Clinical Case Report

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Angioimmunoblastic T-cell lymphoma mimicking drug fever and infectious etiology after a thyroidectomy

A case report

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Abstract

Introduction: Angioimmunoblastic T-cell lymphoma (AITL) is a rare subtype of mature peripheral T-cell lymphoma and accounts for approximately 1% to 2% of non-Hodgkin lymphomas. Although the B symptoms with generalized lymphadenopathy are the most frequent manifestations of AITL, its diagnosis remains a challenge as clinical manifestations and pathological features are frequently misleading.

Patient concerns: We report herein the case of a 70-year-old man with intermittent fever, pulmonary infection, and skin rash developed for 1 month before admission. Previously, he had undergone thyroidectomy for thyroid papillary carcinoma. Fever occurred on the day of discharge and occurred again during the next month. Symptoms worsened despite treatment with antibiotics and papular rash appeared. The local hospital diagnosed it as drug fever and stopped all antibiotics. Fever and rash were controlled temporarily; however, both relapsed 2 days before admission. On the night of admission, the patient developed fever again. Blood culture showed *Staphylococcus epidermidis* and *Staphylococcus haemolyticus* infection.

Interventions: Taking into account the recent history of surgery, the patient was diagnosed with septicemia and was treated with anti-infective treatment. On 13th day after admission, the patient developed fever again accompanied by generalized lymphadenopathy. However, multiple blood cultures were negative and bone marrow aspiration cytology, biopsy, immunohistochemistry, and gene rearrangement results were normal.

Diagnosis: The patient was finally subjected to cervical lymph node biopsy and was diagnosed with AITL.

Outcomes: The patient was transferred to the Department of Hematology for further treatment.

Conclusion: This case highlights the complex diagnostic challenges of AITL. AITL accompanied by thyroid carcinoma may not be a mere coincidence and administration of antibiotics may be a rare cause of AITL.

Abbreviations: AITL = angioimmunoblastic T-cell lymphoma, DAT = direct antiglobulin test, EBV = Epstein–Barr virus, ESR = erythrocyte sedimentation rate, FDC = follicular dendritic cell, Hb = hemoglobin, HEVs = high endothelial venules, LDH = lactate dehydrogenase, OS = overall survival, PTCL = peripheral T-cell lymphoma, TCR = T-cell receptor.

Keywords: angioimmunoblastic T-cell lymphoma, drug fever, infection, thyroid papillary carcinoma

1. Introduction

Angioimmunoblastic T-cell lymphoma (AITL) was described as angioimmunoblastic lymphadenopathy with dysproteinemia, immunoblastic lymphadenopathy, and lymphogranulomatosis X in the early literature.[1] Now, it is well-established as a subtype of mature peripheral T-cell lymphoma (PTCL) by World Health Organization classification of lymphoid neoplasms in 2016.[2] AITL accounts for approximately 1% to 2% of non-Hodgkin's lymphoma and 15% to 20% of PTCL.[3] AITL afflicts advanced-age individuals with the median age at diagnosis 65 years. AITL does not show distinct gender predisposition. The most frequent manifestations of AITL are B symptoms (fevers, unintentional weight loss, and/or drenching night sweats) with generalized lymphadenopathy, other clinical features include hepatosplenomegaly, anemia, positive direct antiglobulin test (Coombs), thrombocytopenia, and polyclonal hypergammaglobulinemia. About 70% of patients possess bone marrow. Rash is seen in 20% to 50% of AITL patients, ranging from urticarial lesions to nodular tumors.[4] Histopathologically, AITL is characterized by polymorphous infiltrate involving lymph nodes and prominent proliferation of high endothelial venules (HEVs) and follicular

Editor: N/A.

This study is supported by the National Natural Science Foundation of China (No. 81572419 and No. 81702396).

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

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Medicine (2019) 98:34(e16932)

Received: 9 January 2019 / Received in final form: 22 June 2019 / Accepted: 29 July 2019

http://dx.doi.org/10.1097/MD.0000000000016932

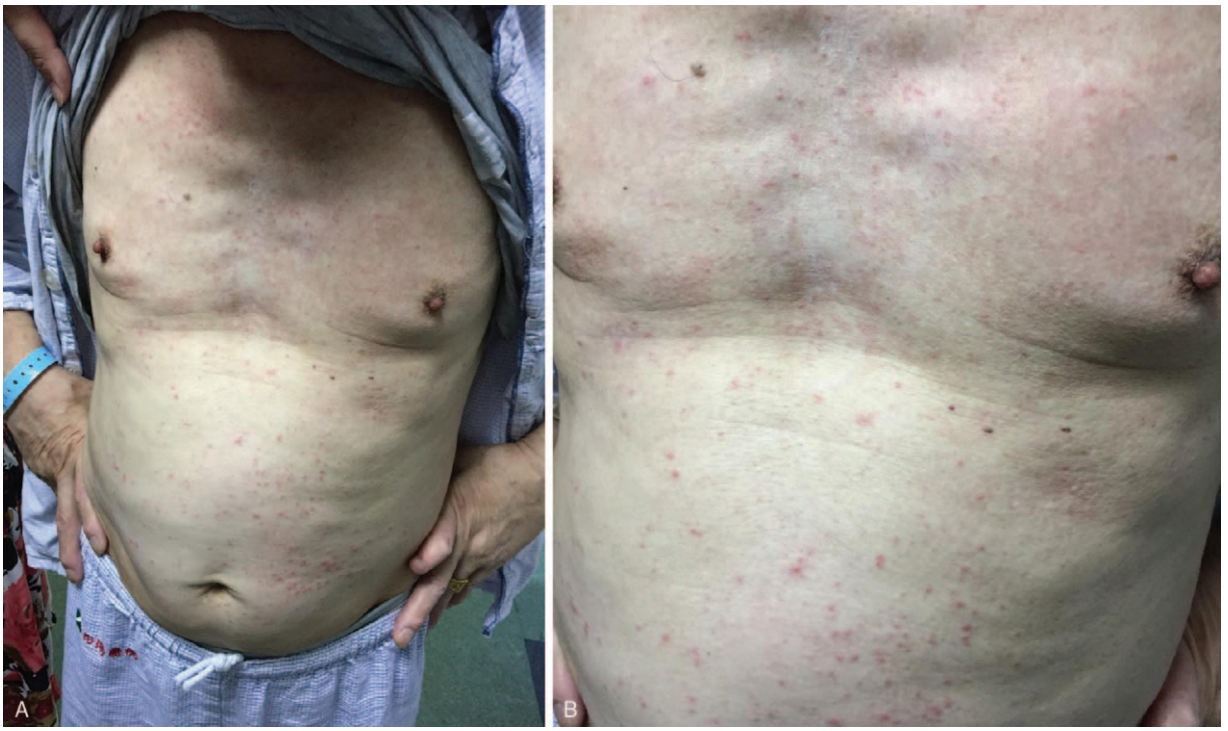

Figure 1. Thoracic and abdominal papular rash of the patient.

dendritic cells (FDCs).[1] We herein report the case of an AITL patient undergone thyroidectomy that mimicked drug fever and infectious etiology and led to complicated diagnosis and disease management.

2. Consent

This study was approved by the Ethics Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (ethical approval no. TJ-IRB20190503). Informed written consent was obtained from the patient for publication of this case report and accompanying images.

3. Case description

A 70-year-old man was transferred to our hospital with 1-month history of recurrent fever, drenching night sweats, weight loss, and rash. All these symptoms started following a thyroid surgery as a result of incidental computed tomography (CT) discovery of thyroid masses, a month before admission. The postoperative pathological diagnosis proved to be papillary thyroid micro-carcinoma. On the day of discharge, he started experiencing chills and fever. These symptoms reappeared during the next month and the body temperature reached up to 40°C. Chest CT scan revealed a minor infection of the right upper lobe. Antibiotic treatment (cefoperazone tazobactam, levofloxacin, and metronidazole) was given. The effect of the antibiotics was poor. The patient developed papular rash on the fifth day of treatment. Considering drug fever and allergic purpura, the doctor stopped all antibiotics and only used loratadine. Fever and rash were controlled temporarily but relapsed soon. Symptoms were relapsed 2 days before admission. His medical history included type 2 diabetes 2 months ago, a history of hepatitis B, and a surgical treatment of varicose veins of the lower extremities. On admission, physical examination showed generalized lymphadenopathy (supraclavicular, cervical, axillary, and inguinal lymph nodes), splenomegaly, and skin rash (Fig. 1). The laboratory data are summarized in Table 1. In simple terms, the counts of lymphocytes, red blood cell (RBC), hemoglobin, and platelets were decreased, whereas lactate dehydrogenase (LDH), β2-microglobulin, hs-CRP, and erythrocyte sedimentation rate were increased. HBsAg was positive; however, hepatitis B virus

Table 1

The laboratory data at admission.

	Our values	Normal range
WBC	5.91×10^9/L	$3.50–9.50 \times 10^9$/L
Lymphocytes	0.54×10^9/L	$1.10–3.20 \times 10^9$/L
RBC	3.71×10^{12}/L	$4.30–5.80 \times 10^{12}$/L
Hb	108 g/L	130–175 g/L
Platelet count	91×10^9/L	$125–350 \times 10^9$/L
AST	11 U/L	0–41 U/L
ALT	17 U/L	0–40 U/L
LDH	418 U/L	135–225 U/L
Total protein	64.6 g/L	64–83 g/L
Globulin	28.4 g/L	20–35 g/L
β2-microglobulin	5.30 mg/L	0.8–2.20 mg/L
Creatinine	98 μmol/L	59–104 μmol/L
Hs-CRP	65.8 mg/L	0–1 mg/L
ESR	27 mm/H	0–15 mm/H
IgG	8.9 g/L	7.51–15.6 g/L
Positive DAT (Coombs)	±	–
HbA1c	6.1%	4.0–6.0%
ANA	1:100	0

ALT = alanine transaminase, ANA = anti-nuclear antibody, AST = aspartate transaminase, ESR = erythrocyte sedimentation rate, Hb = hemoglobin, HbA1c = hemoglobin A1c, Hs-CRP = high sensitive C reaction protein, IgG = immunoglobulin G, LDH = lactate dehydrogenase, RBC = red blood cell, T = direct antiglobulin test, WBC = white blood cell

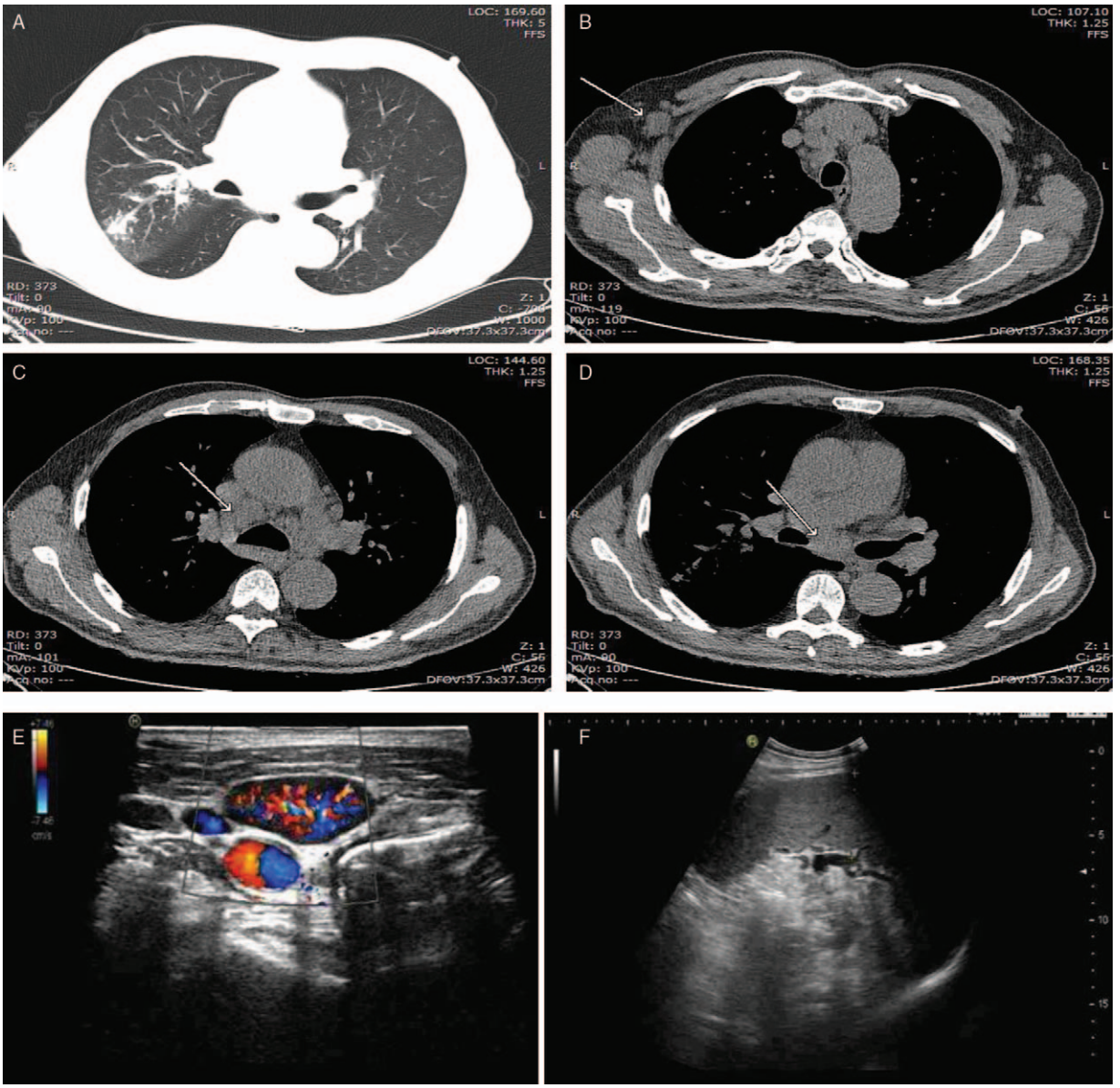

Figure 2. Imaging features of this patient. (A) Chest CT showed infectious lesions of the right upper lobe in the lung window. The arrowhead indicated lymphadenopathy of the axillary (B) and mediastinal (C and D) lymph nodes. Doppler ultrasound showed neck lymphadenopathy (E) and enlarged spleen (F). CT = computed tomography.

DNA was less than 1.0×10^2 IU/mL; Coombs direct antiglobulin test was positive; T-SPOT test was negative; albumin and globulin were within the reference range; the liver and renal functions were normal; serum viral loads of cytomegalovirus and Epstein–Barr virus (EBV) were negative. Chest CT scan showed infectious lesions of the right upper lobe (Fig. 2A) and generalized lymphadenopathy(bilateral axillary and mediastinal lymph nodes) (Fig. 2B–D). Neck color Doppler ultrasound showed bilateral neck lymphadenopathy with the largest one having dimensions 25×12 mm (Fig. 2E). The abdominal color Doppler ultrasound indicated that the spleen was enlarged with a thickness of 50 mm (Fig. 2F). Fine needle aspiration cytology of the left cervical lymph node suggested reactive and proliferative lesions (Supplementary Fig. S1, http://links.lww.com/MD/D188). Blood culture showed *Staphylococcus epidermidis* and *Staphylococcus haemolyticus* infection. Taking into account the recent history of surgery, we diagnosed the patient with septicemia, and therefore, he was treated with anti-infective treatment (linezolid and biapenem). The symptoms of the patient were controlled after admission. However, disease relapsed on the 13th day of admission accompanied by recurrent rash. However, multiple blood cultures were all negative. He still had fever after discontinuation of antibiotics (Fig. 3). Bone marrow aspiration cytology, biopsy, immunohistochemistry, and gene rearrangement results were all normal (Supplementary Fig. S2, http://links.lww.com/MD/D188). Finally, the patient underwent cervical lymph node biopsy. Hematoxylin and eosin staining showed effaced nodal architecture, marked proliferation of HEVs, and diffused infiltration of atypical lymphocytes with clear cytoplasm (Fig. 4), which were consistent with pathological features of AITL. Furthermore, immunohistochemical staining indicated that the neoplastic infiltrate was positive for CD3, CD5, LCA (leukocyte common antigen), B-cell lymphoma/leukemia (BCL)-2, BCL-6, weakly positive for programmed cell death protein 1, and negative for CD10, CD30, CD15, paired box gene 5,

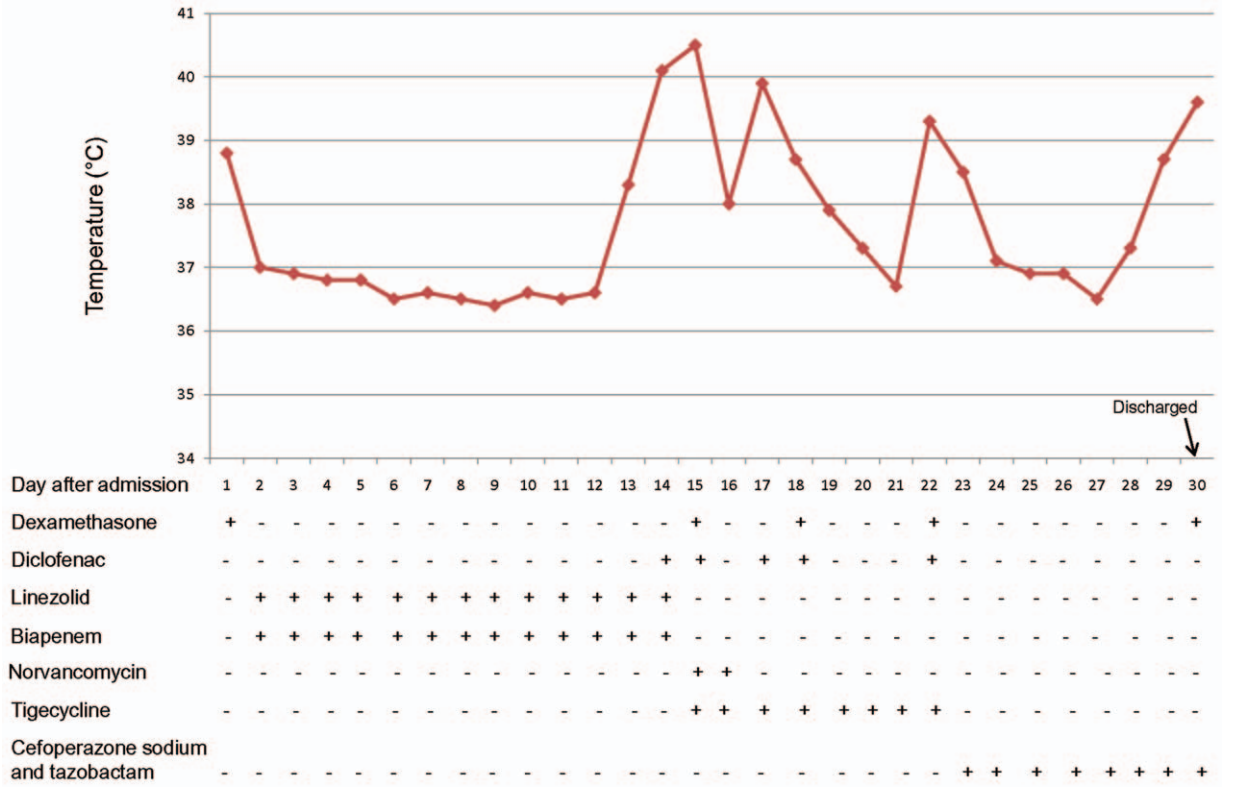

Figure 3. Body temperature trend and corresponding therapeutic drugs after admission.

CD20, CD79a, octamer-binding transcription factor 2, B-cell-specific octamer binding protein 1, multiple myeloma oncogene 1, anaplastic lymphoma kinase1, CD68, CD163, S-100, CD1a, cyclinD1, sex-determining region Y-related high-mobility-group box transcription factor 11, immunoglobulin D, cellular myelocytomatosis oncogene, and protein 53. Both Ki-67 index and minichromosome maintenance complex component 2 index were approximately 40%. Interestingly, irregular hyperplasia of FDC highlighted by immunostaining of FDC markers, including CD21, CD23, and CD35, was also discovered in immunohistochemical staining. Detection of EBV by chromogenic in situ hybridization suggested positive expression by a few background cells. T-cell receptor (TCR) gene rearrangements were detected positive. Based on the aforementioned findings, the patient was diagnosed with AITL and transferred to the Department of Hematology for further treatment.

4. Discussion

AITL is a rare subtype of PTCL, which was first described in the 1970s. It mainly affected older people with a median age of 65 years and most patients showed advanced stage with a poor

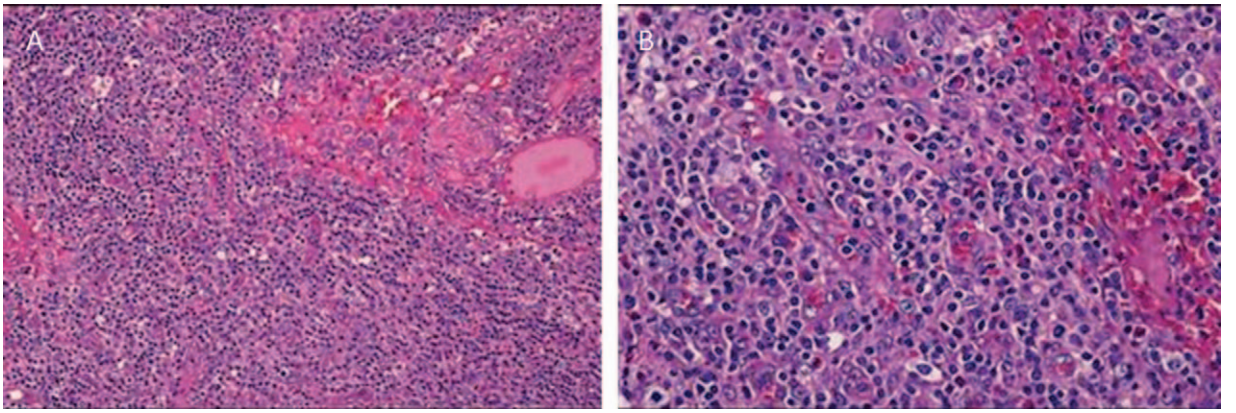

Figure 4. Hematoxylin and eosin staining showed diffused infiltration of atypical lymphocytes with clear cytoplasm and marked proliferation of arborizing HEV consistent with AITL; A, 100×; B, 400×. AITL = angioimmunoblastic T-cell lymphoma, HEV = high endothelial venule.

survival outcome.[5] Among the 157 patients with AITL treated within the Groupe d'Etude des Lymphomes de l'Adulte (GELA) trials, the 2, 5, and 7-year overall survival (OS) rates were 51%, 33%, and 29%, respectively.[6] In a multicenter retrospective study of 207 Japanese AITL patients, the 3, 5, and 7-year OS rates were 54%, 41%, and 35%, respectively.[7] Federico et al[8] reported the data of 243 AITL cases from the International Peripheral T-Cell Lymphoma Project with 5-year OS rate of 33%. More recently, a Chinese group reported a study of 1207 AITL patients with 2, 5, and 10-year OS probabilities of 46.8%, 32.9%, and 21.9%, respectively.[9] Therefore, it is particularly important to identify and diagnose AITL at an early stage.

Most patients with AITL exhibit generalized lymphadenopathy, hepatosplenomegaly, extranodal involvement, systemic disease with B symptoms, skin rash, hypergammaglobulinemia, and autoimmune phenomena.[10] In a recent study by Loghavi et al,[11] the most common clinical and laboratory features were lymphadenopathy (68%), B symptoms (54%), hepatosplenomegaly (45%), skin rash (42%), hypergammaglobulinemia (41%), anemia (29%), pruritus (21%), fatigue (19%), respiratory symptoms (17%), and thrombocytopenia (6%). In our case, the patient showed recurrent fever, generalized lymphadenopathy, splenomegaly, night sweats, weight loss, and rash. The pathology results indicated anemia, thrombocytopenia, and high levels of LDH, C-reactive protein, and β2-microglobulin. However, the tests were negative for hypergammaglobulinemia, EBV infection, and bone marrow invasion.

AITL has a waxing and waning course. In this case, the patient developed fever after a thyroidectomy and anti-infective treatment (cefoperazone/levofloxacin/metronidazole) did not improve the symptoms. Interestingly, fever improved after discontinuation of antibiotics. Thus, it was suspected to be drug fever before admission. We extensively searched literature and found that in most cases, AITL is manifested after exposure to medications, especially antibiotics, including doxycycline,[12] ciprofloxacin,[13] macrolide,[14] and so on. Therefore, we asked whether administration of antibiotics postoperation was the cause of AITL in this patient. Nevertheless, the symptoms persisted with progression of the disease.

AITL was found to be associated with other diseases, such as membranous nephropathy,[15] IgA nephropathy,[16] polyarthritis-resembling rheumatoid arthritis,[17] and myelofibrosis.[18] AITL was also found to be related to thyroid diseases, for example, the most common Hashimoto's thyroiditis.[19,20] The common characteristics of these diseases are autoimmune disorders. The nature of AITL is believed to be a variation of PTCL displaying features of a disordered immune system. Thus, abnormal autoantibodies may be the important factors connecting these diseases with AITL. Ambepitiya[21] reported occurrence of AITL in a 75-year-old woman with thyroid carcinoma in 1989. According to our knowledge, our case is only the second case reporting AITL in a thyroid cancer patient. It is uncertain whether the coexistence of AITL and thyroid carcinoma is mere coincidence; however, altered immunity might cause predisposition to carcinoma. Some solid tumors have been reported to be associated with AITL, such as colorectal cancer[22,23] and mesothelioma.[24]

In summary, this case illustrates the diagnostic challenges of AITL. Sometimes, there are certain inducing factors for AITL, such as EBV infection, drug administration, and so on. AITL is often accompanied by other diseases, especially immune-related diseases and tumors. Moreover, specific immunohistochemical tests and detection of genetic alterations, such as pathological TCR rearrangements or typical chromosomal aberrations by fluorescence in situ hybridization may facilitate the diagnosis of underlying AITL.

Acknowledgment

We thank Professor Liu Jin, Department of Respiratory Medicine, Tongji Hospital, for providing this case. We thank Professor Jinniu Deng (Department of Hematology), Professor Jie Wan and Qilin Ao (Department of Pathology), and Dr Hanlin Mu (Department of Radiology) for their help in the diagnosis of this case. We thank the patient and wish him recovery as soon as possible.

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