False Positive Infectious Serologies Mimicking Viral Exanthem in a Patient with Angioimmunoblastic T-Cell Lymphoma

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ABSTRACT:

Angioimmunoblastic T-cell lymphoma (AITL) represents a severe subtype of peripheral T-cell lymphoma and mimics drug reactions, infection, or autoimmune diseases. Due to its nonspecific clinical features, diagnosing AITL can be difficult and is frequently delayed. We report a case of a 70-year-old Thai male who presented with fever and generalized morbilliform eruption. Initial laboratory investigations revealed positive serological tests for Mycoplasma, Measle virus, and Epstein-Barr virus. The patient was treated with appropriate antibiotics, however, there was no clinical improvement. The lack of response to antibiotic therapy prompted reconsideration of the initial diagnosis. Subsequent careful examination revealed enlarged cervical lymph nodes, lymph node biopsy confirmed AITL. In patient with AITL, we hypothesize that positive serological tests for multiple pathogens often result from immune dysregulation or cross-reactivity rather than true infections. Therefore, physicians must interpret these findings cautiously to avoid misdiagnosis.

Key words: Morbilliform eruption, maculopapular rash, angioimmunoblastic T-cell lymphoma, false positive

Introduction

Angioimmunoblastic T-cell lymphoma (AITL) is a distinctive and rare type of peripheral T-cell lymphoma, often presenting with systemic symptoms such as fever, generalized lymphadenopathy, weight loss, hepatosplenomegaly, and cutaneous involvement, typically as a maculopapular eruption. The nonspecific nature of AITL symptoms poses diagnostic challenges, frequently leading to delayed recognition. We present a case of AITL that initially mimicked an infectious process, characterized by fever, a morbilliform rash, and multiple positive infectious serologies.

Case presentation

A 70-year-old Thai male presented with fever and generalized erythematous maculopapular eruptions on his trunk and extremities for 2 weeks. The rash initially appeared on lower extremities and subsequently spread to the trunk and upper extremities. He

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had no significant medical history or recent exposure to new medications. He visited a private hospital and laboratory investigations were done and revealed positive results for anti-mycoplasma IgM, anti-measles virus IgM, and anti-Epstein-Barr virus (EBV) IgM. The tests for tropical infections, including anti-scrub typhus and anti-murine typhus IgM and IgG, yielded negative results. Similarly, anti-rubella virus IgM, anti-cytomegalovirus (CMV) IgM and anti-HIV were non-reactive. He was initially treated as tropical infection with intravenous ceftriaxone 2 gm/day and oral doxycycline 200 mg/day for 5 days. However, his clinical condition did not improve. As the test for anti-mycoplasma IgM was positive, he was subsequently administered azithromycin 500 mg as a single daily dose for 5 days with no improvement. He was transferred to Maharaj Nakorn Chiang Mai Hospital. On admission, physical examination revealed a partially blanchable morbilliform rash without scale on trunk and extremities, including palms and soles (Figure 1 A, B). There was no evidence of mucosal involvement, conjunctival injection, genital erosion, or nail changes. Palpable submandibular and bilateral cervical lymph nodes measuring 1.5–2 cm were noted, which were mobile and non-tender.

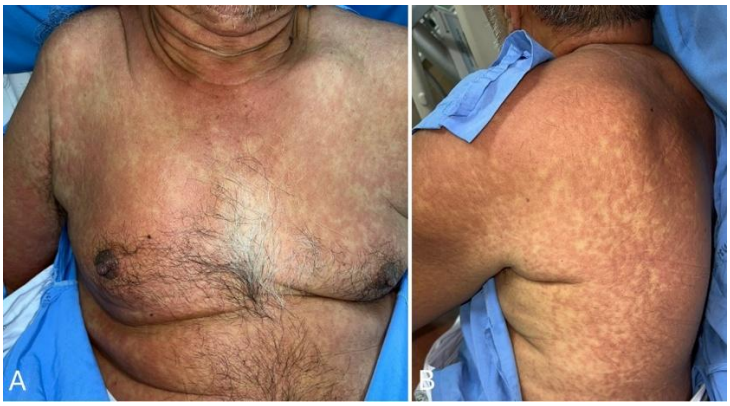

Figure 1 Generalized erythematous maculopapular eruptions on the trunk (A, B)

Initial laboratory data, complete blood counts showed mild anemia. Liver and kidney function tests were within normal ranges. The repeated infectious serology remained positive results for anti-mycoplasma IgM and IgG, anti-measles virus IgM, as well as anti-EBV IgM and IgG. The confirmatory test for EBV revealed positive for anti-EBV-viral capsid antigen (VCA) IgG and anti-Epstein Barr nuclear antigen (EBNA) IgG but negative for anti-EBV-VCA IgM and Paul-Bunnell Heterophile Antibody (PBHA), which consistent with past infection. Additional tests for autoimmune diseases showed weakly positive for antinuclear antibody with 1:80, while rheumatoid factor, anti-dsDNA, and anti-Smith were all negative. Initially, infectious disease specialist suspected that the patient had a nontuberculous mycobacteria (NTM) infection associated with the underlying disease of adult-onset immunodeficiency disease (AOID) and the patient was treated with imipenem 500 mg intravenously every 6 hours and amikacin 750 mg intravenously once daily for 2 weeks (Table 1). The result of anti-IFN gamma came out and showed weakly positive which was inconsistent with AOID. Clinician decided to discontinued treatment for NTM and fever as well as rash still persisted. A dermatologist was consulted, and a skin biopsy was performed, which showed normal basket-weave pattern, absence of spongiosis and

necrotic keratinocytes, mild basal vacuolization of the epidermis and superficial dermal lymphohistiocytic infiltration. No dermal melanophages were identified, and the subcutis appeared unremarkable (Figure 2). The histopathology of skin was inconsistent with either autoimmune diseases, such as lupus erythematosus, or paraneoplastic skin diseases, such as paraneoplastic pemphigus. Due to the prolonged disease course and initial investigations inconsistent with systemic infection, AITL was suspected. A cervical lymph node biopsy was performed, and intravenous dexamethasone 5 mg every 8 hours was initiated, resulting in resolution of fever and rash. Histopathological examination of cervical lymph node confirmed a diagnosis of AITL, revealing prominent vasculature with arborizing high endothelial venules (Figure 3). Immunohistochemical staining of cervical lymph node biopsy demonstrated positive CD3, CD4, CD5, CD8, CD10 (scatter), PD-1, BCL-6 and Ki-67 (40%) (Figure 4), while EBV-encoded small RNAs in situ hybridization (EBER ISH) was negative. Bone marrow aspiration revealed no abnormal lymphoid cells. A full-body CT scan showed several lymphadenopathies in bilateral cervical, bilateral supraclavicular and axillary regions and hepatosplenomegaly.

Table 1 Laboratory findings and treatment

Day of hospital admission	1	4	5	6	7	9	14	16	17	22	25
Day of illness	D15	D18	D19	D20	D21	D23	D28	D30	D31	D36	D39
Hemoglobin (g/dL)	13.3			11.5	11.6			9.8			
Hematocrit (%)	39.8			35.3	35.2			29.4			
White blood cell count (cell/cu.mm.)	14820			9890	9660			7640			
Neutrophil (%)	90.4			88.7	87.1			89			
Lymphocyte (%)	4.5			6.4	6.5			4.1			
Platelet count (cell/cu.mm.)	306000			287000	302000			294000			
LDH (U/L)					299						
Mycoplasma IgM and IgG		Positive									
Anti-CMV IgM		Negative									
Measle IgM	Positive										
Rubella IgM	Negative										
Anti-HIV	Non-reactive										
EBV IgM		Positive									
EBV IgG		Positive									
PB-HA							Negative				
EBV-VCA IgM							Negative				
EBV-VCA IgG							Positive				
EBNA IgG							Positive				
ANA	Weakly positive 1:80										
Anti-Sm (RU/ml)								<2 (<20)			
Anti-RNP (RU/ml)								<2 (<20)			
Anti-dsDNA (IU/ml)								<10			
Anti-IFN-gamma							Weakly positive				
Lymph node biopsy									Done*		
Ceftriaxone	2 gm/day										
Doxycycline	200 mg/day										
Azithromycin			500 mg/day								
Imipenam						2 gm/day					
Amikacin						750 mg/day					
Dexamethasone									15 mg/day		

*The patient was discharged on D25 of admission with oral prednisolone 30 mg/day for 12 days; the lymph node biopsy report became available on D27; and chemotherapy was initiated on D77 (C1D1)

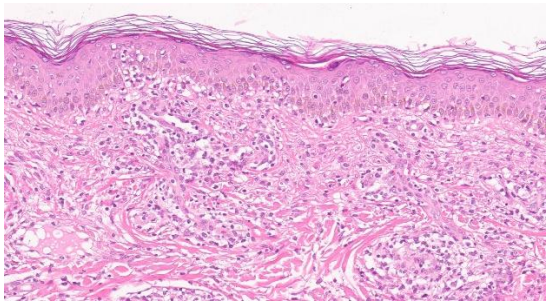

Figure 2 Skin biopsy showed mild basal vacuolization and superficial dermal lymphohistiocytic infiltration (H&E 20X)

The clinical findings and test results led to a diagnosis of stage II AITL. He received on a reduced-dose chemotherapy regimen comprising cyclophosphamide, doxorubicin, vincristine, and prednisolone. After three cycles, he is currently in complete response. Chemotherapy has been stopped, and he is now under close follow-up.

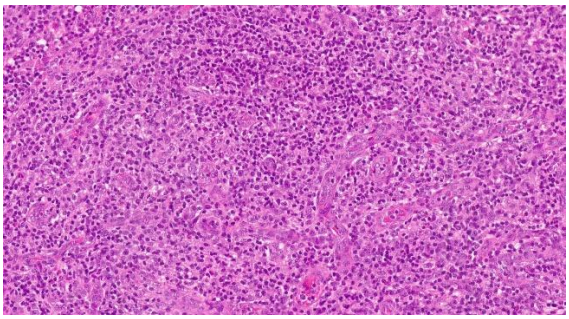

Figure 3 Cervical lymph node biopsy showed prominent vasculature with arborizing high endothelial venules (H&E 20X)

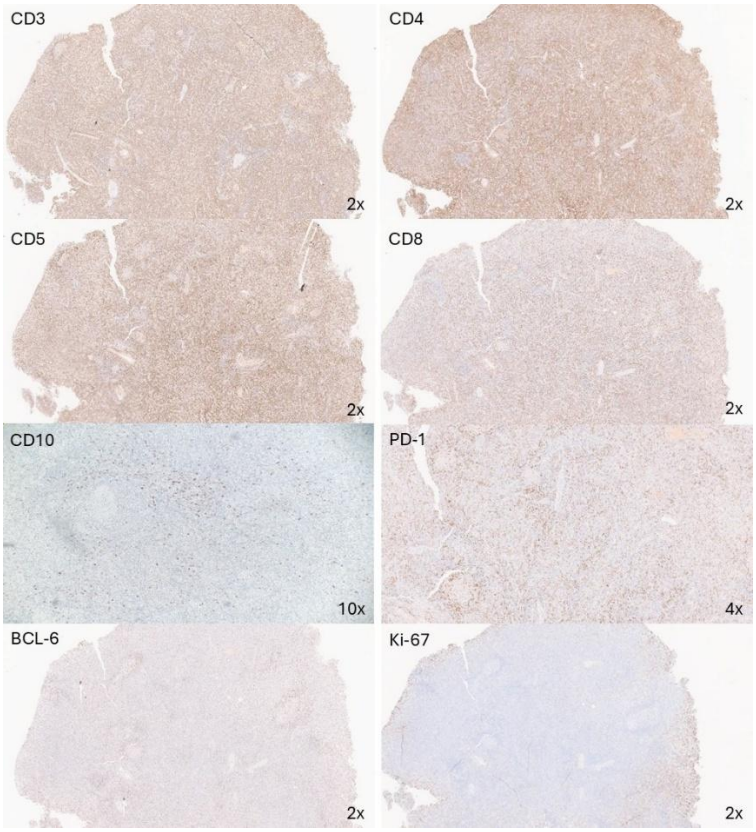

Figure 4 Immunohistochemical staining of cervical lymph node biopsy demonstrated positive CD3, CD4, CD5, CD8, CD-10, PD-1, BCL-6, and Ki-67

Discussion

AITL is a rare and aggressive subtype of PTCL, which typically occurs in elderly individuals[1,2,3]. The pathogenesis of AITL is complex and remains unclear. AITL originates from the neoplastic transformation of T follicular helper (TFH) cells. These TFH cells play role in supporting B-cell responses in the germinal centers of lymph nodes. The pathogenesis of AITL is complex and involves a multistep process encompassing both genetic and immunological dysregulation[4]. Frequently reported mutations include RhoA gene, and epigenetic regulators including TET2 and DNMT3A, which contribute significantly to TFH-cell clonal expansion and lymphomagenesis[1,4].

In AITL, malignant TFH cells secrete cytokines and provide abnormal co-stimulatory signals to B-cells, leading to nonspecific polyclonal B-cell expansion. These B-cells then produce cross-reactive antibodies, resulting in false-positive serological tests for various infectious and autoimmune diseases. In previous case reports of AITL, patients were found to have positive autoimmune and infection-related antibodies, including hepatitis B virus, HIV and parvovirus B19, which often contributed to delayed diagnosis and potential misdiagnosis[5-7]. Kuroda, et al. reported a case of a 61-year-old man who presented with ecchymosis, rash and generalized lymphadenopathy. Laboratory tests revealed multiple positive of autoimmune antibodies and a positive HB core IgM antibody[5]. Shida, et al. described a case of 44-year-old woman who presented with fever, anemia, jaundice, generalized lymphadenopathy, and hepatosplenomegaly. Laboratory studies showed Coombs-positive hemolytic anemia, weakly positive anti-dsDNA IgG and anticardiolipin IgM, as well as positive HIV serology[6]. Similarly, Kunitomi, et al. reported a 74-year-old man presented with malaise, urticarial-like rash, anemia and lymphadenopathy. Laboratory investigations revealed positive direct Coombs test and positive parvovirus B19 IgM antibody[7]. All of these patients were finally diagnosed with AITL.

Several reports have suggested an association between AITL and EBV infection. This relationship may arise from immunodeficient state induced by AITL facilitates EBV reactivation. Moreover, malignant TFH cells contribute to a permissive microenvironment that promotes the expansion of EBV-infected B cells. These infected B cells are often observed in lymph nodes of AITL patients, and in some cases, their proliferation may progress to a secondary diffuse large B-cell lymphoma[4].

The diagnosis of AITL is difficult, and it is sometimes misdiagnosed as infectious diseases, drug reactions or autoimmune diseases. The symptoms of AITL are nonspecific, making the diagnosis challenging and sometimes leading to delayed recognition. The clinical presentation of AITL often nonspecific, making early diagnosis difficult. Patients typically present with constitutional symptoms (fever, unintentional weight loss and/or night sweats), generalized lymphadenopathy and hepatosplenomegaly[1]. Cutaneous manifestations, occasionally the initial presentation like our patient, is observed in half of AITL patients[2,8]. This typically manifests as a maculopapular eruption resembling a viral exanthem and pruritus was observed in about 80% of cases that reported this finding[8]. Other cutaneous manifestations presentations include urticaria, papulovesicular lesions, indurated plaques, nodular formations, ulceration and, in severe cases, toxic epidermal necrolysis (TEN)[8,9].

The histology of skin usually exhibits nonspecific findings. These include superficial and deep perivascular infiltrates composed of lymphocytes and eosinophils with or without pleomorphic atypical lymphocytes, frequently

concomitant with vascular hyperplasia and vasculitis[1,9,10]. In a case which exhibits features of TEN, a confluent epidermal necrosis could be observed. Although there is no characteristic feature of skin histology, immunohistochemical study of TFH markers, such as CD10, PD-1 and CXCL-13, the latter being overexpressed in approximately 88% of cutaneous cases[8], may aid in the diagnosis of AITL. However, definitive diagnosis of AITL requires excisional lymph node biopsy.

In conclusion, we hypothesized that in our case, the false positive serologies for mycoplasma, EBV and measles virus serologies likely reflect cross-reactivity due to abnormal antibody production in AITL. As highlighted in previous reports, clinician should suspect AITL in elderly patients presenting with generalized lymphadenopathy, fever, cutaneous manifestations, particularly a morbilliform rash, along with unexplained positive serological tests, especially when infectious or autoimmune causes have been excluded.

Ethics statement

Written informed consent was obtained from the patient for publication of patient's data and photographs.

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