

Case Report

A Rare Case of Lymphadenopathy: Castleman Disease

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INTRODUCTION

Castleman disease (CD) was originally described in 1956^[1]. It is a rare and unusual condition of unknown etiology consisting of a massive proliferation of lymphoid tissue. We present a case of CD and review the literature on this rare disease.

Clinical features

A 47-year-old female Kuwaiti presented to the medical department complaining of fever, nocturnal sweating, fatigability and palpitations of two months duration. She gave a history of multiple painless axillary swellings over the last four years and a loss of weight of more than 30 kg in the past two years. There was no heat intolerance, diarrhoea, or bleeding tendency. No polyarthralgia, eye symptoms, skin rash or bone pain were noted.

Her 19-year old son was admitted on the same day with a history of fever, weight loss and anemia of six months duration. For the last six months, both mother and son had been in a European country. Neither had a history of drug abuse or sexual contact.

On examination, the mother appeared unwell and cachectic, with marked pallor. Her weight was 40 kg and height 158 cm. and her temperature was 38.9 °C. She had enlarged cervical, axillary and inguinal lymph nodes, ranging in size from 1 to 3 cm, non-tender, mobile, firm and some were matted. She had bilateral mild lower limb edema but the jugular venous pressure was not raised. There were no signs of thyrotoxicosis, jaundice or clubbing. Abdominal examination revealed marked hepatomegaly reaching the right iliac fossa. The liver was firm with an irregular surface but not tender and no bruit was audible. The spleen was enlarged by 8 cm and was not tender. Examination of other systems was unremarkable.

Investigations

Full blood examination revealed the following: WBC 6.9 x 10⁹/L; Hb 6.8 g/dl with low MCV and

MCH; platelet count 460 x 10⁹/L, ESR 105–110 mm/h; and a reticulocyte count of 2.3%. Liver function test showed AST 47 IU/L; ALT 38 IU/L; ALP 227 IU/L; total bilirubin 32 mmol/L; total protein 49 g/L and albumin 19 g/L. Blood glucose estimation was normal as were the renal and coagulation profiles. Examination of the serum and urine did not demonstrate a monoclonal gammopathy.

Chest reontogram revealed no mediastinal or lung masses. Ultrasound abdomen showed a markedly enlarged liver extending to the pelvis and consisting of non-homogenous echopattern. The spleen was enlarged (15 cm) and there were multiple large retroperitoneal para-aortic lymph nodes. Her son had similar clinical and ultrasound findings.

Computerized tomography (CT) of the mother's abdomen and chest showed hepatosplenomegaly, multiple patchy hypodense areas in the liver (1-4 cm), extensive para-aortic lymph nodes (0.5–3 cm in size) but no mediastinal, parenchymal lung or pelvic masses (Fig. 1).

Bone marrow biopsy showed depleted iron stores and no infiltration by malignant cells.

The mother was transfused with four pints of packed red blood cells, and a cervical lymph node biopsy was carried out (Fig. 2). The biopsy showed marked vascular proliferation and hyalinization of germinal center. The interfollicular stroma was prominent with numerous hyperplastic postcapillary venules but no monoclonality or malignant infiltration. The diagnosis of CD (Vascular-hyaline type) was made.

As this disease can be associated with secondary malignancies and a CT liver showed multiple hypodense lesions, a liver biopsy was performed in order to rule out the possibility of a lymphoma. Ultrasound guided needle liver biopsy showed areas of panlobular hepatocellular loss containing mixed inflammatory cell infiltrate. No atypical cells were revealed. Immunocytochemistry, using CD 20,



Fig. 1: CT of the abdomen showing hepatosplenomegaly and extensive para-aortic lymph nodes

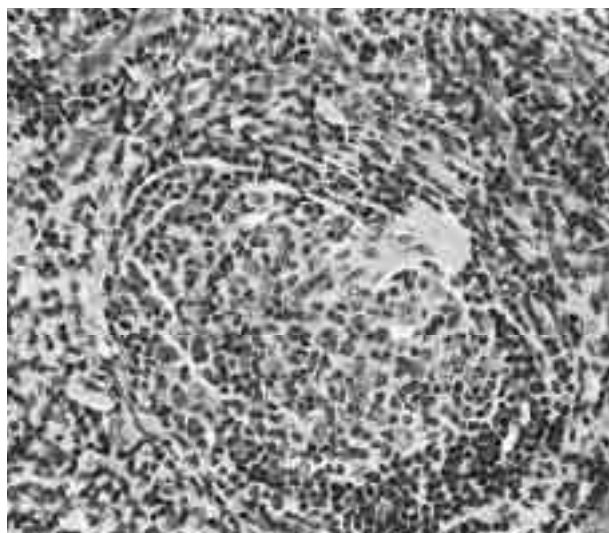


Fig. 2: Haematoxylin-Eosin staining of cervical lymph node showing hyaline-vascular type Castleman disease

CD3, and CD45 Ro demonstrated lymphoid cells. Various other investigations were negative including blood cultures for bacteria, screen for HIV, EB virus, human herpes virus - 8 and hepatitis B and C viruses, connective tissue screen was negative as well as serology for syphilis.

Tests for interleukin-1 (IL-1) and IL-6, tissue necrosis factor (TNF) and vascular endothelial growth factors (VEGF) were not available in Kuwait at the time.

Treatment

The patient was started on high dose dexamethasone (20 mg/day) for two days then prednisolone (60 mg/day) for two weeks with iron supplementation. She developed diabetes and mild proximal myopathy as complications to the steroid therapy. Within two weeks, the patient gradually became more alert, her appetite improved, her

weight increased 5kg and she became afebrile. After three weeks, the cervical and axillary lymph nodes disappeared. Liver size shrunk to 6 cm and spleen to 2cm. The Hb level, ESR and liver enzymes returned to normal values. Azathioprine was added (2 mg/kg) after two weeks to span the dose of prednisolone. The plan was to slowly reduce the steroid dose by 5 mg every two weeks and to keep the patient on long term maintenance. The patient was followed-up weekly for the first 8 weeks and then on a monthly basis. She was advised to report any infection, bleeding tendency and bruises.

Her son was investigated by CT guided abdominal lymph node needle biopsy and histology revealed non-Hodgkin's lymphoma (stage III). He is now in the USA receiving chemotherapy.

DISCUSSION

CD has been known as angiofollicular lymph node hyperplasia, lymphoid hamartoma or benign lymphoma. It is characterized by enlarged hyperplastic lymph nodes histologically characterized by hyperplasia of lymphoid follicles and capillary proliferation with endothelial hyperplasia. It has three histologic variants (hyaline-vascular; plasma cell and mixed) and two clinical types (localized and multicentric). The hyaline-vascular type shows small hyaline-vascular follicles and interfollicular capillary proliferation while plasma cell type is characterized by a massive accumulation of polyclonal plasma cells in the interfollicular region.

The two clinical groups of CD are distinct conditions that have similar histology but different clinical features and responses to treatment. Localized CD of the hyaline-vascular type is usually asymptomatic while the multicentric type has an aggressive course. Most cases resemble the localized plasma cell type. The median age at diagnosis ranges between 15-45 years and there is no sex predilection.

Multicentric type is characterized by systemic symptoms, generalized lymphadenopathy, hepatosplenomegaly, proteinuria and skin rash. An interesting clinical observation is the association of multicentric CD with POEMS syndrome (Polyneuropathy, organomegaly, endocrinopathy, monoclonal protein and skin changes^[2]). Laboratory abnormalities include an elevated ESR, hypergamma-globulinaemia and anemia. The clinical course is variable, ranging from an indolent to an aggressive rapidly fatal illness, usually from infective complications, and less commonly, from malignancies such as lymphoma or Kaposi's sarcoma. The exact diagnosis must be made on a

basis of histological assessment. Although the etiology of CD is unknown, elevated cytokine levels (IL-1, IL-6 and TNF) are thought to be associated with and probably cause many of the clinical symptoms in this disease.

Interleukin-6 has an important role in the pathogenesis of CD^[3]. Polyclonal hypergammaglobulinemia is one of the characteristic features of CD and a possible relationship between immunoglobulin (IgG) production and IL-6 has been suggested^[4]. In one reported case, IgG 4 was markedly elevated while the serum IL-6 and C-reactive protein were low. In another case of CD with glomerulonephritis, serum IL-6 was increased. This discrepancy between the two patients may be attributable to the differences of the clinical types present.

Recently, increased VEGF in patients with CD has been reported. It has been hypothesized that VEGF may be involved in the marked vascular proliferation in the interfollicular space of the lymph node. The decline of serum VEGF level after surgery suggests the involvement of VEGF in the pathogenesis of CD^[5]. It has been suggested that IL-6 induce angiogenesis indirectly by inducing VEGF expression^[6]. Complete surgical resection is curative and remains the treatment of choice for localized disease. Recurrence is rare and has been associated with incomplete resection. Radiation therapy has shown beneficial outcomes in patients with unresectable lesions^[7].

The evaluation of various treatment regimens for the multicentric form of CD is complicated by the variable course of the disease. The results of treatment with high dose steroids have been variable and the treatment must be prolonged, particularly as it may recur after therapy is discontinued. Chemotherapy, on the other hand, seemed to induce a long time response in 27% of reported cases. Chemotherapy has included combinations used for lymphoma. All the patients who achieved a prolonged response are still alive while 39% of the total group receiving intermittent steroid therapy are still alive^[7]. Antibodies against IL-6 and interferon-alpha have transient success in multicentric disease^[8].

In summary, it is not possible to draw a definitive conclusion about therapy. A better understanding of the pathogenesis of this rare disorder may help determine the best therapeutic approach in the future. There have been less than ten cases of CD in the Kuwait Cancer Center (KCCC) since 1976. They were only of the localized type and, in two cases, the diagnosis was initially that of

Hodgkin's disease. This was changed to CD after a review in KCCC, which is a routine procedure. Unfortunately, we could not trace any of the files to give more information.

This case report raises the suspicion of familial cancer. No firm definition of cancer family is available and only empirical guidelines can be offered. There are sporadic reports of non-Hodgkin's lymphoma (NHL) occurring in blood relatives. Viral, environmental and genetic factors have been suggested to play a role in the etiology of NHL. Families with an increased incidence of both Hodgkin's disease and NHL have been described^[9]. Family data for children with NHL has been obtained and it was found that a small but non-significant excess of all tumors occurred in first-degree relatives with a small but non-significant excess of hematological malignancies, particularly Hodgkin's disease, leukemia and osteosarcoma^[10]. It is recommended that such cases be followed up, keeping in mind this remote possibility, either by a well-informed physician or by an oncologist.

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