CASE REPORT

Angioimmunoblastic T-cell Lymphoma (AITL): A Rare Entity, Commonly Misdiagnosed

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ABSTRACT

Angioimmunoblastic T-cell lymphoma (AITL) presents a wide range of clinical and histopathological features, often resembling various reactive and neoplastic diseases. This similarity poses a challenge in making a definitive diagnosis in many cases. Distinguishing the neoplastic T cells can be particularly difficult since they typically constitute a small proportion of the overall cellular infiltration. The tumour and inflammatory cells exhibit polymorphism and variable proportions. Additionally, the concurrent proliferation of B cells can mimic both reactive and neoplastic conditions. Furthermore, the atypical B cells may resemble Reed-Sternberg cells and show positivity for CD30 and CD15, often leading to misdiagnosis as classical Hodgkin lymphoma. In this case report, we present the case of a 65-year-old man initially diagnosed with classical Hodgkin lymphoma who underwent ABVD chemotherapy. Upon experiencing symptoms of disease relapse, the diagnosis was revised to AITL.
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INTRODUCTION

Angioimmunoblastic T-cell lymphoma (AITL) is a rare, often aggressive form of peripheral T-cell lymphoma (PTCL), accounting for only 1-2% of non-Hodgkin lymphoma cases. It is more prevalent in Europe (28.7%) compared to Asia (17.9%) (2). It tends to affect males more than females, with a median age of onset at 65 years (1).

Among common symptoms observed in affected patients include widespread lymphadenopathy and autoimmune-like symptoms. Some individuals may also present with hepatosplenomegaly, skin rashes, pruritus, pleural or peritoneal effusion, and arthritis.

AITL arises from mature T-follicular helper (TFH) cells, which are a type of T-cell subset involved in supporting B-cell maturation and the development of germinal centres. It is distinguished by a polymorphous lymph node infiltrate, showing a marked increase in follicular dendritic cells (FDCs) and high endothelial venules (HEVs) with a background of reactive cells like lymphocytes, plasma cells, histiocytes and eosinophils. The complex pathogenesis involving Epstein-Barr virus and B cell dysregulation can be challenging to diagnose. The diagnosis of AITL has been facilitated by advances in immunohistochemical and molecular signatures. The lymphoma cells typically show positivity for certain markers, such as cluster of differentiation 4 (CD4), CD5, CD2, and TFH cell markers like CD10, chemokine ligand 13 (CXCL13), inducible T-cell costimulatory (ICOS), B-cell lymphoma 6 (BCL6), and programmed cell death-1 (PD1) (1).

Despite aggressive treatment approaches, AITL has a poor prognosis, with a median survival of less than three years (2). Treatment strategies for AITL focus on achieving complete remission to increase the number of patients eligible for transplantation and to improve long-term survival.

CASE REPORT

A 65-year-old man presented with neck swelling in November 2020 that had lasted for a month. He also reported experiencing lethargy, bilateral leg swelling, shortness of breath, and night sweats for the past two months. An excision biopsy of the cervical lymph node

revealed lymphocyte-rich classical Hodgkin lymphoma. A staging positron emission tomography (PET) scan showed multiple extensive hypermetabolic nodal lesions with a Deauville score of 5. By June 2021, he had completed the Adriamycin, Bleomycin, Vinblastine Sulphate, and Dacarbazine (ABVD) chemotherapy regimen. A subsequent PET scan in July 2021 showed no evidence of active lymphoma.

Three months later, the patient complained of breathing difficulties that had persisted for a week. Upon physical examination, bilateral lung crepitation, hepatosplenomegaly, and rashes over both hands extending to the elbow were observed. A computed tomography (CT) scan showed cardiomegaly with pleural effusion, as well as multiple mediastinal, pericardial, and bilateral axillary lymphadenopathy, suggesting disease relapse. Based on clinical evaluation, the patient was diagnosed with relapsed Hodgkin lymphoma.

His full blood count revealed bicytopaenia, with a haemoglobin level of 9.3 g/dL, a platelet count of 13 x 10^9/L, and a white cell count of 11.6 x 10^9/L. The lymphocyte and monocyte counts were increased, measuring 5.26 x 109/L and 2.43 x 10^9/L, respectively. The peripheral blood smear showed reactive lymphocytes, some of which exhibited convoluted nuclei (Figure 1). Occasional large mononuclear cells with clump chromatin and irregular nuclear outlines with a moderate amount of basophilic cytoplasm were also observed. A leukoerythroblastic picture was present, but no blast cells were detected.

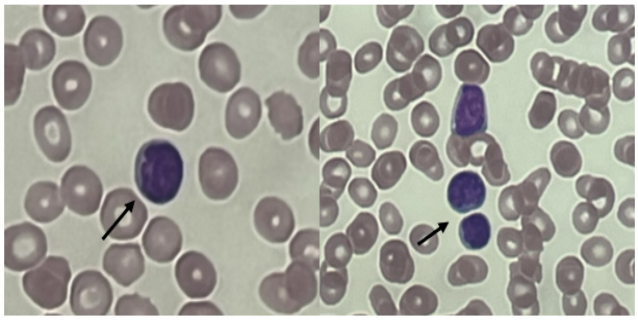

Figure 1: Peripheral blood film showed convoluted lymphocytes (arrows). (Wright stain, magnification x400)

A bone marrow examination revealed hypercellular fragments with increased lymphopoiesis. Abnormal mononuclear cells, characterized by moderate to large, clumped chromatin, irregular nuclear outlines, and ample cytoplasm, were occasionally seen. The other cell lines were unremarkable. Immunophenotyping did not reveal any aberrant lymphoid populations. Whereas his bone marrow cytogenetics showed a normal male karyotype without other abnormalities detected.

The trephine biopsy of the bone marrow demonstrated hypercellular marrow spaces with altered topography. Some of the marrow spaces showed infiltration of abnormal lymphoid cells arranged in nodules near the interstitium and paratrabecular areas (Figure 2). The abnormal cells were primarily small to medium in size, with larger cells exhibiting vesicular nuclei, small nucleoli, and irregular nuclear borders. Immunostaining showed that the abnormal cells were positive for CD45, CD2, CD3, CD5, CD7, CD4, CD8 (CD4>CD8), PD1, and CD30 (focal), while negative for MPO, CD20, CD79a, PAX5, MUM1, CD10, BCL6, CD15, CD56, ALK1, EMA, and TIA1 (Figure 3). CD21 and CD23 immunostaining revealed focal irregular dendritic meshwork patterns. The Ki67 proliferation index was 10%. The features observed in the bone marrow and trephine biopsy suggested CD4+ T-helper cell lymphoma.

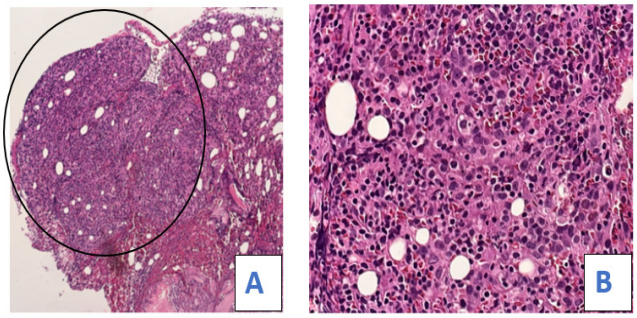

Figure 2: Abnormal lymphoid cell infiltration in the marrow spaces, arranged in nodules at the interstitium and paratrabeculae area (A & B). (H&E stain, A: x100, B; x400)

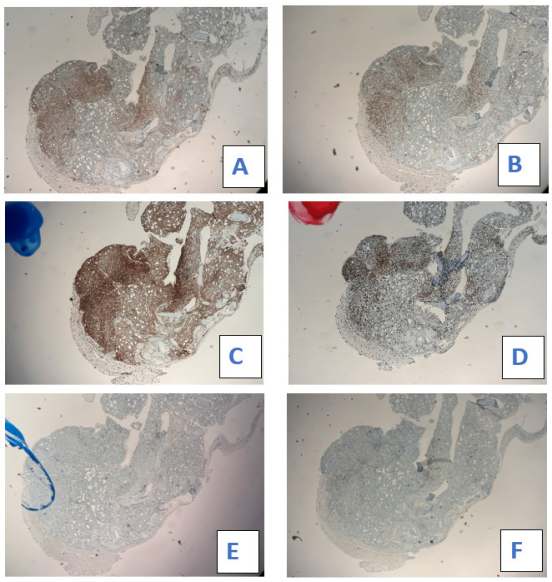

Figure 3: AThe malignant cells were positive for CD3 (A) and CD7 (B). They are expressing stronger CD4 (C) compared to CD8 (D), negative for CD15 (E) and focally positive for CD30 (F). (Magnification x 200)

Due to the findings in the bone marrow trephine biopsy, the initial cervical lymph node biopsy was reviewed and the diagnosis was revised to angioimmunoblastic T-cell lymphoma (AITL). Therefore, the final diagnosis was bone marrow involvement of AITL. Although a new chemotherapy regimen was planned, the patient ultimately succumbed to the aggressive nature of the illness.

DISCUSSION

Hodgkin lymphoma and AITL are two types of lymphoma with significantly different prognoses. Hodgkin lymphoma generally has a good prognosis, with a 5-year survival rate of over 80%. On the other hand, AITL has a poor prognosis (2).

In this case, the patient displayed common clinical manifestations of AITL, including generalized lymphadenopathy (91%), splenomegaly (69%), B symptoms (66%), pleural effusion (53%), hepatomegaly (50%), dyspnoea (38%), and skin rash (31%) (3). These symptoms indicate systemic manifestation in patients with bone marrow involvement (3). The patient also experienced anaemia, thrombocytopenia, and lymphocytosis. Anaemia (33%-69%) is the most significant change observed in peripheral blood examination, followed by leukocytosis (41%), neutrophilia (34%), eosinophilia (33-39%), circulating lymphomatous cells (33%), and thrombocytopenia (20-50%) in most patients (4).

In most AITL cases, bone marrow aspiration does not reveal significant findings or atypical lymphocytes, thus providing little useful information (4). Despite AITL being known for almost 50 years (1), diagnosing the condition remains challenging for clinicians and pathologists. The diagnosis of AITL relies on lymph node biopsy, but distinguishing characteristics between AITL and classical Hodgkin lymphoma, such as destruction of lymph node structure and infiltration of plasma cells, Reed Sternberg-like cells, and other inflammatory cells, make diagnosis difficult. B-cell or plasma cell expansion is common in AITL, often leading to misinterpretation as B-cell lymphoma, classical Hodgkin lymphoma, or even plasma cell myeloma (4).

Furthermore, there is limited knowledge about the distribution of T follicular helper cells in healthy, reactive bone marrows, or in samples affected by other lymphomas (4). Misdiagnosis of AITL is not uncommon due to the lack of specific pathological characteristics. Reported cases of misdiagnosis include reactive lymphadenopathy, diffuse large B-cell lymphoma, Richter syndrome, plasma cell leukaemia, and inflammatory dermatosis (5).

Bone marrow involvement is documented in up to 70% of cases (3). When bone marrow examination precedes lymph node biopsy, misinterpretations are also common, including multiple myeloma, chronic idiopathic myelofibrosis, idiopathic thrombocytopenic purpura, hypercellular marrow with reactive plasmacytosis, erythroid hyperplasia, and normocellular marrow (3).

The lymphoma cells in AITL often display CD30 positivity, partial CD15 expression, and Reed-Sternberg-like morphology with a background of small lymphocytes, which may lead to misdiagnosis as classical Hodgkin lymphoma. However, classical Hodgkin lymphoma lacks prominent venules and FDC expansion and does not exhibit atypical T cells (1).

Immunohistochemical findings in bone marrow biopsy are more challenging than in lymph node biopsy, as the expression of TFH markers is weaker. PD-1 (97%) and BCL6 (66%) are the most consistently expressed markers, with other positive markers including CD10 (18.5%-65%), CXCL13 (0-13%), and ICOS (13%) (2). CXCL13 and CD10 are more specific, while PD-1 and ICOS are more sensitive (2).

In our case, the malignant cells demonstrated positivity for PD-1 and negativity for both BCL6 and CD10, while CXCL13 and ICOS staining were not available at our centre. The follicular dendritic cell (FDC) proliferation was supported by CD21 and CD23 positivity (3). The expression of at least two of these TFH markers, along with positive CD4 and hyperplasia of FDC and HEV, is required for AITL diagnosis (1). AITL should be considered when small polymorphous lymphoid aggregates arranged in nodules are observed in the bone marrow. Immunohistochemistry staining, especially with PD-1 and BCL6 markers, can greatly assist in establishing the diagnosis.

The neoplastic cells are usually CD4+ and also express multiple TFH-related antigens like PD1, CD10, BCL6, CXCL13, ICOS, SAP, CD200 and CXCR5. However, none of these markers are 100% sensitive or specific for the TFH phenotype and yet not all can be detected in a typical case of AITL (4). Many studies showed the expression of TFH markers in the bone marrow was more subtle than in lymph nodes (4). In some patients, the diagnosis can only be made after 2–3 lymph node biopsies, nevertheless in a bone marrow biopsy. CD10 is usually positive in only a small subset of the neoplastic cells and may show variable staining intensity (4).

This patient does not show any karyotypic abnormalities, which are commonly found in AITL. To date, no characteristic abnormalities have been found that have led to a therapeutic option.

CONCLUSION

AITL is a rare disease with a poor prognosis. Despite its benign sounding name, AITL has a fatal natural history, highlighting the importance of accurate diagnosis and treatment. A better understanding of clinicopathologic

features and recognizing the morphology and immunophenotypic is crucial for an early and accurate diagnosis. AITL is challenging to diagnose and treatment is often delayed by misdiagnosis.

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