CASE REPORT

Angioimmunoblastic T-cell Lymphoma Mimicking Systemic Lupus Erythematosus: A Case Report and Literature Review

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ABSTRACT

Objective • This study aimed to investigate the clinical features of angioimmunoblastic T-cell lymphoma (AITL) mimicking systemic lupus erythematosus (SLE) and raise awareness about AITL among rheumatologists in order to prevent misdiagnosis and missed diagnosis. The study reports on a case of AITL mimicking SLE and provides a literature review.

Methods • Using key words as search terms, relevant articles published in PubMed before 2022-05 were searched, and their clinical characteristics were collected and analyzed.

Results • The literature review retrieved six case reports, including four cases initially diagnosed with SLE and then with AITL. The other two case diagnoses were SLE and AITL, respectively. The two diseases are pathogenically associated and share some common features. The clinical manifestations of AITL are complex. The disease is closely associated with abnormal immune functions and is highly heterogeneous.

Conclusion • Patients with AITL generally have a poor prognosis. Rarely do reported cases show AITL mimicking SLE. AITL should be considered during clinical practice to prevent missed diagnoses or misdiagnoses. (*Altern Ther Health Med.* 2023;29(8):733-737).

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INTRODUCTION

Angioimmunoblastic T-cell lymphoma (AITL) is a subtype of peripheral T-cell lymphoma, a rare type of non-Hodgkin's lymphoma. The present study aimed to report a case of AITL mimicking SLE and to present an accompanying literature review.

CASE PRESENTATION

The Department of Hematology of Qilu Hospital of Shandong University admitted a 76-year-old female patient for fatigue and chest tightness with two days of aggravating symptoms following two weeks of physical activities. The patient was previously admitted at another local hospital two weeks earlier with similar complaints. A routine blood test revealed anemia (hemoglobin (Hb), 55 g/L), and she underwent a blood transfusion. However, cold agglutinin disease occurred, and crossmatching failed. Subsequently, our Department of Hematology admitted the patient for severe anemia and suspicion of hemolytic anemia.

The patient had a 10-year history of myocardial infarction and received long-term aspirin. Physical examination upon admission revealed: temperature of 36°C, cardiac frequency of 104 beats/min, respiratory rate of 20 breaths/min, blood pressure of 106/60 mm Hg, and body mass index of 22 kg/m² kg. The patient had clear consciousness, poor spirits, and skin pallor. Upon palpating the whole body, physicians observed jaundice in the skin and sclera and no enlargement in the lymph nodes. The patient exhibited rough breathing sounds in both lungs, with some moist rales detected. The heart sounds were normal, and the heartbeat was regular without any pathological murmurs. The abdomen felt soft without any tenderness or rebound pain. We could not palpate the spleen. There was no edema in the lower limbs.

A blood test panel showed a white blood cell (WBC) count of 11.76×10^9/L, neutrophil count of 9.09×10^9/L, red blood cell (RBC) count of 0.87×10^{12}/L, Hb level of 41.00 g/L, and platelet (PLT) count of 321×10^9/L. Besides, the erythrocyte sedimentation rate (ESR) was 160 mm/h, and the percentage of reticulocytes was 24.58%. We observed agglutination of erythrocytes, abundant polychromatic erythrocytes, and scattered platelets, while the WBC morphology was normal. Routine urine and stool tests were normal. Liver function test showed alanine transaminase (ALT) of 28 U/L, aspartate transaminase (AST) of 64 U/L,

Figure 1. Bone marrow cell morphology. An increase in the percentage of erythrocytes and distorted morphology of immature erythrocytes

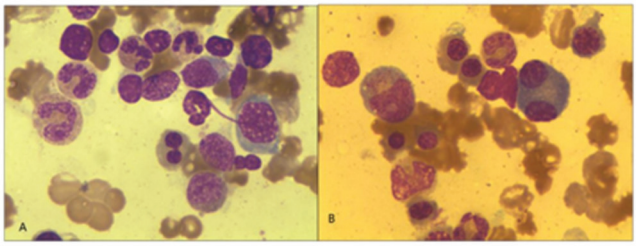
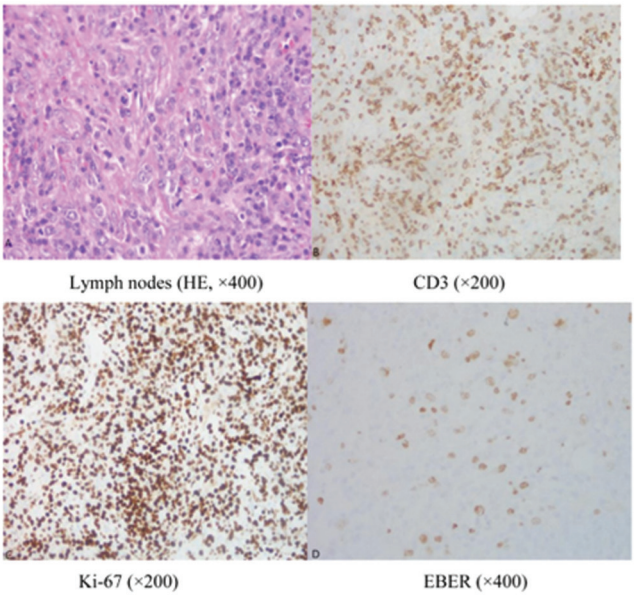


Figure 2. (Cervical) lymph node pathology. **A.** Massively proliferating lymphocytes upon HE staining; **B.** Positive for CD3 under the high-magnification lens (×200); **C**. Positive for Ki-67 under the high-magnification lens (×200); **D**. ERBR in-situ hybridization: ERBE (+)



gamma-glutamyl transferase (γ-GT) of 50 U/L, alkaline phosphatase of 83 U/L, total protein of 102.3 g/L, albumin of 32.3 g/L, globulin of 70.1 g/L, total bilirubin of 70.4 μmol/L, indirect bilirubin of 61.4 μmol/L, and direct bilirubin of 9.0 μmol/L. Serum levels of creatinine and blood urea nitrogen were normal. The direct Coombs test was positive. Creatine kinase isoenzyme was 8.80 ng/mL. Besides, myoglobin, troponin, and B-type natriuretic peptide levels were >500.00 ng/mL, 0.36 ng/mL, and 230.00 pg/mL, respectively.

The results of enzyme-linked immunosorbent assay (ELISA) showed antinuclear antibody (ANA, 1:100), anti-dsDNA of >200 (0-25) IU/ml, and serum tested was weakly positive for anti-mitochondrial M2 antibody. According to the anti-Sm results, the patient was negative for rheumatoid factors and anti-SSA, anti-SSB, and anti-nucleosome antibodies. Serum levels of immunoglobulin G (IgG), (IgM), and IgA were 31.30 (normal range, 7-16), 5.46 (normal range, 0.4-2.3), and 3.78 (normal range, 0.7-4.0) g/L, respectively. Serum levels of complement C3 and complement C4 were within normal ranges. In addition, there was no detection of anti-cardiolipin and anti-β2 glycoprotein I antibodies, and the Epstein-Barr virus and cytomegalovirus DNA were absent. The 24-h urine protein quantitation showed 0.3 g/24 h.

A neck computed tomography (CT) scan showed multiple bilateral enlarged lymph nodes in the supraclavicular fossa. There was a thickened middle section of the wall of the esophagus. The recommendation was a gastroscopy. There were calcified foci in the right lung. Fibrotic lesions and mild ground-glass opacification existed in both lungs. Multiple enlarged lymph nodes were present in the mediastinum and bilateral axillary regions. The cardiac shadow showed enlargement and observation of the aorta and coronary artery calcification. The abdomen and the pelvic cavity exhibited no abnormalities. The bone marrow showed significant hyperplasia, with a remarkable erythroid proliferation (47%) and lesser granulocytic hyperplasia (Figure 1). The percentage of lymphocytes decreased. We counted six megakaryocytes. In the peripheral blood, there were ten nucleated erythrocytes/100 WBCs, indicating a pattern of hemolytic anemia in the myelogram. We found regional wall motion (RWM) abnormalities consistent with previous myocardial infarction and a left ventricular ejection fraction rate of 52%. We also noted reduced left ventricular diastolic function, an enlarged left atrium, and moderate mitral, tricuspid, and aortic regurgitation. We also observed moderate pulmonary hypertension.

According to the 2009 SLE classification issued by the American College of Rheumatology, the patient fulfilled SLE-based criteria. Hemoglobin level returned to normal after intravenous immunoglobulin administration at 20 g/d for three consecutive days, and transfusion of two units of RH (-) washed packed RBCs for three days. Simultaneously, 80 mg methylprednisolone was administered for three days, which changed to 60 mg/d. She continued to take methylprednisolone (28 mg/d) after discharge, along with tripterygium glycosides (20 mg thrice a day), hydroxychloroquine (200 mg for twice a day) and calcium supplementation therapy. The patient gave up the subsequent visit after discharge.

One year later,the patient returned to the rheumatology clinic due to itching of the whole body for over three months and fatigue. Physical examination upon admission showed pale skin and mucosa, scattered subcutaneous hemorrhagic spots indicative of telangiectasia on both feet and red, scattered pimples and scratches with the size of millet grains in four limbs and trunk. Two enlarged non-tender lymph nodes were tough in texture and movable. There were about 1.5×1.5 cm in size and were palpable in the left supraclavicular fossa. There was a lesion consistent with herpes in the right mouth corner, and pitting edema was present in both feet.

A blood test at readmission showed a WBC count of 8.12×10^9/L, neutrophil count of 6.16×10^9/L, RBC count of 2.13×10^{12}/L, Hb level of 68g/L, and PLT count of 48×10^9/L. The percentage of reticulocytes was 3.8%. The Coombs test was negative. The dipstick urine test showed blood 3+ and

Table 1. Summary of case reports related to AITL and SLE

Year	Author	Journal	Age (years)	Gender	Clinical manifestations	Autoantibody	Pathology	Diagnosis	Prognosis
1979	Pierce DA	Arthritis and Rheumatism	67	Male	Skin rashes, alopecia, arthritis, cough, dyspnea, dry mouth, dry eyes, bilateral parotid gland enlargement, and lymph node enlargement	ANA1: 160; dsDNA+ Polyclonal hyperglobulinemia; Coombs test +	The cytoplasm of plasma cells is stained deeply, and kappa light chain is indicated. Some immunoblasts are lightly stained, while others are not stained at all	Systemic lupus erythematosus, Sjogren's syndrome, immunoblastic lymphadenopathy	Poor
1986	Rosenstein ED	Seminars in Arthritis and Rheumatism	18	Male	Raynaud's phenomenon, fingertip ulceration, muscle weakness, fever, left pleural pain, zygomatic redness and left knee swelling and pain. Cervical lymph node enlargement	ANA1:320, spotted type; RNP+; reduced complement C4	Proliferated immunoblasts and lymphoplasmacytes are observed, and normal nodule structures disappear. Cells are depleted at germinal center, accompanied by focal vascular proliferation with endothelial cell proliferation	Mixed connective tissue disease, systemic lupus erythematosus, angioimmunoblastic lymphadenopathy	Poor
2005	Kojima M	Pathology Research and Practice	30	Female	Facial rashes and light sensitivity, fever, fatigue, lymph node enlargement	ANA1: 160 (homogenous, spotted type)	The lymph node structure disappears. In the high-power field, the pleomorphic groups of small and medium-sized lymphocytes, plasma cells, plasmacytoid cells, large basophilic transformed lymphocytes and immunoblasts are diffusely infiltrated into the subcortical area.	Systemic lupus erythematosus, atypical lymphoplasmacyte and immunoblastic proliferation	Poor
2014	Suzuki A	Modern Rheumatology	76	Female	Fever, night sweat and general discomfort, lymph node enlargement, and hepatosplenomegaly	RF306.3IU/ml, ANA 1:160, homogeneous type and nucleolar type; dsDNA 79.4IU/ml	A large number of reactive follicles, hyperplasia of germinal center and paracortical expansion are observed under low magnification. Mixed fusion of small and medium-sized lymphocytes, immunogenic cells, plasma cells and histiocytes are observed near the cortex under high magnification, and clusters of medium-sized clear cells with nuclei are visible. Scattered large to medium bcl-6 positive lymphocytes with irregular nuclei are found in the inter follicular area. CD23 staining shows irregular cell proliferation. A large EBER positive nucleus is found in the inter follicular area.		Poor
2016	Wenya Zhu	Clinical Misdiagnosis & Mistherapy	50	Male	Fever with cervical lymph node enlargement	ANCA1: 32, MPO: 25.7 RU/ml, PR3: 165RU/ml, ANA1:1000, ACL50.74 RU/ml, anti-β2-GPI34.9 RU/ml C3 0.655 g/L, C4 0.099g/L; IgG 27.5 g/L, IgM 6.47 g/L. Coombs test (+)	Most of the lymph node structures are destroyed, and a few residual lymphoid follicles can be seen. Branch-shaped high endothelial venule hyperplasia is observed in the subcortical area, with small to medium-sized pleomorphic T lymphocyte infiltration. The cytoplasm of heterotypic lymphocytes is light or transparent. Proliferating immunoblasts are scattered in the subcortical area, and the high endothelial venule hyperplasia is surrounded by the follicular dendritic network. Immunohistochemistry shows that: LCA, CD2, CD3, CD4, CD5, and CD7 in tumor cells (+++), CXCL13 (+ +) , CD10 and P53(+), EMA(±), GRB, CD56, ALK and AE1/AE3 (-) , Ki67 positive rate 50%; Bcl-2 in reactive B cells (+ + +), CD20, PAX-5, MUM-1 and Oct-2 (++), Bcl-6(+); immunoblasts CD30 (++), CD15 (+); T lymphocyte CD8 (++), TIA-1 (+); follicular dendritic network CD21 (+ + +); plasma cell CD138 (++). Molecular pathological examination (in situ hybridization) shows EBER (+).	Angioimmunoblastic T-cell lymphoma	Poor
2020	Tay HB	European Journal of Case Reports in Internal Medicine	71	Female	Fever, alopecia, hepatosplenomegaly, lymph node enlargement	Antinuclear antibody >1:640, (homogeneous), anti-double stranded DNA+, (324.63 IU). Low levels of serum complement C3 (0.43g/l) and C4 (0.03g/l)	Proliferative and closed germinal centers and poorly defined fault zones can be seen under low magnification. The paracortical area is enlarged by small and medium-sized lymphocytes with vascularization. The nuclei of paracortical lymphocytes are irregular and the cytoplasm is clear under high magnification. Immunohistochemical staining shows that there are atypical T cells expressing CD2, CD3 and CD5 in the paracortical lymphoid tissue. The expression of CD7 is slightly down regulated, and the proliferation index is up to 50%. Overexpression of CD4, ICOS and less expression of PD-1 and CD10 outside follicles are consistent with T-follicle helper phenotype.	Angioimmunoblastic T-cell lymphoma, systemic lupus erythematosus	Poor
2020			76	Female	Fever, rashes, hemolytic anemia, lymph node enlargement	ANA 1:100; dsDNA >200 (0-25) IU/ml; weakly positive for anti-mitochondrial M2 antibody. Immunoglobulin G 31.30 g/L, immunoglobulin M 5.46 g/L, immunoglobulin A 3.78 g/L	HE staining shows a large number of proliferating lymphocytes. Immunohistochemistry: CD3(+), CD43(+), CD5(focal+), PD-L1(focal +), CD21(extended FDC network, and proliferating blood vessels around), CD10 (scattered large cells+) Bcl-2(+), Bcl-6(+), CD30 (scattered large cells +), CD23 (focal+), CD20 (B lymphocytes+), CD79a (B lymphocytes+), CyclinD1 (scattered +), MPO (occasionally+), MUM-1(-), CD4(-), CD68 (histocytes+), CD38 (plasma cells+), CD138 (plasma cells+), Ki-67(+, 70%). In situ hybridization: EBER (+)	Angioimmunoblastic T-cell lymphoma	Poor

A: first diagnosed as SLE and then as AITL; B: first diagnosed as AITL and then as SLE; C: concomitant diagnosis

urine proteins 2+. Liver function test indicated ALT of 8 U/L, AST of 13 U/L, γ-GT of 22 U/L, ALP of 63 U/L, total protein of 67 g/L, albumin of 28.7 g/L, globulin of 38.3 g/L, total bilirubin of 16.4 μmol/L, indirect bilirubin of 12.9 μmol/L, and direct bilirubin of 3.5 μmol/L. Serum creatinine and blood urea nitrogen levels were 91 μmol/L and 10.93 mmol/L, respectively. In addition, ANCA, ANA, and anti-dsDNA antibodies were negative. Serum levels of IgG, IgM, IgA, and IgE were 19.30 g/L, 0.88 g/L, 7 g/L, and 17800 (normal range, 0-100) IU/ml, respectively. Complement test results showed low complement C3 (0.25 g/L) and complement C4 (<0.064 g/L) levels. The patient tested negative for antiphospholipid antibodies and anti-beta 2 glycoprotein 1 antibodies. The total protein-to-creatinine ratio was 1.92. CT scan showed

bilateral hilar enlargement and multiple enlarged lymph nodes in the mediastinum, bilateral armpits, abdominal cavity, and retroperitoneal region. The cervical lymph nodes received a biopsy. The immunohistochemistry showed the following results: CD3 (+), CD43 (+), CD5 (focal+), PD-L1 (focal+), CD21 (extension of FDCs, perivascular hyperplasia), CD10 (scattered large cells+), Bcl-2 (+), Bcl-6 (+), CD30 (in scattered large cells +), CD23 (focal +), CD20 (B-cells +), CD79a (B-cells +), CyclinD1 (scattered+), MPO (individual+), MUM-1 (-), CD4 (-), CD68 (histiocytes+), CD38 (plasmacytes+), CD138 (plasmacytes+), and Ki-67 (70%) (Figure 2). In-situ hybridization showed Epstein Barr virus-encoded small RNAs (EBERs). The patient was diagnosed with AITL and transferred to the hematology department for further examination and treatment.

DISCUSSION AND LITERATURE REVIEW

This study reported that a 76-year-old female patient presented with mouth ulcers, hematological damage, and positivity for various autoantibodies. AITL was first reported in 1974 and initially described as an immunodeficiency-related, benign lymphoid hyperplasia with slow onset. The presence of focal T-lymphoid hyperplasia of the hyaline vascular type characterizes AITL. Pathological features of involved lymph nodes include diffuse lesions of the lymph nodes, dendritic vascular hyperplasia, and inflammatory infiltration (e.g., immunoblasts).[1] Researchers have reported[2] some cases of spontaneous remission and later observed a transition from benign to malignant transformation.

AITL accounts for 19-20% of all patients with peripheral T-cell lymphoma. The incidence of AITL is higher in China than in Western countries.[3,4] The clinical manifestations of AITL vary highly, and lymphoid tissues may be involved in addition to non-specific manifestations, such as fever, skin rashes, anemia, and polyarthritis. AITL may exhibit with hematopoietic malignancy, including secondary B-cell lymphoma. Pierce DA reported the first case of SLE complicated with AITL in 1979. This case was a 42-year-old male patient presenting with fever, skin rashes, arthritis, cough, dyspnea, dry mouth, dry eyes, and enlarged lymph nodes. Laboratory tests showed hemolytic anemia, hyperglobulinemia, and the presence of ANA (+), anti-double-stranded DNA (+), and lupus band test (+) antibodies, indicating SLE. Lymph node pathology revealed deeply stained cytoplasm of plasmacytes and the presence of a kappa light chain. Some immunoblasts were only lightly stained, while others were never stained. According to the findings above, this patient was diagnosed with AITL, a unique case of overlapping symptoms of AITL, SLE, and secondary Sjögren's syndrome.

Six cases of AITL mimicking SLE have been reported, including three men and three women, with an average age of 52. The most common symptom was fever (N = 6); skin rashes accompanied the fever in two cases. Three cases exhibited positivity of SLE-specific anti-ds-DNA antibodies, three identified with decreased complement levels, and one was positive for ANCA antibodies. Other immunological findings in AITL included autoimmune hemolytic anemia with a positive Coombs test and thrombocytopenic purpura.[5,6] Autoantibodies, such as ANA, anti-Sm, and rheumatoid factor (RF), are mainly found in AITL. A growing body of evidence has shown that AITL may coexist with proliferative glomerulonephritis and polyarteritis nodosa.[7,8]

According to the reports, all AITL patients presented with enlarged lymph nodes, which could be associated with connective tissue diseases. However, the clinical significance of enlarged lymph nodes in AITL remains unclear, and there is no consensus. According to some reports,[9-11] enlarged lymph nodes may be the initial symptom of SLE. If the combination of SLE with enlarged lymph nodes is unresponsive to treatment, the possibility of AITL should be excluded based on lymph node biopsy.

Pathology is the gold standard for the diagnosis of AITL. At first, researchers pathologically described AITL as only lymphocytes with medium size and hyaline cytoplasm, found among polymorphic cells related to an inflammatory response and high endothelial venules and follicular dendritic cells. T-follicular helper (TFH) cells derive AITL cells, which express CD2, CD3, CD5, programmed cell death protein 1 (PD-1), CD10, B-cell lymphoma 6 (BCL6), C-X-C motif chemokine ligand 13 (CXCL13), inducible co-stimulator (ICOS), signaling lymphocyte activation molecule (SLAM)-associated protein (SAP), and CXCR5. CD30 may also be present.[12]

The underlying mechanism involved in AITL mimicking SLE remains elusive. TFH cells reportedly derive AITL cells.[13] The development of SLE is related to the hyperactivation of T-lymphocytes and B-lymphocytes. B-cells' proliferative differentiation and functional abnormalities may play a significant role in developing AITL. Both are related to the chemokine CXCL13 secreted by TFH. Under normal circumstances, CXCL13 is only expressed on the surface of TFH cells, inducing the production of lymphokine β by B-cells, thereby promoting the proliferation of follicular dendritic cells and CXCL13 secretion. CXCL13 further acts on TFH cells to promote TFH proliferation and also on B-cells to promote B-cell proliferation. Thus, a feedback chain responding to immunostimulants may exist. From the perspective of pathological mechanisms, SLE may represent the early stage of AITL, or the two diseases may be comorbidities.

In conclusion, clinical manifestations of AITL are diverse, requiring further clinicians' attention. SLE and AITL are pathogenically associated with each other and share some common features. AITL is closely associated with abnormal immune functions, and it is highly heterogeneous. The correct diagnosis of SLE rests on a patient's medical history and clinical or laboratory findings. Enlarged lymph nodes in connective tissue diseases are also worthy of further investigation. Overdiagnosis and overtreatment, as well as missed diagnoses, should be avoided.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

YW and ZP designed the study and performed the experiments; YW collected the data; ZP analyzed the data; YW and ZP prepared the manuscript. All authors read and approved the final manuscript.

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