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Angioimmunoblastic T Cell Lymphoma Mimicing Tuberculosis: A Rare Case Report

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Abstract

A 54 year old female diagnosed with sputum smear negative tuberculosis and on antitubercular therapy for one month presented with on and off fever,generalised weaknesss,cough with expectoration and itching and rashes of whole body. Patient had pallor , significant right cervical lymphadenopathy. On auscultation patient had bilateral diffuse coarse crepitation. CECT thorax was suggestive of bilateral patchy consolidation and and nodular opacities with Mediastinal lymphadenopathy. There was clinicoradiological detoriation. CECT abdomen suggestive of abdominal lymphadenopathy. FNAC of lymphnode was non conclusive and on lymph node biopsy followed by H&E staining and IHC revealed Angioimmunoblastic lymphoma.

Case Report

A 54 year old female diagnosed as sputum smear negative tuberculosis and on Antitubercular therapy for one month presented with on and off fever,generalised weaknesss, cough with expectoration and itching and rashes of whole body , loss of weight and decreased appetite.

Fever was low grade intermittent in nature and not associated with chills , rigor , vomiting , or altered sensorium. Cough was productive with whitish expectoration not associated with haemoptysis, shortness of breath or any diurnal variation.

Patient had no significant past history, family history. patient was non smoker non alcoholic and addicted to tobacco chewing. Patient was married and had two children .Normal bowl and bladder habit. .

Patient Patient had pallor , significant right cervical lymphadenopathy of size 1*1 cm which was firm ,non tender, freely mobile and skin over the gland was normal .No other lymphnodes were palpable .On auscultation patient had bilateral diffuse coarse crepitation.

On investigation patient had Hb -7.9 gm% , Platelet - 73000/cc ,ESR – 150mm/Ist hr , serum protein – 7.0 , serum albumin – 2.7 , serum LDH – 384.peripheral smear suggestive of normocytic normochromic anaemia with clumped RBC , Leukopenia , Thrombocytopenia – Immune hamolysis. DCT was positive. CRP and ANA were positive .

There was clinicoradiological detoriation.(fig 1 & 2). CECT thorax (fig 3)was suggestive of bilateral patchy consolidation and and nodular opacities with Mediastinal lymphadenopathy. CECT abdomen suggestive of abdominal lymphadenopathy .

Bronchoscopy was done and in BAL culture and sensitivity there was growth of Klebsiella species sensitive to Amikacin and colistin.

FNAC of lymphnode showed immature an mature lymphoid cells with areas of fibrosis and occasional areas of necrosis and on lymph node biopsy followed by H&E staining and IHC revealed Angioimmunoblastic lymphoma.

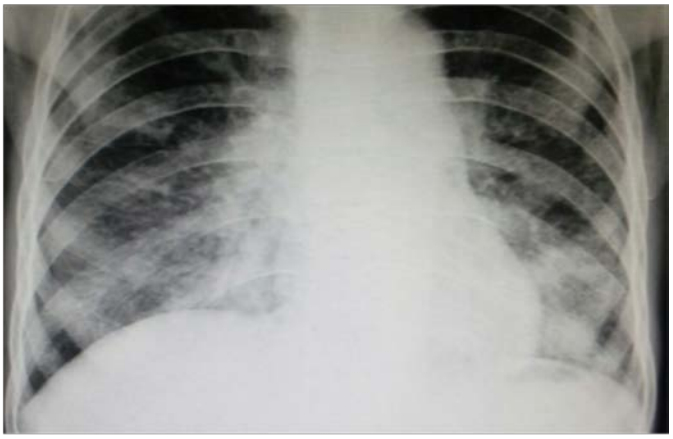

Fig. 1: B/L MID and Lower Zone Reticulonodular Opacities

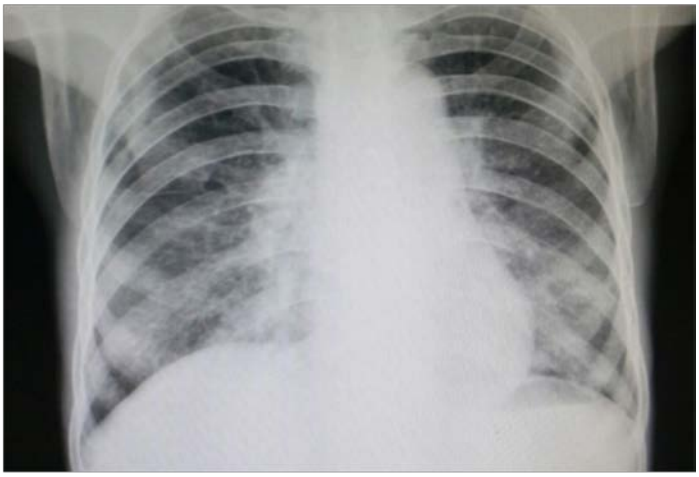

Fig 2: B/L Reticulonodular Opacities In All Zones

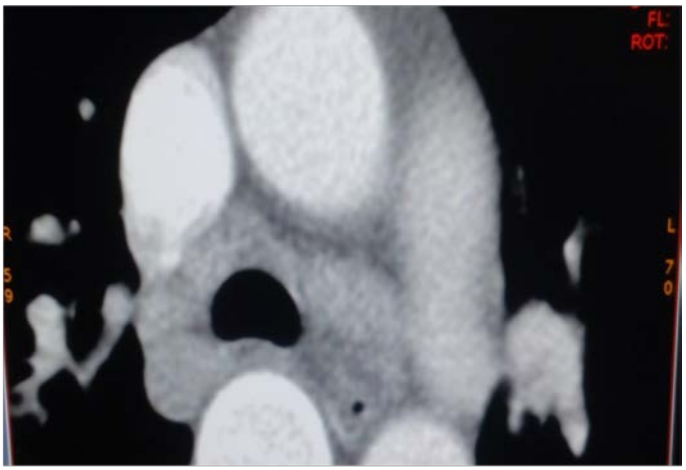

Fig 3: CECT Thorax Showing Mediastinal Lymphadenopathy

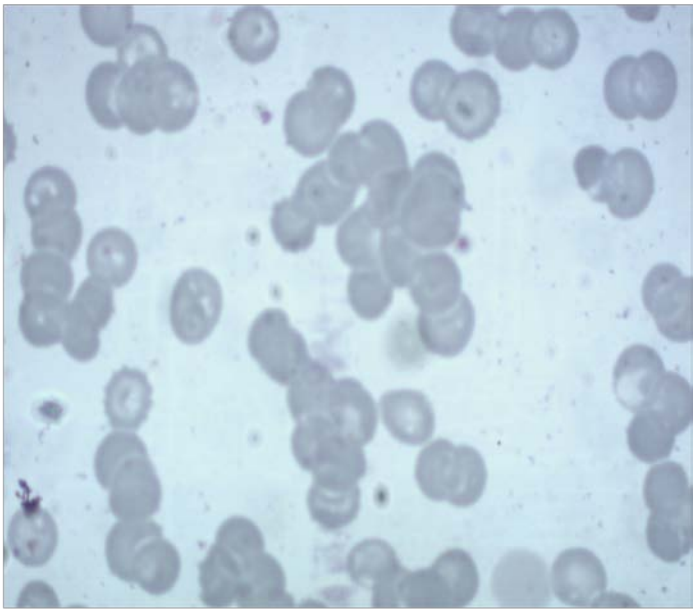

Fig 4: Peripheral Smear Showing Rbc Lumps Indicative of Immune Mediated Haemolysis

Discussion

Angioimmunoblastic T cell lymphoma is a rare and rapid growing form of T cell lymphoma. [1] AITL is characterized by malignant transformation of T cell [2] and one of the unique feature of AITL is dysfunction of immune system [2]. AITL is classified under nodal T-cell lymphomas with follicular T helper phenotype [3].AITL and follicular helper subtype of PTCL (PTCL -FH)have many biological features in common hence grouped together for treatment purposes [1.]

Classification [10]

Mature T-cell Leukaemias

1. T-Prolymphocytic Leukaemia (T-PLL)
2. T-Large Granular Lymphocytic Leukaemia (T-LGL)
3. Chronic Lymphoproliferative disease of NK cells (CLPD-NK)
4. Aggressive NK-cell Leukaemia
5. Adult T-cell Leukaemia lymphoma (ATL) II.

Nodal PTCL

1. Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS)

2. Angio-immunoblastic T cell lymphoma
3. Anaplastic Large cell lymphoma- ALCL III.

Extranodal PTCL

1. Extranodal NK/T-cell lymphoma, nasal type
2. Enteropathy-Associated T-cell lymphoma (EATL)
3. Hepatosplenic T-cell lymphoma
4. Subcutaneous panniculitis-like T-cell lymphoma SPTCL

Epidemiology

AITL represents only 1% to 2% of all cases non-Hodgkin lymphoma (NHL), but nearly 1 in 5 cases of PTCL diagnosed per annum.[4] [5] AITL commonly affects advanced-age individuals with a median age of diagnosis of 65 years of age with no significant gender predisposition.[6] [7]

Causes [2]

AITL is believed to be caused due to a dysfunctional immune response to an unknown antigen .No specific risk factors have been confirmed to be associated with AITL.Suspected risk factors viruses including the Epstein-Barr virus, cytomegalovirus, hepatitis C virus, human herpes viruses 6 and 8, and the human immunodeficiency virus. Tuberculosis and Cryptococcus have also been linked to AITL.

The Epstein-Barr virus has been found in more than 90 percent of individuals with AITL. EBV positive B cells are found very early in the disease process and researchers suggest that the virus may play a more important role in causing AITL. VEGF -A is also been found to play a critical role in development of AITL.

Signs and symptoms[8]

Palpable lymphadenopathy is the most common sign . Hepatomegaly and splenomegaly are also very common. The majority of patients have “B” symptoms including fevers, night sweats, and/or unintentional weight loss.

AITL is usually associated with morbilliform cutaneous eruption on the trunk ,though a more diffuse, pruritic, maculopapular rash can occur. Evidence of cutaneous involvement is rarely established by skin biopsy. Other well described but less common signs and symptoms include polyarticular arthritis, pleural effusion, and ascites.

Angioimmunoblastic T cell lymphoma with dysproteinemia (AILD) syndrome is characterized by AITL with any of the following:

- polyclonal hypergammaglobulinemia,
- a positive direct antiglobulin (Coombs’) test,
- plasmacytosis in the peripheral blood.

Various autoimmune diseases such as vasculitis, hypo or hyperthyroidism, arthritis with or without a detectable rheumatoid factor, immune thrombocytopenic purpura, and hemolytic anemia are commonly described. In addition to a positive Coombs’ test, patients may also have cold agglutinins or cryoglobulinemia with or without rash and anemia. Peripheral neuropathy can occur, even without direct neurologic involvement. Patients may develop a sensory neuropathy or a motor neuropathy similar to chronic inflammatory demyelinating polyneuropathy. Uveitis may rarely occur.

Pathology

Microscopic (histologic) description

- **Lymph nodes**
  - Partial effacement of lymphonodular architecture, often with perinodal infiltration but with preservation of subcapsular and trabecular sinuses
  - Prominent arborizing high endothelial venules with thickened, hyalinized PAS+ walls surrounded by CD21+ follicular dendritic cells and irregular homogenous eosinophilic material

- Burnt out germinal centers with increased follicular dendritic cell meshworks (mediated through expression of CXCL13 by neoplastic follicular helper T cells)
- Predominantly paracortical aggregates of polymorphic small to medium sized cells with clear / pale cytoplasm, distinct cell membranes and minimal cytologic atypia
- Small clusters of neoplastic cells around follicles and high endothelial venules, variable numbers of small reactive lymphocytes, eosinophils, plasma cells, histiocytes
- Paracortical expansion of B immunoblasts linked to the functional properties of neoplastic follicular helper T cells
- Three different histologic patterns described, I - III, with increasing degrees of architectural effacement, commonly coexisting in the same specimen, arbitrary cutoffs

- **Bone marrow**
  - Focal or diffuse marrow involvement
  - Focal lesions have indistinct margins
  - Contain polymorphous infiltrate of lymphocytes, immunoblasts, plasma cells, histiocytes, eosinophils and neutrophils
  - Often vascular proliferation with prominent endothelial cells and fibroblasts
  - Perivascular clustering of neoplastic clear cells in 41%
  - Variable epithelioid histiocytes
  - Usually no amorphous PAS+ material (found in nodal lesions)
  - Uninvolved marrow may be hypercellular
- **Peripheral blood**
  - Reactive lymphocytes, immunoblasts, immunocytes, increased eosinophils, various cytopenias, rouleaux
  - May also see circulating lymphoma cells
- **Skin**
  - Subtle infiltrate with nonspecific mild perivascular accumulation of lymphocytes; overtly lymphomatous infiltration uncommon
  - Eosinophils, vascular proliferation and large immunoblasts not obvious
  - Rare EBV+ cells 10 (Gorczyca: Atlas of Differential Diagnosis in Neoplastic Hematopathology, Third Edition, 2014)

Positive stains

- **Lymph nodes**
  - Pan T cell antigens: CD2, CD3, CD5 and CD7 with frequent aberrant loss of one or more of these antigens
  - T helper cell marker: CD4
  - Follicular T helper cell markers: CD10, BCL6, CXCL13 (more specific), PD-1 (CD279), ICOS
  - Follicular dendritic cell networks: CD21, CD23, CD35, CNA.42 or clusterin
  - Scattered B cells: EBV+ 11 (Miranda: Atlas of Lymph Node Pathology (Atlas of Anatomic Pathology), 2013 Edition, 2013)
- **Bone marrow**
  - Uncommon expression of CD10 (25%)
  - Lack of CXCL13 expression
  - PD-1 in 85%
  - BCL6 / CD3 dual staining 12 (Hum Pathol 2010;1:79)

Negative stains

- CD8, CD56, pan B cell markers, immunoglobulins, cytotoxic antigens, CD1a, CD99, TdT

Diagnosis [2]

Biopsy of an affected lymph node or other affected areas such as the skin or bone marrow is mandatory to establish the diagnosis.

Testing for clonal T cell receptor rearrangement can be helpful [9.] Additional diagnostic tests may be recommended to assess the extent of AITL , which includes : [2]

- elevated lactic acid dehydrogenase (LDH) level
- elevated beta-2 microglobulin
- elevated erythrocyte sedimentation rate
- lymphopenia
- anemia
- thrombocytopenia
- hypoalbuminemia
- Hypereosinophilia .

Staging should include blood and bone marrow examination and radiology as well as assessment of performance status and prognostic factors to allow assignment of a prognostic score and planning of therapy [10]

Treatment [10]

Rarely, AITLmostly follows an aggressive course and very rarely resolves spontaneously. Combination chemotherapy may be required . There have been reports of both single agent and combination chemotherapeutic regimens, such as CHOP, CVP (cyclophosphamide, vincristine, prednisone), VAP (vincristine, asparaginase, prednisone), steroids with or without cyclophosphamide, high-dose methylprednisolone, prednisone with or without COPBLAM . Although a complete remission rate of 50% can be achieved with combination chemotherapy, relapse rates remain high. Overall, combination chemotherapy appears to be superior to steroids alone (Pautier et al, 1999). Other therapeutic approaches include low-dose methotrexate together with steroids (Gerlando et al, 2000), fludarabine (Ong et al, 1996; Hast et al, 1999; Tsatalas et al, 2001) and cladribine (Sallah et al.,1999). Gemcitabine (Sallah et al, 2001) can be beneficial, but again studies are based on a small number of patients, which does not allow statistically significant conclusions. Interferon-alpha has been used for consolidation–maintenance therapy following conventional treatment to prolong chemotherapy-induced remissions by its differentiating, immunomodulating and antiproliferative effects (Feremans & Khodadadi, 1987; Hast & Gustafsson, 1991; Schwarzmeier et al, 1991; Siegert et al, 1991; Pautier et al, 1999). Ciclosporin has also been given (Murayama et al, 1992; Advani et al, 2007; Takemori et al, 1999). Thalidomide has been used as an anti-angiogenic agent in a few patients, either following relapse or in refractory AITL, with promising results (Strupp et al, 2002, Dogan et al, 2005). Lenalidomide has also shown activity and there is a current trial in France evaluating CHOP+lenalidomide in AITL (REVAIL). Recently, it has been demonstrated that VEGF-A is expressed on both lymphoma cells and endothelial cells in AILT and that increased levels of VEGF-A were related to extranodal involvement and short survival time (Foss et al. 1997, Zhao et al, 2004). In a single case report complete remission was observed in a patient with AILT following bevacizumab (Bruns et al., 2005). Phase II trials are in progress, including a study of CHOP + bevacizumab. Monoclonal antibodies are being investigated in combination with chemotherapy. Case reports and small trials have shown responses to alemtuzumab (36% ORR), (Halene et al, .2006) diphtheria toxin fusion protein (denileukin difitox, ORR 50%) (Talpur et al., 2002a ; Foss et al., 2008) and to antibodies directed against CD2 or CD4; (Hagberg et al., 2005).

Many cases of AITL have a substantial infiltrate of CD20+ B-cells, providing a rationale for use of rituximab. Rituximab has being investigated in combination with CHOP chemotherapy by the GELA group (Joly et al, 2004). In 25 patients the 2 year PFS was 43% and OS 62% which was not thought to be superior to CHOP alone.

Prognostic factors[9]

- Five year overall and failure free survivals were 33% and 18%, respectively
- Poor prognostic factors: age > 60 years, performance status ≥ 2, extranodal sites > 1, B symptoms, platelet count < 150×10^9/L.
- Other prognostic factors: anemia, elevated white blood cell count and IgA levels.

Summary

In this case the patient had symptoms of itching , rashes , fever and weight loss. Patient had cervical lymphadenopathy. Investigations revealed pancytopenia ,autoimmune haemolysis , positive DCT ,raised ESR,serum protein and LDH but had decreased albumin . CRP and ANA were positive. Chest X ray showed bilateral reticulonodular shadows. In CT thorax there were random nodular opacities ,patchy airspace consolidation and mediastinal lymphadenopathy. abdominal lymphadenopathy was found on CECT abdomen .Diagnosis was established by lymphnode biopsy.

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