periurban settings, where humans live in closer proximity to these vertebrate hosts, in particular domestic pigs. In most temperate areas of Asia, JEV is transmitted mainly during the warm season, when large epidemics can occur. In the tropics and subtropics, transmission can occur year-round but often intensifies during the rainy season and pre-harvest period in rice-cultivating regions.

Diagnosis

Individuals who live in or have travelled to a JE-endemic area and experience encephalitis are considered a suspected JE case. Initial diagnosis of JE can be made by clinical examination followed by a lumbar puncture. A laboratory test is required to confirm JEV infection and to rule out other causes of encephalitis. WHO recommends testing for JEV-specific IgM antibody in a single sample of cerebrospinal fluid (CSF) or serum, using an IgM-capture ELISA. If tested negative, a convalescent sample may be tested. Testing of CSF sample is preferred to reduce false-positivity rates from previous infection or vaccination.

Surveillance of the disease is mostly syndromic for acute encephalitis syndrome. Confirmatory laboratory testing is often conducted in dedicated sentinel sites, and efforts are undertaken to expand laboratory-based surveillance. Case-based surveillance is established in countries that effectively control JE through vaccination.

Treatment

Encephalitis is a medical emergency and requires urgent medical attention. There is no antiviral treatment for patients with JE. Treatment is supportive and includes stabilization and relief of symptoms.

Those who have lived through encephalitis often have health-care needs requiring long-term treatment and care including rehabilitation. The ongoing psychosocial impacts of disability from encephalitis can have medical, educational, social and human

rights-based implications. Despite the high burden of sequelae on people with encephalitis, their families and the community, access to both services and support for these conditions is often insufficient, especially in low- and middle-income countries. Individuals and families with members disabled by encephalitis should be encouraged to seek services and guidance from local and national Organizations of Disabled People (ODPs) and other disability focused organizations, which can provide vital advice about legal rights, economic opportunities and social engagement to ensure people disabled by encephalitis are able to live full and rewarding lives.

Prevention and control

Progress has been made in Asia with the implementation of JE vaccination programmes, with most endemic countries having country-wide or targeted programmes in place. A decline in incidence of the disease has been reported in recent years, which is likely due in part to vaccination. Gavi supports JE catch-up campaigns and co-finances the vaccine for routine immunization in eligible countries.

Safe and effective JE vaccines are available to prevent disease. WHO recommends having strong JE prevention and control activities, including JE immunization in all regions where the disease is a recognized public health priority, along with strengthening surveillance and reporting mechanisms. Even if the number of JE-confirmed cases is low, vaccination should be considered where there is a suitable environment for JE virus transmission. Introduction of the vaccine should be done in conjunction with a one-time catch-up campaign.

There are three main types of JE vaccines currently in use: several inactivated Vero cell-derived vaccines, a live attenuated vaccine, and a live recombinant (chimeric) vaccine. One inactivated vaccine and the two live vaccines are WHO prequalified.

The risk to travellers to Japanese encephalitis-endemic areas is normally low, but travellers should take precautions to avoid mosquito bites. Personal preventive measures include the use of mosquito repellents, long-sleeved clothes, coils and vaporizers. Travellers spending extensive time in JE endemic areas are recommended to get vaccinated before travel.

In endemic areas, there is little evidence to support a reduction in JE disease burden from interventions other than the vaccination of humans. Thus, vaccination of humans should be prioritized over vaccination of pigs and mosquito control measures. However, the spread of JEV in new areas has been correlated with agricultural development and intensive rice cultivation supported by irrigation programmes.

WHO response

WHO responds to Japanese encephalitis in the following way:

- supports countries in the confirmation of outbreaks through its collaborating network of laboratories;
- develops surveillance standards and case definitions for reporting;
- provides guidance on clinical management of disease and long-term care;
- supports vector control efforts in conjunction with the Global Vector Control Response;
- develops guidance on the optimal use of vaccines through the publication of vaccine position papers;
- prequalifies vaccines as a service to UNICEF and Gavi.
- WHO is implementing the Intersectoral global action plan on epilepsy and other neurological disorders in consultation with Member States to address many challenges and gaps in providing care and services for people with epilepsy and other neurological disorders such as JE that exist worldwide.

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4. Kidney disease

- Kidney disease includes acute kidney injury (AKI) and chronic kidney disease (CKD).
- Simple blood (serum creatinine) and urine tests (for albuminuria) used in primary health care can detect CKD.
- An estimated 674 million people have chronic kidney disease worldwide; most reside in low- and middle-income countries.
- The most severe form of CKD is kidney failure, which requires dialysis or kidney transplantation to sustain life.
- The global burden of acute kidney injury (AKI) is unknown.

Overview

Kidney disease occurs when the kidneys can no longer remove waste and excess fluid from the bloodstream normally. Acute kidney injury (AKI) has an abrupt onset and is often reversible with timely intervention. In contrast, chronic kidney disease (CKD) progresses gradually and is frequently irreversible, with severity ranging from mild dysfunction to kidney failure. People with kidney failure typically require dialysis or kidney transplantation to survive.

Kidney disease causes substantial morbidity, disability, and premature mortality, in part because it causes and is caused by cardiovascular disease. The

burden of kidney disease is rising in parallel with diabetes, hypertension and population ageing. Global inequities in access to testing, essential medications, health- care workers and kidney replacement therapies are a key global challenge and contribute to millions of preventable deaths each year.

Symptoms

Kidney disease is often asymptomatic until late stages, which is why regular testing is important for people at risk. In advanced or severe kidney disease, symptoms may include fatigue, breathlessness, generalized itchiness, leg swelling, muscle cramps, nausea or vomiting.

Chronic kidney disease (CKD)

CKD has a wide range of causes, including diabetes, hypertension, cardiovascular disease, glomerulonephritis (inflammation of the kidney's filtering units), some genetic conditions, certain drugs and toxins and infections. In low- and middle-income countries (LMICs), a substantial proportion of people with CKD do not have a known exposure to known risk factors.

CKD is diagnosed by using serum creatinine results to estimate glomerular filtration rate (eGFR); low eGFR suggests the presence of kidney disease. Two values of eGFR <60 ml/min/1.73m2 obtained at least 90 days apart indicate that CKD is present. Persistently elevated urinary albumin excretion ("albuminuria") is identified by urinary albumin-creatinine ratio (ACR) of >3 mg/mmol (30 mg/g) and also indicates the presence of CKD.

The risk of developing CKD can be reduced by a healthy lifestyle, including regular physical activity, maintaining a healthy body weight and refraining from tobacco use. In people with diabetes, hypertension and cardiovascular disease, good control of blood pressure, blood glucose and blood lipids, alongside these lifestyle measures, can further help to reduce the risk of developing CKD.

Integrating kidney health into primary care is essential for early diagnosis and timely treatment. Routine testing ("case-finding") with eGFR and albuminuria can be arranged in primary care for people with hypertension, diabetes and cardiovascular disease, aiming to diagnose and treat kidney disease at an early stage.

The management of CKD focuses on slowing progression, reducing cardiovascular risk, and preventing complications of advanced kidney disease. For treatment of kidney failure, kidney replacement therapy (dialysis or kidney transplantation) may be required.

Where transplantation or dialysis is unavailable, unaffordable, or not desired by the individual, conservative kidney management provides supportive care focused on symptom control and quality of life.

Acute kidney injury (AKI)

AKI represents a deterioration of kidney function over hours to days and can be reversible with timely care. Although AKI and CKD differ in onset and reversibility, they are closely connected: AKI can lead to CKD, and CKD increases the risk of AKI. Even a single episode of AKI raises the risk of CKD and death.

Common causes of AKI include sepsis, major surgery, trauma, complications of pregnancy, nephrotoxic medications and volume depletion. AKI is diagnosed by rising serum creatinine levels above baseline (pre-illness) values, and/or abnormally low levels of urine output.

AKI can be prevented by avoiding and treating dehydration, infections and pregnancy-related complications. Management of AKI focuses on treating the cause and correcting fluid/electrolyte disturbances and providing temporary dialysis when needed.

WHO response

In May 2025, the World Health Assembly agreed a Resolution on reducing the burden of noncommunicable diseases through the promotion of kidney health and strengthening the prevention and control of kidney disease. The Resolution calls for promoting kidney health across the life course, improving early detection and management of kidney disease – especially in people with diabetes and hypertension – and ensuring equitable access to essential medicines and services.

5. Marburg virus disease

KEY FACTS

- Marburg virus disease (MVD), formerly known as Marburg haemorrhagic fever, is a severe, often fatal illness in humans.
- The average MVD case fatality rate is around 50%. Case fatality rates have varied from 24% to 88% in past outbreaks.
- Early supportive care with rehydration, and symptomatic treatment improves survival.
- There are currently no approved vaccines or antiviral treatments for MVD, but a range of vaccines and drug therapies are under development.
- *Rousettus aegyptiacus*, a fruit bat of the *Pteropodidae* family, is considered the natural

host of Marburg virus. The Marburg virus is transmitted to people from fruit bats and spreads among humans through human-to-human transmission.
- Community engagement is key to successfully controlling outbreaks.

Overview

Marburg virus (MARV) and Ravn virus (RAVV) of the species *Orthomarburgvirus marburgense* are the causative agents of Marburg virus disease (MVD). The disease has a case fatality ratio of up to %88, but it can be much lower with good and early patient care.

Both viruses are part of the *Filoviridae* family (filovirus) to which *Orthoebolavirus* genus belongs. Though caused by different viruses, Ebola and Marburg diseases are clinically similar. Both diseases are rare but have the capacity to cause outbreaks with high fatality rates.

MVD was initially detected in 1967 after two simultaneous outbreaks in Marburg and Frankfurt in Germany, and in Belgrade, Serbia. These outbreaks were associated with laboratory work using African green monkeys (*Cercopithecus aethiops*) imported from Uganda. Subsequently, outbreaks and sporadic cases have been reported in Angola, the Democratic Republic of the Congo, Equatorial Guinea, Ghana, Guinea, Kenya, South Africa (in a person with recent travel history to Zimbabwe), Tanzania and Uganda. In 2008, two independent cases were reported in travellers who had visited a cave inhabited by *Rousettus aegyptiacus* bat colonies in Uganda. In September 2024, Rwanda reported the country›s first outbreak and Tanzania declared another outbreak in January 2025.

Transmission

Initially, human MVD infection results from prolonged exposure to mines or caves inhabited by Rousettus fruit bat colonies. Once introduced in the human population, Marburg virus can spread through human-to-human transmission via direct contact (through broken skin or mucous membranes) with the blood, secretions, organs or other bodily fluids of infected people, and with surfaces and materials (e.g. bedding, clothing) contaminated with these fluids.

Healthcare workers have frequently been infected while treating patients with MVD. This has occurred through close contact with patients when infection control precautions are not strictly practiced. Transmission via contaminated injection equipment or through needle-stick injuries is associated with more severe disease, rapid deterioration, and possibly a higher fatality rate.

Burial ceremonies that involve direct contact with the body of the deceased can also contribute to the transmission of Marburg virus.

People cannot transmit the disease before they have symptoms and remain infectious as long as their blood contains the virus.

Symptoms of Marburg virus disease

The incubation period (interval from infection to onset of symptoms) varies from 2 to 21 days.

MVD begins abruptly, with high fever, severe headache and severe malaise. Muscle aches and pains are a common feature. Severe watery diarrhoea, abdominal pain and cramping, nausea and vomiting can begin on the third day. Non-itchy rash have been reported in patients between 2 and 7 days after onset of symptoms.

From day 5 of the disease, patients may develop haemorrhagic manifestations, including fresh blood in vomitus and faeces, and bleeding from the nose, gums and vagina. Bleeding at venepuncture sites (where intravenous access is obtained to give fluids or obtain blood samples) can also be observed. Involvement of the central nervous system can result in confusion, irritability and aggression. Orchitis (inflammation of one or both testicles) has been reported occasionally in the late phase of disease.

In fatal cases, death occurs most often between 8 and 9 days after symptom onset, usually preceded by severe blood loss and shock.

Diagnosis

It can be difficult to clinically distinguish MVD from other infectious diseases such as malaria, typhoid fever, shigellosis, meningitis and other viral haemorrhagic fevers. Confirmation that symptoms are caused by Marburg virus infection are made using the following diagnostic methods:
- antibody-capture enzyme-linked immunosorbent assay (ELISA)
- antigen-capture detection tests
- reverse transcriptase polymerase chain reaction (RT-PCR) assay
- virus isolation by cell culture in maximum containment laboratories.

Samples collected from patients are an extreme biohazard risk; laboratory testing on non-inactivated samples should be conducted under maximum biological containment conditions. All non-inactivated biological specimens should be packaged using the triple packaging system when transported nationally and internationally.

Treatment and vaccines

Early intensive supportive care including rehydration and treatment of specific symptoms, can improve survival. Currently there are no vaccines or antiviral treatments approved for MVD.–

There are candidate monoclonal antibodies (mAbs) and antivirals, along with candidate vaccines that can be evaluated in clinical trials.

Marburg virus in animals

Rousettus aegyptiacus bats are considered natural hosts for Marburg virus. There is no apparent disease in these fruit bats. As a result, the geographic distribution of Marburg virus may overlap with the range of *Rousettus* bats.

African green monkeys (*Cercopithecus aethiops*) imported from Uganda were the source of infection for humans during the first MVD outbreak.

Experimental inoculations in pigs with different *Orthoebolavirus* species indicated that pigs are susceptible to filovirus infection and shed the virus. Therefore, pigs should be considered as a potential amplifier host during MVD outbreaks. Precautionary measures are needed in pig farms in Africa to avoid pigs becoming infected through contact with fruit bats.

Prevention and control

Community engagement is key to successfully controlling any outbreaks. Outbreak control relies on using a range of interventions, such as case management, surveillance and contact tracing, good laboratory service, infection prevention and control in health facilities, safe and dignified burials and social mobilization.

Raising awareness of risk factors for MVD and protective measures that individuals can take is an effective way to reduce human transmission.

Risk reduction messaging should focus on several factors:

- Reducing the risk of bat-to-human transmission arising from prolonged exposure to mines or caves inhabited by fruit bat colonies. People with visiting or working in in mines or caves inhabited by fruit bat colonies, people should wear gloves and other appropriate protective clothing (including masks). During outbreaks all animal products (blood and meat) should be thoroughly cooked before consumption.
- Reducing the risk of human-to-human transmission in the community arising from direct or close contact with infected patients, particularly with their body fluids. Close physical contact with MVD patients should be avoided. Patients suspected or confirmed for MVD should be isolated in a designated treatment centre for early care and to avoid transmission at home.
- Communities affected by MVD should make efforts to ensure that the population is well informed, both about the nature of the disease itself and about necessary outbreak containment measures.
- Outbreak containment measures include safe and dignified burial of the deceased, identifying people who may have been in contact with someone infected with MVD and monitoring their health for 21 days, separating the healthy from the sick to prevent further spread and providing care to confirmed patient and maintaining good hygiene and a clean environment need to be observed.

Controlling infection in healthcare settings

Healthcare workers should always take standard precautions when caring for patients, regardless of their presumed diagnosis. These include basic hand hygiene, respiratory hygiene, use of personal protective equipment (to block splashes or other contact with infected materials), safe injection practices and safe and dignified burial practices.

Healthcare workers caring for patients with suspected or confirmed MVD should apply extra infection control measures to prevent contact with the patient's blood and body fluids and contaminated surfaces or materials such as clothing and bedding.

Laboratory workers are also at risk. Samples taken from humans and animals for investigation of Marburg virus infection should be handled by trained staff and processed in suitably equipped laboratories.

Care for MVD survivors

All survivors, their partners and families should be shown respect, dignity and compassion. WHO does not recommend isolation of male or female convalescent patients whose blood has been tested negative for Marburg virus. MVD survivors might suffer from both clinical and psychological sequelae. WHO encourages affected countries to consider the establishment of a survivor care programme to alleviate sequelae, support to community reintegration and offer counselling and biological testing.

Marburg virus is known to persist in immune-privileged sites in some people who have recovered. These sites include the testicles and the inside of the eye. Extrapolating from data on other filoviruses, the virus may persist in the placenta, amniotic fluid and foetus of women infected while pregnant and in breast milk of women infected while breastfeeding. Relapse-symptomatic illness in the absence of re-infection in someone who has recovered from MVD is a rare event but has been documented. Reasons for this phenomenon are not yet fully understood.

Marburg virus transmission via infected semen has been documented up to seven weeks after clinical recovery. To mitigate the risk of potential transmission via exposure to infected semen, a semen testing programme should be implemented to:

Table: Chronology of major Marburg virus disease outbreaks

Year	Country	Cases	Deaths	Case fatality rate
2024	Rwanda	66	15	23%
2023	Tanzania	9	6	67%
2023	Equatorial Guinea	40	35	88%
2022	Ghana	3	2	67%
2021	Guinea	1	1	100%
2017	Uganda	3	3	100%
2014	Uganda	1	1	100%
2012	Uganda	15	4	27%
2008	Netherland (ex-Uganda)	1	1	100%
2008	United States of America (ex-Uganda)	1	0	0%
2007	Uganda	4	2	50%
2005	Angola	374	329	88%
1998 to 2000	Democratic Republic of the Congo	154	128	83%
1987	Kenya	1	1	100%
1980	Kenya	2	1	50%
1975	South Africa	3	1	33%
1967	Yugoslavia	2	0	0%
1967	Germany	29	7	24%

- offer counselling to male MVD survivors and their sexual partners, as needed, to inform them on potential risk and support them adhering to safer sex practices (including condom provision and good hand and personal hygiene); and
- offer monthly semen testing until obtention of two consecutive negative test results.

After obtention of two consecutive negative test results, MVD survivors can safely resume normal sexual practices with minimized risk of Marburg virus transmission. In the absence of semen testing programme, male survivors should follow safer sex practices for 12 months.

WHO response

WHO aims to prevent MVD outbreaks by maintaining surveillance for MVD disease and supporting at-risk countries to develop preparedness plans. The following document provides overall guidance for control of Ebola and Marburg disease outbreaks:

· Ebola and Marburg virus disease epidemics: preparedness, alert, control, and evaluation

When an outbreak is detected WHO responds by supporting surveillance, community engagement, case management, laboratory services, infection prevention and control, logistical support and training and assistance with safe burial practices.