CASE REPORT

Angioimmunoblastic T-cell Lymphoma Presenting With a Neutrophilic Leukemoid Reaction: A Diagnostic Challenge

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ABSTRACT

Angioimmunoblastic T-cell lymphoma (AITL) accounts for 1-2% of all non-Hodgkins lymphoma. Patients present with lymphadenopathy, hepatosplenomegaly, polyclonal hypergammaglobulinemia and skin lesions. The presence of rash and neutrophilia in the absence of circulating abnormal lymphocytes in the peripheral blood film leads to a misdiagnosis. A 33-year-old presented with cervical lymphadenopathy with WCC of 104.9 g/dl, maculopapular rash, loss of weight and appetite associated with B symptoms. His peripheral blood film revealed hyperleukocytosis with a neutrophilic leukemoid reaction. Neutrophil alkaline phosphatase (NAP) score was high. Bone marrow aspirate and trephine were suggestive of neutrophilic leukemoid reaction with features of granulocytic hyperplasia with no lymphoid aggregates suggestive of neutrophilic leukemoid reaction secondary to underlying malignancy with a differential of myeloproliferative neoplasm if no reactive causes of granulocytic hyperplasia could be found. A lymph node biopsy was done later and was consistent with AITL. This case illustrates the rare presentation of AITL with a neutrophilic leukemoid reaction in the absence of anaemia, eosinophilia and abnormal lymphoid cells.
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Keywords: Angioimmunoblastic T-cell lymphoma; Neutrophilic leukemoid reaction; Non-Hodgkins lymphoma

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INTRODUCTION

Angioimmunoblastic T-cell lymphoma (AITL) is a rare type of lymphoma and accounts for only 1-2% of all non-Hodgkins lymphoma. Patients may present with generalised lymphadenopathy, hepatosplenomegaly, polyclonal hypergammaglobulinemia and skin lesions. The skin lesions are not specific and vary from a maculopapular rash to a vesicular rash. A good correlation of physical examination with the correct preliminary investigations assists in making an accurate diagnosis. Bone marrow examination without a lymph node biopsy would misdiagnose the disease as a myeloproliferative neoplasm in the presence of elevated white blood cell counts with neutrophilia. A significantly high white cell count with neutrophilia has only been reported in a single case.

CASE REPORT

We present a case of AITL presenting with a very high white cell count with a neutrophilic leukemoid reaction.

Case report: A 33-year-old Malay man in Hospital Sultanah Aminah, JB, presented with bilateral cervical lymph node enlargement with the largest 5x8cm, 1- week post-vaccination. He was treated as having an infection with oral antibiotics but no improvement. Subsequently, he was noted to have a high white cell count of 104.9 g/dl. He had weight loss and appetite associated with B symptoms, such as fever and night sweats for the past month. He also complained of a generalised maculopapular rash and itchiness for the past week which looked like a drug-induced rash that antibiotics could have triggered. Physical examination revealed multiple lymphadenopathies at the cervical and inguinal areas. There was no stridor or any signs of obstruction. No hepatosplenomegaly was noted. He had bilateral pedal edema.

His full blood count showed haemoglobin 12.9g/dl, Platelet $374x10^9$/l and white blood cell count $114x10^9$/l. His peripheral blood film showed hyperleukocytosis with left shift and occasional blast cells. Initial differential diagnoses were either leukemoid reaction secondary to an underlying infection, malignancy or Chronic myeloid leukaemia. The neutrophil alkaline phosphatase NAP score was high, ruling out CML. Bone marrow aspirate showed hypercellularity with granulocytic hyperplasia and a moderate increase in megakaryocytes with no blast

or abnormal lymphoid cells, suggestive of leukemoid reaction. The trephine biopsy supported the marrow aspirate with features of granulocytic hyperplasia with no evidence of leukaemia, granuloma formation, lymphomatous or non-hematopoietic infiltration. Immunophenotyping of the bone marrow aspirate had no abnormal population of cells.

A lymph node biopsy showed an effacement of the architecture and was replaced by a vaguely nodular lymphomatous infiltrate with residual small lymphoid follicles seen. The lymphomatous infiltrate consists of a heterogeneous population of lymphocytes with round to irregular nuclear contours, slightly dispersed chromatin and occasional nucleoli with relatively ample cytoplasm, accompanied by small lymphocytes with condensed chromatin and clear cytoplasm. Scattered large cells with lobated nuclei and prominent nucleoli are seen, and numerous prominent high endothelial venules are in the background. Clusters of epithelioid histiocytes forming loose granulomata, many neutrophils and plasma cell aggregates are seen.

The immunohistochemistry showed expression of pan T-cell markers CD2, CD3 and CD5 with a weak, heterogeneous expression of CD30 in the vague nodules of larger, atypical T-cells that lack CD20. Double immunostaining for CD30 and PAX5 confirms the lack of PAX5 expression in the CD30+ atypical T-cells, thereby excluding classical Hodgkin lymphoma. The atypical T-cell population stains positive for PD1, CD4 and bcl6, but are negative for CD10. CD8 and TIA1 highlights scattered reactive cytotoxic T-cells but are negative in the neoplastic T-cell population. In particular, the nodules of weakly CD30+ large T-cells stain negative for TIA1, which rules against anaplastic large cell lymphoma. Scattered EBER+ large B-cells are noted in the background, in keeping with EBV reactivation. Therefore, the diagnosis of Angioimmunoblastic T cell lymphoma was made.

DISCUSSION

Angioimmunoblastic T cell lymphoma (AITL) is a subtype of peripheral T cell lymphoma and is a rare malignancy that progresses with an aggressive course. The disease has a male predominance and is more prevalent in the elderly, with a median age of 62 years old. The primary site of AITL is usually the lymph node, and most patients (80%) present in the advance stage of 3 to 4. Extranodal involvement in AITL are hepatosplenomegaly, fever and rash. AITL patients present with significant B symptoms, such as loss of weight, appetite, night sweats and fever. There is an elevated LDH, hypergammaglobulinemia, anaemia, thrombocytopenia and hypereosinophilia (1). Skin manifestations are seen in about 35-45% of patients, range from macular to papular, plaque or nodular eruptions, purpura, petechia and vesicular (1).

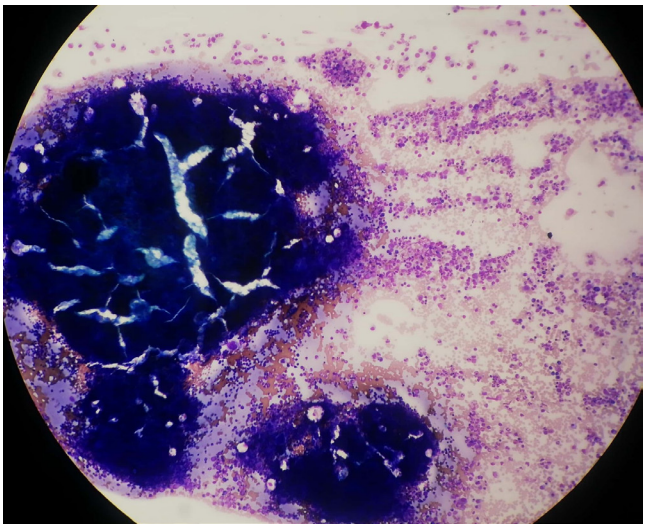

Figure 1 : Hypercellular bone marrow fragments and cellular trails (Magnification x 4).

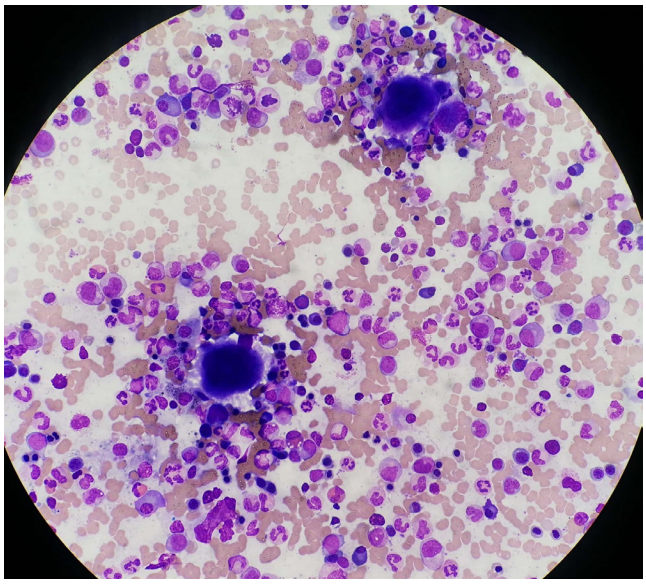

Figure 2 : Granulocytic hyperplasia in the bone marrow aspirate (Magnification x 40).

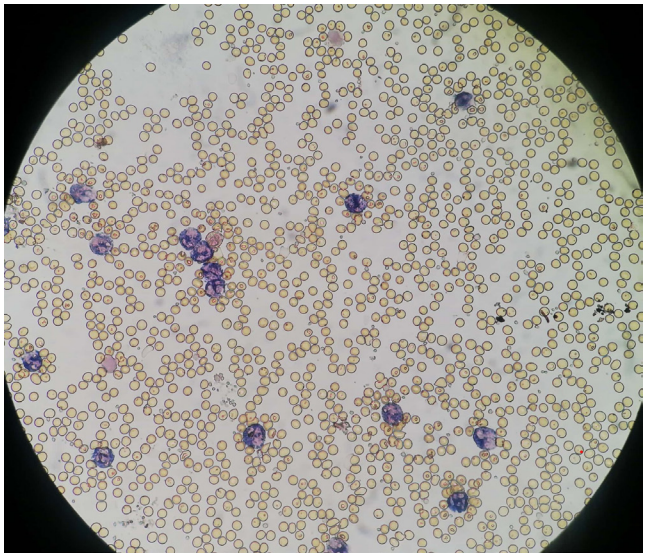

Figure 3 : High NAP score of the peripheral blood film. (Magnification x 40).

The wide range of skin manifestations that may present can misdirect the clinician towards an accurate diagnosis. Many times, the skin rash is preceded by the administration of a drug, most often an antibiotic. This may result in the misdiagnosis of drug-induced toxic erythema. As stated in the case report, there was a history of antibiotic treatment prior to the development of the rash. The coexistence of lymphadenopathy and B symptoms in AITL leads to a correct preliminary diagnosis.

Hyperleukocytosis with neutrophilia has been reported once in AITL in a single case report whereby, the patient presented with vesicular rash and hypergranulopoiesis of the bone marrow (2). The presence of rash, hyperleukocytosis and neutrophilia with the absence of circulating abnormal lymphoid cells in the peripheral blood film may divert the diagnosis to leukemoid reaction or Myeloproliferative neoplasm, as the bone marrow aspirate, and trephine was done prior to a lymph node biopsy due to the misleading haematological changes. However as the patient had lymphadenopathy with no hepatosplenomegaly, no pancytosis and high NAP score, myeloproliferative neoplasm was unlikely.

Paraneoplastic leukemoid reaction are seen in 10% of leukemoid reactions among patients with solid tumors. Studies have found an increase in serum levels of granulocyte colony stimulating factor (G-CSF) and granulocyte macrophage colony stimulating factor (GM-CSF), especially in solid tumors (3). The high levels of G-CSF and GM-CSF and the release of interleukins in AITL may contribute to the development of neutrophilic leukemoid reaction. As we know, AITL is associated with an increase in the expression of CXCR5 and CXCR13. These chemokine receptors are needed for the differentiation of CD4 T cells to T follicular helper cells. The expression of these chemokines leads to immunoglobulin production and hypergammaglobulinemia (4). In the pathogenesis of AITL, there is the activation of the JAK–STAT pathway that is responsible for the activation of molecules involved in cell signaling processes and leads to an increase in proliferation (4). These could be the causes of neutrophilic leukemoid reaction in AITL, as the JAK-STAT pathway mutation is related to the development of myeloproliferative neoplasm. Covid-19 vaccination could likely contribute to the formation of leukemoid reaction as described in a single case report where bone marrow only showed leukemoid reaction with no features of leukemia (5).

CONCLUSION

Angioimmunoblastic T-cell lymphoma is a rare disease that is not frequently encountered. The unusual presentation of hyperleukocytosis in a patient with skin lesions, without typical clinical features of myeloproliferative neoplasm warrants thorough investigations as illustrated by this case. Concomitant lymph node biopsy, together with a bone marrow aspirate and trephine, leads to an accurate diagnosis. The significance of a neutrophilic leukemoid reaction in AITL is not well established and has only been reported once. AITL should be considered in the presence of enlarged peripheral lymph nodes, skin manifestations and neutrophilic leukemoid reaction.

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