

Case Report

Carbamezepine Induced Pseudolymphoma

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ABSTRACT

Aromatic anticonvulsants like phenytoin, carbamezepine, and phenobarbitone are rarely associated with a syndrome that mimics malignant lymphoma and is known as pseudolymphoma syndrome (PLS). A 20-year-old female after being started on carbamezepine for epilepsy for four weeks presented with two-week history of high grade fever with chills and rigors, a generalized itchy erythematous rash, lymphadenopathy, jaundice and hepato-splenomegaly. Her complete blood count (CBC) showed eosinophilia (17%) and liver function tests

(LFTs) showed marked elevation of transaminases and direct hyperbilirubinemia. Lymph node biopsy showed reactive hyperplasia. She improved dramatically after stopping her carbamezepine therapy and is doing fine on topiramate 400 mg orally twice daily. With a two year follow up, there was no recurrence of the reported symptoms. The differentiation of PLS from true lymphoma is very important as making a wrong diagnosis of malignant lymphoma in a patient with PLS can be catastrophic.

KEYWORDS: anticonvulsant therapy, lymphoma

INTRODUCTION

Pseudo lymphoma syndrome is a rare side effect of anticonvulsant therapy characterized by fever, skin rash and lymphadenopathy that mimics malignant lymphoma and mycosis fungoides. The condition is potentially life threatening and clinician awareness of this rare side effect of anticonvulsant therapy is important because early recognition and withdrawal of the offending agent most of the times results in dramatic and complete recovery, although death can occur with extensive skin involvement, liver failure or agranulocytosis.

CASE REPORT

A 20-year-old female patient presented with a two-week history of high grade fever with sweating, chills and rigors. Fever was associated with a generalized erythematous itchy rash all over her body. For the last one week she also noticed yellow discoloration of her eyes and skin with dark colored urine. She had been on carbamezepine therapy for tonic-clonic seizures for the past four weeks. There was history of joint pains in all the joints without redness or swelling and limitation of movement on examination. She had a temperature of 39 °C, a pulse rate of 110/min and was jaundiced, with bilateral submandibular, cervical and axillary lymph nodes 2-3 cm in size, firm, non-tender and mobile. There was an erythematous, maculopapular rash involving her face, trunk, back and limbs with

scratch marks over it. She had hepato-splenomegaly as well. Rest of her systemic examination was unremarkable. Her CBC and LFT results are summarized in Table 1 and 2 respectively. Her chest X-ray was normal. Serum carbamezepine level was 3.1 mg/ml and a throat swab showed no growth. Her IgM antibodies to cytomegalovirus (CMV), Epstein bar virus (EBV) and hepatitis A virus (HAV) were negative, hepatitis B surface antigen (Hb_sAg) and hepatitis C virus antibodies (HCVAb) were also negative. Monospot test and antinuclear antibodies (ANA) were negative. Abdominal ultrasound confirmed hepato-splenomegaly and no other intra-abdominal masses were detectable. Echocardiography was normal. Her lymph node biopsy showed reactive hyperplasia with no malignant cells. Bone marrow aspiration and biopsy was normal. Her carbamezepine was stopped and she was started on topiramate for her epilepsy. No systemic steroids were given. After two days, her fever subsided and by the 5th day the rashes started to fade out along with reduction in the size of lymph nodes. She was discharged home 10 days after admission in good health and was seen three months later in our outpatient clinic. There were no palpable lymph nodes, liver or spleen, her haematological indices and LFTs were also found to be normal. With a two-year follow up, there was no recurrence of the reported symptoms.

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Table 1: Complete blood count

	On admission	After 10 days	After 3 months
WBC (X10 ⁹ /l)	5.30	5.40	4.80
HB (gm/dl)	11	11.1	12
MCV (fl)	84.3	85	82.4
MCH (pg)	28.4	29.3	30
Platelets (X10 ⁹ /l)	286	425	350
N	41%	40%	50%
L	36%	44%	39%
EOS	17%	5%	4%
MONO	5%	11%	6%
ESR (mm/hr)	15	20	19

N: Neutrophils, L: Lymphocytes, EOS: Eosinophils, M: Monocytes

DISCUSSION

Carbamezepine is an aromatic anticonvulsant with tricyclic structure related to phenytoin, phenobarbital and primidone^[1]. Pseudolymphoma syndrome (PLS) is a rare side effect of carbamezepine therapy but is well known with phenytoin therapy as dilantin hypersensitivity syndrome^[2] or phenytoin syndrome^[3]. Patricia Tennis *et al*^[4], reported the risk of developing hypersensitivity syndrome with carbamezepine as 1 - 4.1 per 10,000 new users and 2.3 to 4.5 per 10,000 new users of phenytoin.

Some authorities suggested that we differentiate between anticonvulsant hypersensitivity syndrome and PLS on clinical ground but the differentiation seems to be arbitrary as there is considerable overlap in clinical presentation and histopathological findings for the two entities^[1,3]. Patients may present with fever (75-100%) which is usually high grade and swinging, skin rash (90%), facial edema (25-88%), lymphadenopathy (63-70%) which may be tender, hepatomegaly and hepatitis (25-60%), myalgia and arthralgia (21%), pharyngitis (10%)^[2,3]. Haematological abnormalities are protean and range from leucocytosis and leucopenia, agranulocytosis, lymphocytosis, atypical lymphocytes, blast cells, eosinophilia, monocytosis, pancytopenia, coagulation disorders to hypo and hypergamma-globulinemia. Our patient also showed eosinophilia of 17% in her initial CBC, which returned to normal within two weeks after withdrawal of the offending drug.

Hepatic injury is usually mild and most of the times patients recover within a few weeks after the cessation of causative agent. Failure to stop the causative drug early may lead to more severe hepatic injury^[2,3] and severe hepatitis is a poor prognostic sign. Death can occur due to liver failure. Our patient showed marked impairment of her liver function tests in the initial report in the form of predominantly direct hyperbilirubinemia, high alkaline phosphatase and transaminases, which started to improve after the cessation of the offending drug and returned to normal within three months.

Table 2: Serum biochemistry and LFTs

	On admission	After 10 days	After 3 months
Urea (mmol/l)	2.5	3.6	3.5
Creatinine (µmol/l)	41	46	43
Total bilirubin(µmol/l)	150	54	16
Direct bilirubin(µmol/l)	125	39	3
Total proteins (gm/l)	56	65	71
Albumin (gm/l)	25	29	32
Alk Phos (U/l)	980	756	150
ALT (U/l)	262	129	47
AST (U/l)	194	99	29
GGT (U/l)	539	453	47

Alk Phos: Alkaline Phosphatase, ALT: Alanine amino transferase, AST: Aspartate aminotransferase, GGT: Gamma glutamyl transferase

Lung involvement may occur in the form of pneumonitis^[1], bronchiolitis obliterans organizing pneumonia (BOOP)^[5], bronchial mucosal ulceration and desquamation^[6] which can be fatal. Serious disturbances in pulmonary diffusion capacity may be present even in the absence of changes on chest X-ray^[7].

Lymph node biopsy most of the times shows reactive hyperplasia (as in our patient) but features resembling malignant lymphoma may be seen such as destruction of nodal architecture^[8], atypical lymphocytes with CD3, CD20, CD30 positivity^[3,9,10] and large cells indistinguishable from Reed Sternberg cells^[11]. Cutaneous biopsies may show features resembling mycosis fungoides (MF) such as epidermotrophism of atypical lymphocytes and Partier's microabscesses. However, features favouring PLS over MF are the presence of marked spongiosis, necrotic keratinocytes and eosinophilic infiltrate in the epidermis, and in the dermis papillary dermal edema, extravasated erythrocytes, lymphocytes within the dermis larger than those in epidermis and infiltration of various inflammatory cells including neutrophils^[3]. T cell receptor- gene rearrangement studies may show monoclonal rearrangement in PLS caused by valproate but not in PLS caused by carbamezepine^[3,9].

The exact pathophysiology of PLS is not known. However, toxic metabolic theory proposed by Shear and Spielberg^[12] and Spielberg *et al*^[13,14] seems to be most appropriate. According to this theory aromatic anticonvulsants (carbamezepine, phenytoin and phenobarbital) are metabolized by cytochrome P450 to a toxic metabolite arene oxide, which is detoxified by the enzyme epoxide hydrolase. Deficiency of this enzyme leads to accumulation of arene oxide in the body that acts as haptens^[2,3,4]. This also explains the cross reactivity seen between aromatic anticonvulsants. Also the first degree relatives of the patients with PLS are at increased risk of developing the syndrome if exposed to aromatic anticonvulsant due to the deficiency of the

enzyme epoxide hydrolase. An autosomal pattern of inheritance has been suggested for this deficiency^[2]. But as PLS can be caused by valproate, which has a different structure and is not metabolized to arene oxide, it seems that other mechanisms may operate, of which T-cell dysregulation or dysfunction is one possibility.

Immediate management other than supportive measures includes cessation of the causative agent and this usually results in rapid recovery. Systemic corticosteroids are of no benefit, but patients with progressive disease despite cessation of causative agent may benefit from them. However, data supporting this, is lacking. For future control of epilepsy in these patient anticonvulsants with a different structure such as Lamotrigine, gabapentin and topiramate can be used.

CONCLUSIONS

PLS is a rare side effect of carbamazepine therapy for which early recognition and cessation of the causative agent is important as it results in dramatic and complete recovery. Death can occur in PLS due to extensive skin involvement, liver failure and agranulocytosis.

Once PLS occurs during the course of any anticonvulsant therapy, this will affect the future management of the underlying disorder for which the anticonvulsant was used, as there is cross reactivity between aromatic anticonvulsants and valproate. Lamotrigine, gabapentin and topiramate can be used in these patients. Aromatic anticonvulsants should be used with caution in first degree relatives of the patients with PLS as they are at higher risk of developing the syndrome.

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