CASE REPORT
HEPATOLOGY

Diseases & Research

Angioimmunoblastic T Cell Lymphoma Complicated by Cirrhosis Decompensation

Jinghan Peng[1], Wanying Xie[2], Hong Yu[1], Zhibin Zhu[1], Jun Chen[1,#]

[1] Department of Liver Diseases, The Third People's Hospital of Shenzhen, The Second Affiliated Hospital of Southern University of Science and Technology, Shenzhen, Guangdong 518100, China
[2] Department of Pathology, The Third People's Hospital of Shenzhen, The Second Affiliated Hospital of Southern University of Science and Technology, Shenzhen, Guangdong 518100, China

Abstract: A 55-year-old male with a history of hepatitis B was hospitalized for persistent cough, fever, rash, and abdominal bloating. Despite treatment for suspected respiratory infection with multiple antibiotics, his symptoms worsened. Lymph node biopsy showed no abnormalities. After taking traditional Chinese medicine, he developed a rash, pruritus, and ascites, and ultrasound indicated liver cirrhosis. He had lost 15 kg during the course of his illness. However, the patient was diagnosed with Angioimmunoblastic T Cell Lymphoma (AITL) after the second lymph node biopsy.

Keywords: Liver cirrhosis; Fever; Rash; Cachexia; AITL.

Introduction

Angioimmunoblastic T Cell Lymphoma (AITL) is a rare subtype of T cell lymphoma, accounting for only 1-2% of non-Hodgkin's lymphomas[1]. The disease mainly presents with systemic lymphadenopathy, rash, splenomegaly, fever, night sweats, and cachexia[2]. The early symptoms of the disease are atypical, making it prone to misdiagnosis and missed diagnosis. In this case, the patient exhibited signs of liver cirrhosis and ascites, initially diagnosed with decompensated liver cirrhosis due to hepatitis B, and the first lymph node biopsy showed no abnormalities. As the disease progressed, the diagnosis was confirmed after a second lymph node puncture and bone marrow puncture biopsy. Therefore, for clinical suspicion of lymphoma, and when other diseases cannot fully explain symptoms such as fever, rash, and cachexia, multiple biopsies at different sites are necessary, providing more ideas and experience for clinical diagnosis and treatment.

Case Presentation

History of present illness

A 55-year-old male was admitted on July 11, 2022, presenting with a three-month history of cough, two-month fever, rash, and recent abdominal distension. Initially, he had a nocturnal cough with scanty white sputum. Blood tests revealed leukocytosis with a normal platelet count and elevated CRP, with negative respiratory virus screens. Chest X-ray indicated bilateral hilar enlargement, and treatment with moxifloxacin for a presumed respiratory infection was ineffective. Two months into his illness, he experienced high fevers up to 39.3 ℃, with pronounced fatigue during episodes, returning to normal mental status post-fever. Despite self-medication with antipyretics, fever and cough persisted. Further evaluation at another facility showed persistent leukocytosis, normal platelet count, and elevated CRP. A lung CT scan revealed multiple inflammatory lung lesions, a possible tracheal diverticulum, coronary atherosclerosis, and enlarged mediastinal and axillary lymph nodes, with minimal exudate around the gallbladder fossa and pancreatic head. He was treated with levofloxacin and theophylline for cough suppression without significant improvement. Admitted to an external hospital on May 30, 2022, he developed abdominal bloating. Laboratory tests showed leukocytosis, decreased platelet count, hypoalbuminemia, and elevated inflammatory markers. Chest CT on June 11, 2022, revealed mild interstitial lung inflammation and splenomegaly. An enhanced chest and abdominal scan on June 15, 2022, showed progression of lung inflammation and increased pleural effusion. He was treated with a regimen of antibiotics, including amoxicillin clavulanate, doxycycline, and piperacillin tazobactam, without resolution of fever. Self-treatment with traditional Chinese medicine led to temporary afebrile periods. However, after initiating a specific herbal formula (Cinnamon Twig 10 g, Amomum Fruit 15 g, Anemarrhena Rhizome 10 g, Licorice Root 5 g, Alisma Rhizome 10 g, Aucklandia Root 10 g, Moutan Cortex 15 g, Rehmannia Root (cooked) 20 g, White Peony Root (fried) 15 g, Soft-shelled Turtle Shell with Vinegar 20 g, Polyporus Sclerotium 20 g, Artemisia annua 20 g, Poria Sclerotium 20 g, Ginger Peel 15 g), he developed a systemic erythematous maculopapular rash, which resolved with continued treatment, but abdominal distension worsened. An ultrasound on July 5, 2022, at a traditional

Correspondence: Jun Chen. E-mail: drchenjun@163.com. Address: Department of Liver Diseases, The Third People's Hospital of Shenzhen, The Second Affiliated Hospital of Southern University of Science and Technology, Shenzhen, Guangdong 518100, China.
Received 13 July 2024; Revised 4 September 2024; Accepted 27 September 2024; Available Online 5 November 2024
DOI: 10.54457/DR.202402006

Chinese medicine hospital showed features consistent with liver cirrhosis, splenomegaly, and ascites. He was admitted to our facility with a diagnosis of decompensated liver cirrhosis due to hepatitis B, spontaneous bacterial peritonitis, and a suspected drug-induced rash. Since the onset, he has had poor mental status, appetite, and sleep, with normal bowel movements, slightly reduced urine output, and a weight loss of approximately 15 kg.

History of past illness

Diagnosed with hepatitis B 19 years ago, not treated. Underwent bilateral lower extremity varicose vein surgery 8 years ago, and inguinal hernia surgery 4 years ago.

Personal and family History: Uncle died of "liver cirrhosis due to hepatitis B".

Physical Examination

T 36.6 ℃ P 127 beats/min, R 22 breaths/min, BP 96/69 mmHg. Conscious, scattered dark red circular maculopapular rashes on the trunk and extremities, most of which have scabbed over. No jaundice of the skin or sclera, suspected liver palms, no spider nevi or chest capillary dilation seen. Clear breath sounds in both lungs, no dry or moist rales heard, regular heart rhythm, no abnormal heart sounds or murmurs. Abdomen bulging and soft, mild tenderness and rebound pain in the whole abdomen, liver not palpable below the costal margin, Murphy's sign negative. Spleen 4 cm below the costal margin, hard in consistency, blunt edges, no nodules palpable on the surface, no tenderness over the liver or kidney areas, shifting dullness positive, bowel sounds 4 times/min, flapping tremor negative.

External Hospital Auxiliary Examination

Right cervical lymph node pathological biopsy suggested "atypical lymphoid hyperplasia" EBER negative; TCRB, TCRD, TCRG gene rearrangement tests negative.

Laboratory Examination

Complete Blood Count: White Blood Cells (WBC): 8.07×10^9/L, Neutrophils (N): 77.5%, Hemoglobin (Hb): 85 g/L, Platelets (PLT): 66×10^9/L.

Infectious Markers: C-Reactive Protein (CRP): 16.56 mg/L; Procalcitonin (PCT): 0.2 ng/mL; Interleukin-6 (IL-6): 13 pg/mL; Ferritin: 573 ng/mL.

Liver Function Tests: Albumin: 31.7 g/L, Alanine Aminotransferase (ALT): 11 U/L, Aspartate Aminotransferase (AST): 14.9 U/L, Gamma-Glutamyl Transferase (GGT): 62 U/L, Alkaline Phosphatase (ALP): 154 U/L, Choline Esterase: 2841 U/L, Lactate Dehydrogenase (LDH): 402 U/L.

Coagulation Function: Prothrombin Time (PT): 14.1 seconds, D-Dimer: 3.31 μg/mL.

Hepatitis B Panel: HBsAg, 2.72 IU/mL, other items negative. HBV-DNA quantitative PCR: < 20 IU/mL.

Ascitic Fluid Routine: Rivanol test: Positive, White Blood Cell (WBC) count: 576×10^6/L, Mononuclear cell count: 478×10^6/L, Serum-Ascites Albumin Gradient (SAAG): 19.1 g/L.

Ascitic Fluid Lymphocyte Tuberculosis Immune Detection: Lymphocyte Activity Antigen: Negative; Tuberculosis-Specific Antigen: Positive.

Microbiology: No pathogenic bacteria found in ascitic fluid by Next Generation Sequencing (NGS).

Pleural Fluid Routine: Rivanol test: Positive, White Blood Cell (WBC) count: 18.347×10^6/L, Red Blood Cell (RBC) count: 17.000×10^6/L, Mononuclear cell count: 6.154×10^6/L, Polymorphonuclear (PMN) cell count: 12.193×10^6/L.

Pleural fluid acid-fast bacilli smear negative, Pleural tuberculosis RNA (−).

Autoimmune Disease Related Antibodies: Negative.

Gamma Globulins: 27.8% (11.1-18.8%).

Infectious Disease Related Tests: Blood cultures for bacteria, fungi, anaerobes, tuberculosis, aspergillus antigen, Brucella antibodies, Cryptococcus capsular antigen, Mycoplasma pneumoniae antibodies, (1-3)-β-D-glucan, G-negative lipopolysaccharide, Weil-Felix test, Influenza A and B virus RNA, markers for hepatitis A, C, and E viruses were all normal.

Other: Thyroid function, renal function, alpha-fetoprotein, carcinoembryonic antigen, carbohydrate antigen 19-9 were normal.

Imaging examinations Admission CT with contrast reveals: (1) Persistent nodule in the right lower lobe, suspecting right diaphragmatic bulge. (2) Resolving inflammation in the left upper lobe and bilateral lower lobes. (3) Minimal pleural effusions, decreased from prior. (4) Mediastinal and right hilar lymphadenopathy, with axillary lymph node enlargement, indeterminate. (5) Cirrhosis with portal hypertension, splenomegaly, ascites, worsening since last assessment. (6) Gallbladder wall thickening indicative of inflammation. (7) Mesenteric lymphadenopathy with some enlargement. (8) Bilateral renal cysts.

Diagnosis and differential diagnosis

The patient was admitted to the hospital with symptoms such as cough, fever, abdominal bloating, and weight loss, with a history of hepatitis B. Before admission, he had a history of using various antibiotics and traditional Chinese medicine. A systemic rash appeared during the use of traditional Chinese medicine. Ultrasound at an external hospital suggested liver cirrhosis, ascites, and splenomegaly. After admission, enhanced CT scan indicated liver cirrhosis, splenomegaly, and ascites, and complete blood count suggested anemia and thrombocytopenia, with the diagnosis considered as hepatitis B with spontaneous bacterial peritonitis. Based on the above clues, the main differential diagnoses are as follows: (1) Hematological diseases: Supporting points: fever, excessive sweating, weight loss, rash, lymphadenopathy, splenomegaly, anemia, increased ferritin, etc. Unsupported points: external hospital lymph node biopsy did not support. (2) Autoimmune diseases: Supporting points: the patient has fever, skin itching, multiple lymphadenopathy, and multiple serous membrane cavity effusions. Unsupported points: significant splenomegaly, autoimmune-related indicators are all negative. (3) Drug-induced liver injury: Supporting points: the patient had a history of using various drugs and traditional Chinese medicine, accompanied by fever and rash, and ascites gradually appeared afterward. Unsupported points: the patient mostly had high fever, and the white blood cells in the chest and abdominal fluids were significantly increased.

Diagnosis and treatment course

After admission, the patient was treated with cefazolin + met-

ronidazole, piperacillin tazobactam for infection, diuretics, antiallergics, cough suppression, and chest and abdominal cavity puncture drainage, and ascitic fluid NGS was sent for examination to exclude pathogenic bacterial infection. During the hospital stay, the patient had persistent diarrhea and irritative cough, a term that could be better translated based on clinical context), and stool culture was positive for Candida. On July 18, 2023, the patient had a body temperature of 39.8 ℃, accompanied by chills and rigors, and the reexamination of WBC was 9.55×10^9/L, with a N percentage of 89.30%; CRP was 41.680 mg/L, PCT was 8.04 ng/mL, and interleukin-6 was 348.00 pg/mL. On July 18, 2023, the patient was treated with meropenem + fluconazole for infection, and the body temperature gradually returned to normal. On July 25, 2023, the patient had a high fever and excessive sweating at night, accompanied by exacerbated cough, and expectoration of white pseudomembranous material. A throat swab indicated EB-DNA 10^5 copies/mL, and Candida was present in large amounts.

Considering the patient's worsening condition after admission, with the recurrence of high fever, excessive sweating, skin itching, and other symptoms that could not be solely explained by decompensated liver cirrhosis with spontaneous bacterial peritonitis, to further clarify the diagnosis, we suggested that the patient undergo another lymph node puncture for pathological examination.

Inguinal Lymph Node Pathology Results, see Fig. 1.

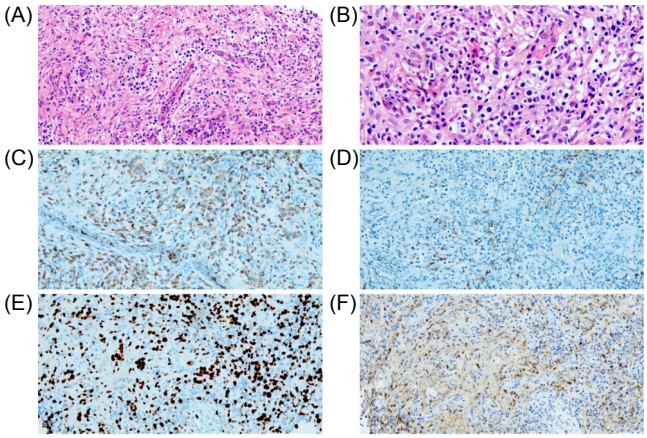

Fig. 1. Microscopic pathologic findings of the Lymph node.
A. The normal structure of the lymph node is destroyed, with diffuse infiltration of small to medium-sized tumor cells. The cellular composition is mixed, with the presence of eosinophils, plasma cells, and histiocytes; accompanied by high endothelial venule proliferation (HE. × 200).
B. Scattered immunoblasts, and multiple mitotic figures can be seen (HE. × 400).
C. CD3 expression is positive (× 200).
D. CD20 expression is low (× 200).
E. Ki67 expression is positive (× 200).
F. CXCL-13 expression is positive (× 200).
Lymph node pathological examination to diagnose: Angioimmunoblastic T Cell Lymphoma.

Treatment and Follow-up Results

The patient received chemotherapy with the CHOP regimen (cyclophosphamide, doxorubicin, vincristine, and prednisone). The patient's ascites rapidly decreased, and the abdominal drainage tube was removed. The body temperature returned to normal, and anemia improved. Chest and abdominal CT scans indicated that the lymph nodes in the mediastinum, axilla, and para-aortic region had decreased in size. The patient was followed up until after four courses of chemotherapy and then was lost to follow-up.

Discussion

AITL is a relatively rare aggressive T cell lymphoma[3,4]. The main clinical manifestations include lymphadenopathy, night sweats, fever, hepatosplenomegaly, hypergammaglobulinemia, and skin involvement[5].

In this case, another prominent manifestation was the rash and pruritus, with about 44% of AITL patients having truncal papuloplaques, which can also present as purpura, infiltrative or urticarial plaques, vesicular lesions, nodules, and erythroderma[6]. Rashes can be caused by allergies, infections, tumors, and other reasons. The patient developed a rash and pruritus after using traditional Chinese medicine and was initially misdiagnosed with a drug-induced rash.

In 2022, the prevalence of HBsAg in the Chinese population was 5.6%[7]. Despite a three-dose vaccination rate of 99% for children born in 2020[8], 92% of individuals infected with hepatitis B are over 30 years of age[9].

The patient had a history of chronic hepatitis B and presented with "confusing" manifestations of liver cirrhosis and ascites, which increased the difficulty of diagnosis. Upon physical examination, multiple enlarged lymphnodes were found, which is a common clinical manifestation of AITL and can often be confirmed by biopsy. However, the patient's first lymph node biopsy at an external hospital did not reveal any specific findings, and it was not until the second biopsy of the cervical and inguinal lymph nodes that the diagnosis was confirmed. This suggests that lymphoma sometimes requires multiple biopsies at different sites to obtain a positive result[10]. The pathogenesis of AITL is not well understood, but it is currently believed to be closely related to the potential latent infection of Epstein-Barr Virus (EBV), and most EBV in AITL is in a latent and clonal state[11-13].

Currently, the first-line chemotherapy regimens recommended by guidelines include CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), CHOEP (CHOP regimen + etoposide), and dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) regimens, and high-dose chemotherapy (HDT) with autologous stem cell transplantation is also an acceptable treatment option[14]. After the patient was transferred to the Hematology Department, he underwent multiple courses of chemotherapy, with the body temperature returning to normal, ascites and rash receding, indicating some effectiveness of the treatment. However, the overall prognosis of this disease is limited[3].

This case presented with multiple "manifestations" such as liver cirrhosis, fever, and ascites, and visited multiple hospitals several times. The final diagnosis of AITL was made after two lymph node pathological examinations, which was within our expectations. Carefully tracing back the medical history, phenomena such as high fever, weight loss, rash, and splenomegaly all pointed to hematological diseases. Therefore, when diagnosing and treating diseases, it is necessary to look beyond one's own specialty and seek evidence from multiple perspectives and disciplines. The patient's final diagnosis involved multiple disciplines including Hepatology, Infectious Disease, Hematology, Interventional Ultrasound, Pathology, and Respirology. A multidisciplinary approach to the diagnosis and treatment of difficult cases is particularly important.

Abbreviations

AITL, Angioimmunoblastic T Cell Lymphoma; ALP, Alkaline Phosphatase; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; CD, Cluster of Differentiation; CHOEP, Cyclophosphamide, Doxorubicin, Etoposide, Vincristine, and Prednisone; CHOP, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone; CRP, C-reactive protein; CT, Computed Tomography; CXCL-13, C-X-C motif ligand 13; EB DNA, Epstein-Barr Virus DNA; EBER, Epstein-Barr virus-encoded RNA; GGT, Gamma-Glutamyl Transferase; Hb, hemoglobin; HBsAg, Hepatitis B virus surface antigen; HE, Hematoxylin-Eosin; LDH, Lactate Dehydrogenase; N, neutrophils; NGS, Next Generation Sequencing; PCT, procalcitonin; PLT, platelt; PMN, Polymorphonuclear; RBC, Red Blood Cell; SAAG, Serum Ascites Albumin Gradient; TCRB, T cell receptor beta; TCRG, T cell receptor gamma; TCRL, T Cell Receptor Ligand; WBC, white blood cell count.

Funding

This work was supported by the grants from the construction of key medical disciplines in Shenzhen No.SZXK076.

Ethical approval and consent to participate

The participant in this study has provided informed written consent before enrollment.

Conflict of interest

The authors declare no competing financial interests.

Authors' contributions

JHP, HY, ZBZ and JC fomulated and implemented treatment for this patient. JHP and JC prepared figures and wrote the manuscript. WYX provided diagnostic and guidance for the pathology.

References

[1] Kwong YL, Chan T, Tan D, et al. PD1 blockade with pembrolizumab is highly effective in relapsed or refractory NK/T-cell lymphoma failing l-asparaginase. Blood, 2017, 129(17): 2437-2442.

[2] Frizzera G, Moran EM, Rappaport H. Angio-immunoblastic lymphadenopathy: Diagnosis and clinical course. Am J Med, 1975, 59(6): 803-18.

[3] Vose J, Armitage J, Weisenburger D. International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. J Clin Oncol, 2008, 26(25): 4124-4130.

[4] Lunning MA, Vose JM. Angioimmunoblastic T-cell lymphoma: the many-faced lymphoma. Blood, 2017, 129(9): 1095-1102.

[5] Bernstein JE, Soltani K, Lorincz AL. Cutaneous manifestations of angioimmunoblastic lymphadenopathy. J Am Acad Dermatol, 1979, 1(3): 227-32.

[6] Papadavid E, Panayiotides I, Dalamaga M, et al. Cutaneous involvement in angioimmunoblastic T-cell lymphoma. Indian J Dermatol, 2010, 55(3): 279-80.

[7] Cooke GS, Flower B, Cunningham E, et al. Progress towards elimination of viral hepatitis: a Lancet Gastroenterology & Hepatology Commission update. Lancet Gastroenterol Hepatol, 2024, 9(4): 346-365.

[8] WHO. Global Health Observatory data repository: hepatitis B (HepB3) immunization coverage estimates by country. Available from: https://apps.who.int/gho/data/view.main.80300. [Last accessed on 2023]

[9] CDA Foundation. Available from: https://www. devex. com/organizations/center-fordisease-analysis-foundation-cdaf-132936.

[10] Sandhaus LM. Fine-needle aspiration cytology in the diagnosis of lymphoma: the next step. Am J Clin Pathol, 2000, 113(5): 623-627.

[11] Chen YH, Gong Y. Cytopathology in the diagnosis of lymphoma. Cancer Treat Res, 2014, 160: 211-240.

[12] Bahri R, Boyer F, Halabi MA, et al. Epstein-Barr Virus (EBV) Is Mostly Latent and Clonal in Angioimmunoblastic T Cell Lymphoma (AITL). Cancers, 2022, 14(12): 2899.

[13] Bayda N, Tilloy V, Chaunavel A, et al. Comprehensive Epstein-Barr Virus Transcriptome by RNA-Sequencing in Angioimmunoblastic T Cell Lymphoma (AITL) and Other Lymphomas. Cancers, 2021, 13(4): 610.

[14] Horwitz SM, Ansell S, Ai WZ, et al. T-Cell Lymphomas, Version 2.2022, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Cancer Netw, 2022, 20(3): 285-308.