ANGIOIMMUNOBLASTIC LYMPHADENOPATHY - A FULMINANT CASE

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ABSTRACT

A 60 year old male presented with pruritus, excoriations and enlargement of several groups of lymph nodes associated with constitutional symptoms following the intake of an aspirin preparation. Lymph node biopsy established the diagnosis of angioimmunoblastic lymphadenopathy. The need to be aware of this condition is highlighted when patients present with clinical features suspicious of lymphoma.

Keywords: Drug rash, angioimmunoblastic lymphadenopathy, immunoblasts, lympho-histiocytic infiltrate.

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INTRODUCTION

Angioimmunoblastic lymphadenopathy (AIL) is a rare, non-neoplastic systemic disease representing an extreme form of hypersensitivity reaction. It is a well recognised clinicopathologic entity characterized by rapid onset of fever, weight loss, generalised lymphadenopathy, hepatosplenomegaly, skin rashes, polyclonal hypergamma globulinaemia, Coombs-positive haemolytic anaemia as a consequence of persistent hyperproliferation of B lymphocytes and perhaps a profound deficiency of suppressor T cells. AIL can be precipitated by chronic antigenic stimulation possibly by drugs in some patients, such as aspirin, phenytoin, penicillin, halothane, methyldopa and allopurinol. It was first described by Frizzera et al[1] and subsequently by Luke and Tindle[2]; most of the original descriptions were confirmed by later workers[3,4]. Although the clinical course of the disease is 'stormy' or 'malignant' in most patients, the histopathologic features are that of an abnormal immune proliferation. Though the skin, bone marrow, liver, spleen, colon and lung are involved, the lesions seen in the lymph nodes are distinctive and diagnostic[3,5]. Prior to its recognition, AIL was misdiagnosed as lymphoma due to the aggressive course and in some cases due to the infiltration of node capsule and perinodal fat - features regarded as criteria for malignancy. Frequently, it was mistaken for Hodgkin's disease since occasional immunoblasts appeared multinucleated and resembled Reed-Sternberg cells. Dermatologists often manage patients with drug reaction and awareness of this unusual disorder will lead to increased recognition. However, a lymph node biopsy is absolutely warranted in suspected cases.

CASE REPORT

A 60 year old Malay man presented with fever and skin rashes of 3 weeks duration associated with swellings of the neck and groin. He had taken a headache powder containing 477 mg of acetylsalicyclic acid; within few hours he developed maculopapular rash, intense pruritus and fever. There was no history of asthma, diabetes mellitus or hypertension. His blood pressure was 120/80 mm and the temperature 38.5°C. The skin was dry and there was extensive excoriations involving the trunk and limbs with mild erythematous rash on the chest and back. There was generalised lymph node enlargement involving the cervical, occipital, submental, axillary and inguinal groups which were painless and non-tender; most of the nodes were about 3 to 4 cm in size, firm, discrete and moveable but a few were matted. Liver was enlarged 7 cm from the right costal margin, smooth, firm and non-tender. Clinical features of generalised lymphadenopathy, hepatomegaly in the presence of constitutional symptoms including fever, weight loss and pruritus were suggestive of lymphoma. Investigations showed a marked increase in the eosinophils, 31% with 8% atypical lymphocytes; the ESR was 110mm and alkaline phosphatase 79 Iu/L (normal 15 - 50 Iu/L). Other relevant investigations were normal or negative. Serum protein electrophoresis was not done. Skin biopsy showed dermal perivascular infiltrate composed of lymphocytes, plasma cells, neutrophils and eosinophils.While awaiting the lymph node biopsy report, patient was given prednisolone for the initial possibility of drug reaction. He continued to be febrile and against our advice, he was taken home, where he died of lung infection. A lymph node biopsy showed features of AIL with loss of architecture, moderate proliferation of small blood vessels (Fig 1, 2), proliferation of immunoblasts, plasmacytoid lymphocytes, plasma cells (Fig 3) and few atypical histiocytes.

Fig 1. - Lymph Node in AIL : Effacement of Nodal Architecture and Authorizing Blood Vessels (H & E x 40).

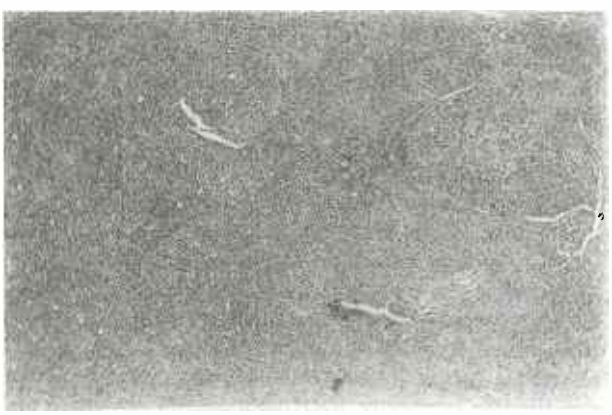

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Fig 2. - Pleomorphic Cellular Infiltrate and Dilated Blood Vessels (H & E x 100).

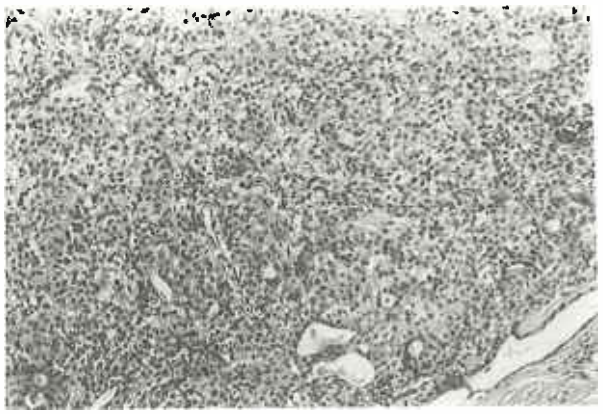
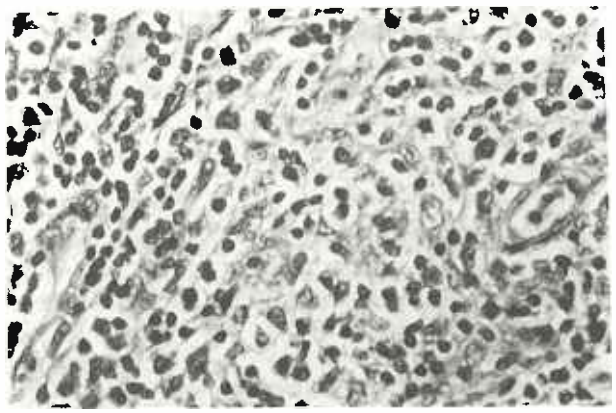


Fig 3. - Cellular Infiltrate—Predominantly Immunoblasts, Lymphocytes and Plasma Cell (H & E x 400).



DISCUSSION

In 1974, Frizzera et al reported 15 patients aged 48 to 80; twelve of them were more than 60 years who presented with acute onset of constitutional symptoms, generalised lymphadenopathy with characteristic histologic features. One-third of them were controlled with immunosuppressants. Subsequently Lukes and Tindle reported 32 patients with similar symptoms but noted malignant changes in the cellular proliferation in three into immunoblastic sarcoma. The histopathologic triad of an involved lymph node are:

1. Effacement or loss of nodal architecture by a pleomorphic cellular infiltrate ranging from small and large lymphocytes, immunoblasts, plasma cells and also histiocytes and eosinophils.
2. Profound branching network of arborizing small blood vessels mainly post-capillary venules showing endothelial hyperplasia.
3. Interstitial deposition of granular, acidophilic material representing cellular debris resulting from high rate of cell death.

These features were more in favour of an abnormal immune response than of a malignant disease. However, in 1978 Nathwani et al[6] reviewed 84 patients; 48 of them had angioimmunoblastic lymphadenopathy with dysproteinaemia (AILD) and 36 AILD with immunoblastic lymphoma (AILD + IL) and highlighted their observation of malignant transformation of AILD into IL in 35% or eight of the 23 patients with AILD. They proposed histologic criteria for recognizing the evolution of IL in a lymph node with features of AILD such as the presence of transformed large lymphoid cells compactly arranged in multiple clusters or in islands which, as the disease advances become confluent and form diffuse monomorphic, neoplastic, cellular proliferation which completely replaced the lymph node. Unusual histologic findings were the intravascular localization of these cells and areas of cells with clear cytoplasm.

Japanese investigators found not only an abnormal polyclonal B-cell activation but in some cases a definite T-cell nature of proliferating cells in the lymph nodes in the form of clear or convoluted cells. They considered these cells neoplastic in nature, proposed the term immunoblastic lymphadenopathy (IBL)-like T-cell lympoma, suggested that clear cells appeared to be specific for T cell lymphoma and reported the prognosis of the patients according to clear and or convoluted cells — presence showing poor and absence favourable prognosis[7]. Histologically, the prominent cell in a lymph node is the immunoblast — an antigenically stimulated lymphocyte; a large cytoplasmic cell containing relatively a large and oval nucleus with prominent nuclear membrane, distinct nucleoli and clumped chromatin.

Skin, an important structure which gives clues to internal disorders, is involved in 40% of the cases with AIL and 80% of those with associated skin lesions had previous drug intake[8] although the cause and pathogenesis of this disorder are not well understood. Whilst lymph node and visceral organs have been extensively investigated, skin findings in AIL have not been studied adequately. In AIL, skin can be involved months before or coincide with the generalized lymphadenopathy[9]. It should be emphasized that unlike the lymph nodes, the histologic features of skin lesions in AIL are not pathognomonic and the morphology of the lesions are non-specific. Pruritus is a very prominent symptom and our patient, although had maculopapular rash at the onset, presented with extensive excoriations as a result of severe scratching and was unresponsive to antihistamines. Other cutaneous lesions found in AIL are ulcerations, purpura, plaques and nodules[8]. In one study[9] the histology of the skin lesion, when specifically looked for, showed perivascular lymphohistiocytic infiltrate with vessel proliferation and destruction, fibrin deposition, extravasation of RBC and scattered plasma cells but no leococytoclastic vasculitis. The histologic differential diagnosis that should be included are allergic granulomatosis, lymphomatoid granulomatosis and Wegener's granulomatosis.

The course of AIL is unpredictable but ultimately fatal in 50% of cases within one to 20 months. Prednisolone and other immunosuppressants are the mainstay in the management but the response is variable. In the reported patient there was no evidence of malignant transformation of the lymph node into IL. We would like to stress that physicians managing patients with drug-induced eruption of prolonged duration associated with systemic symptoms and generalized lymphadenopathy, should immediately proceed with a lymph node biopsy for confirmation of AIL when, in addition, a skin biopsy shows features of lymphohistiocytic vasculitis, vascular proliferation and extravasation of RBCs.

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