Unusual Presentation Of Angioimmunoblastic T-Cell Lymphoma As A Solitary Lymph Node: A Case Report And Review Of Literature.

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INTRODUCTION: Angioimmunoblastic T cell lymphoma [AITL] is an aggressive subtype of Peripheral T cell lymphoma [PTCL] characterized by systemic disease. It is a rare subtype of Non-Hodgkins lymphomas. However it forms a major subset of peripheral T cell lymphomas. Lymph node is the primary site of disease and virtually all patients present with generalized Lymphadenopathy. CASE REPORT: A 42 year old male presented with fever of short duration and a solitary axillary lymph node swelling on the right side. Systemic examination revealed moderate ascites and hepato-spleenomegaly. Haematological investigations revealed pancytopenia and abnormal liver function test. Axillary lymph node showed histological features suggesting AITL and was confirmed by a panel of immunohistochemistry [IHC]. CONCLUSION: AITL presenting as solitary axillary lymph node enlargement is unusual. Such atypical presentation mandates careful clinical and laboratory evaluation. IHC is an effective ancillary tool for confirmation of diagnosis of this distinct clinicopathological entity.

INTRODUCTION

Angioimmunoblastic T-cell lymphoma [AITL] is a Peripheral T cell Lymphoma [PTCL] characterized by systemic disease, a polymorphous infiltrate involving lymph nodes with a prominent proliferation of endothelial venules and follicular dendritic cells [FDC]. Spleen, liver, skin and bone marrow are also frequently involved. Though it is one of the more common specific subtypes of peripheral T cell lymphoma, accounting for approximately 20% of cases, it constitutes only 1-2% of all Non-Hodgkins lymphoma. It occurs in the middle aged and elderly with an equal incidence in males and females. Originally described in 1974 as “immunoblastic lymphadenopathy” by Rappaport and Lukes, AITL is recognized in the current World Health Organization [WHO] classification as a peripheral T-cell lymphoma [PTCL] with distinct clinicopathologic features. The postulated normal counterpart is CD4+ follicular helper T cell [TFH]. This subset of T cell is located at the boundary between the mantle zone and germinal center light zone and is supposed to provide help to germinal center B cells during their terminal differentiation. The patients present with generalized Lymphadenopathy [up to 90%], hepato-spleenomegaly [50-79%], Cutaneous rash [50%], hypergammaglobulinaemia [50%], pleural effusion [37%], and autoimmune phenomena [20%]. The laboratory findings include circulating immune complexes, cold agglutinins with haemolytic anaemia, positive rheumatoid factor and anti-smooth muscle antibodies. EBV-positive cells are nearly always present. Characteristically, the neoplastic cells show phenotype of normal TFH expressing CD10, CXCL13 and PD-1 in 60-100% of cases. Cytogenetic and molecular studies have consistently shown clonal chromosomal abnormalities and monoclonal or oligoclonal T-cell populations in most cases, which strongly supports a T-cell neoplasm. Patients with AITL have a poor prognosis with conventional treatment, with a median overall survival of less than 3 years. Patients achieving a good clinical response seem to benefit from a consolidation with high-dose therapy and autologous stem cell transplantation.

CASE REPORT

A 42 year old male presented with fever of four days duration and easy fatigability. General physical examination revealed a solitary lymph node in the right axilla measuring 4x2.5x2 cm. No other lymph nodes were enlarged. Abdominal examination revealed moderate ascites,
hepatomegaly and massive splenomegaly. Blood investigations were done. Haemoglobin was decreased [5.4gms/dl], leukocyte count was reduced [2300 cell/cumm] and platelet count was reduced [62,000/cumm]. Peripheral smear also suggested pancytopenia. Coombs test was negative. Bone marrow examination did not reveal any pathological findings. HIV was negative and HBsAg was non-reactive. Biochemical investigations showed increased levels of postprandial glucose [150mg/dl], total proteins [11gms/dl], alkaline phosphatase [207U/L] and LDH [693U/L]. Serum Albumin was reduced [3.3gms/dl]. Ultrasonography of abdomen showed moderate ascites mild hepatomegaly and massive splenomegaly. Considering these features the present case corresponds to Ann Arbor stage III ES, International prognostic index [IPI] score of four and prognostic index for PTCL/Unspecified [PIT] score of two.

The axillary node was excised and sent for histopathological examination. Grossly the lymph node measured 3.5x2.5x1.5cm. Cut section showed homogeneous grey white appearance. Sections from the lymph node showed effacement of architecture and follicular depletion [Fig 1].

**Figure 1**
Fig.1. Photomicrograph of tissue section showing effacement of lymph node architecture [H&E, x40].

Prominent arborising post capillary venules lined by plump endothelial cells were seen. [Fig.2]. Clusters of tumour cells having vesicular nuclei and prominent nucleoli, showed vaguely convoluted borders, clear to pale cytoplasm and mitotic figures [Fig.3]. Mature lymphocytes, plasma cells, histiocytes and significant number of eosinophils were also seen in the background of patchy hyaline material. [Fig.4].

**Figure 2**
Fig.2. Photomicrograph of lymph node section showing post capillary venules lined by plump endothelial cells [arrows] [H&E, x400].

**Figure 3**
Fig.3. Photomicrograph of lymph node section showing tumor cells having convoluted nuclear borders and prominent nucleoli and good number of mitotic figures [arrows] [H&E, x400].
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Figure 4
Fig.4. Photomicrograph of lymph node section showing background of reactive lymphocytes, eosinophils, plasma cells and histiocytes [H&E, x400].

Immunohistochemistry (IHC) was performed which showed neoplastic cells as diffusely distributed CD3 positive cells [Fig.5] and CD10 positive cells [Fig.6]. CD30 positive cells were scattered and comparatively scant [Fig 7]. Residual reactive B lymphocytes were CD20 positive [Fig.8]. These findings confirmed the histological diagnosis of AITL.

Figure 5
Fig.5. Photomicrograph of lymph node section showing diffuse immunopositivity for CD3 neoplastic cells [IHC, x400].

Figure 6
Fig.6. Photomicrograph of lymph node section showing diffuse immunopositivity for CD10 neoplastic cells [IHC, x200].

Figure 7
Fig.7. Photomicrograph of lymph node section showing scattered immunopositivity for CD30 neoplastic cells [IHC, x400].
DISCUSSION

Angioimmunoblastic T-cell lymphoma [AITL] is a rare and complex lympho-proliferative disorder, clinically characterized by widespread lymphadenopathy, extranodal disease, immune-mediated haemolysis, and polyclonal hyper gammaglobulinemia. It represents a distinct clinicopathological entity among nodal peripheral T-cell lymphomas. AITL is a systemic disease involving lymph nodes, spleen, and bone marrow. AITL was first described by Ree et al who reported progression of two such cases into typical AITL. It is an aggressive peripheral T-cell lymphoma whose natural history is poorly understood.

Mourad et al recorded the median age of 62yrs while Cho et al recorded the median age of 58.5 yrs in their studies. AITL occurs in middle aged and elderly with an equal incidence in males and females. M Rodriguez-Justo et al and Attygalle et al observed occurrence of AITL in middle aged and elderly with male preponderance. Lymph node is the primary site of disease and virtually all patients present with generalized lymphadenopathy. Cho et al recorded generalized lymphadenopathy as commonest presentation [91%] in their study. In contrast, the middle aged patient in the present case presented with solitary right axillary lymph node. Lymph node enlargement was accompanied by an episode of fever and easy fatigability. M Rodriguez-Justo et al observed organomegaly [hepatomegaly or spleenomegaly] in 33% of cases. Attygalle et al and Cho et al also observed hepatosplenomegaly in their studies. Mourad et al observed pleural effusion or ascities or edema in 16% of cases in their study. Even in the present case, the patient had hepato-splenomegaly, deranged liver function and ascities. Most of the cases present at an advanced stage [III-IV].

Peripheral blood picture suggested pancytopenia. However, bone marrow did not show tumor infiltration and coombs test was negative. Thirty three percent of cases had haemolytic autoimmune anaemia in a study conducted by M Rodriguez-Justo et al. Mourad et al recorded anaemia in 65% of cases and positive coombs test in 33% of cases. M Rodriguez-Justo et al and Cho et al observed bone marrow involvement in 22% cases and 70% cases in their studies. Mourad et al observed bone marrow involvement in 38% of anaemic patients. Serum LDH level was elevated in the present case. Similar elevations of serum LDH were noted in studies conducted by Mourad et al and Cho et al.

Mourad et al considered 5 criteria for histological diagnosis: partial or diffuse effacement of the nodal architecture, vascular proliferation with prominent arborisation of high endothelial venules, extrafollicular meshwork of FDCs, atypical population of CD3+ T cells, and large CD20+ B cells. Similar criteria were considered in the present case. But CD20+ B cells were present as reactive residual component of the lesion. The constellation of microscopic features of this case corresponded with pattern II of AITL described by Attygalle et al. In the present case, neoplastic cells were diffusely positive for CD3 and CD10. CD30+ cells showed scattered positivity and were comparatively scant. CD20+ cells represented reactive residual B cells. Mourad et al observed that neoplastic cells were CD3 in 100% cases and CD10 in 71% cases in their study. Cho et al noted that CD3 and CD5 were strongly positive and aberrant expression of CD10 was observed in 65% of cases. Attygalle et al observed that CD10 was positive in tumour cells in 90% of AITL. In contrast, M Rodriguez-Justo et al observed that only small proportion of neoplastic cells [5-10%] expressed CD10. CD30 staining was done in only three cases and was positive in all the three cases.

The aetiology and pathogenesis of AITL are unknown. In a high percentage of cases the diagnosis is preceded by allergic reactions, infections and/or exposure to drugs, particularly antibiotics. Ebstein Barr Virus [EBV] and Human Herpes Virus [HHV6 and HHV8] may play a role in pathogenesis of AITL and this might explain its response to anti-viral therapy with valacyclovir. Although it has not been thoroughly investigated, it was suggested that the increase in T-cell immunoblasts would indicate...
transformation into a PTCL. An increase in EBV infected B cells may also occur and in rare cases, an overt diffuse large B-cell lymphoma develops. The physiologic role of CD10 is thought to involve hydrolysis of polypeptides such as inflammatory mediators in the extracellular milieu. Expression of CD10 may regulate apoptosis by interfering with negative or positive signals present in the extracellular environment. It is possible that aberrant CD10 expression in neoplastic T cells in AITL may be an indicator of disturbed apoptotic cell death. Interestingly it has been suggested that production of interleukin-21 by Follicular helper T cell is responsible for B-cell activation and hypergammaglobulinemia seen in AITL. It has been recently shown that CXCL13, a chemokine critically involved in B-cell migration into germinal centers, was highly up-regulated in the TFH subset. It was hypothesized that the clinical effects of AITL are due to marked dysregulation of the immune system rather to direct complications of tumor growth. Peculiar histologic features of AITL where tumor cells are greatly outnumbered by the surrounding reactive cells and found in intimate contact with the expanding meshwork of FDCs. Hence AITL can be considered as an immunologically functional disease in which the clinical behaviour is determined by the resultant cross talk between the malignant cells and the immunologic microenvironment. T-cell receptor genes show clonal rearrangement in 75-90% of cases. Clonal immunoglobulin gene rearrangement may be found in 25-30% cases. Trisomy 3 and 5 and an additional X chromosome are the most frequent cytogenetic abnormalities detected in AITL.

CONCLUSION
Solitary axillary lymph node enlargement is an unusual presentation of AITL. In view of such atypical presentation and taking into consideration the aggressive nature of this distinct clinicopathological entity, careful clinical and laboratory evaluation is necessary. Immunophenotyping serves as an effective auxiliary weapon for the confirmation of diagnosis.

References
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