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Case Report

Fever of unknown origin characterized by acute kidney injury and nephrotic syndrome diagnosed as intravascular large B-cell lymphoma of kidney: case report and literature review

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Abstract: A 60-year-old Chinese female patient was admitted to the hospital with complaint of intermittent fever for more than seven months. The main clinical manifestations were acute kidney injury and nephrotic syndrome which developed into a hemophagocytic syndrome. The symptoms did not improve with antibiotics. Moreover, prednisone could only reduce the fever. Finally, a kidney biopsy showed many CD20-positive cells in the glomerulus and some in the peritubular capillaries. This led to a diagnosis of renal intravascular large B-cell lymphoma.

Keywords: Fever of unknown origin, nephrotic syndrome, intravascular large B-cell lymphoma, renal lymphoma

Introduction

Intravascular large B-cell lymphoma (IVLBCL) is a rare and aggressive non-Hodgkin lymphoma involving different organs and has different clinical manifestations. Renal IVLBCL is extremely rare. Therefore, its diagnosis is often delayed and difficult to make until a biopsy is done. The disease has been recognized by the 2008 World Health Organization classification of tumors of the hematopoietic and lymphoid tissues. Previously, it was known as intravascular large B-cell lymphoma, intravascular lymphomatosis, angiotropic large-cell lymphoma, and malignant angioendotheliomatosis. Given the rarity of renal IVLBCL, we present a case report of a 60-year-old female patient with IVLBCL and conduct a comprehensive literature review.

Case presentation

A 60-year-old female patient was admitted to the hospital with intermittent fever for more than seven months. The patient developed fever, chills, sweating, and bilateral calf pain after an episode of a cold seven months ago. Her highest body temperature did not exceed 39°C. The patient was having irregular fever accompanied mainly by a dry cough. The patient had no hemoptysis, no headache, and no rash. After one week, she was admitted to a local hospital and given ampicillin to prevent infection. The antibiotic treatment reduced the fever for six days. However, the effect was not long-lasting. After taking traditional Chinese medicine, the patient's temperature normalized. However, other symptoms, like cough, sweating, dry mouth, nausea, and occasional vomiting of the stomach contents persisted. After three months, she developed repeated episodes of fever, dry cough, and shortness of breath. Also, her body temperature was between 37.5-39°C. She was admitted to another hospital. The blood routine examination revealed the following picture: WBC: $5.59*10^9$/L, N: 59%, HB: 88 g/L, PLT: $200*10^9$/L, ferritin: 984.3 ng/ml, triglyceride: 3.17 mmol/L, and serum creatinine: 167 μmol/L. The bone marrow biopsy report revealed the following picture: bone marrow hyperplasia was significantly active, erythroid lines were active, and hemophagocytic features were shown. Despite receiving six days of treatment, including oxygen

Table 1. The blood routine and serum creatinine of the patients before and after glucocorticoid treatment

Date	Blood routine test			Renal function	Treatments
	WBC ($\times10^9$/L)	Hb (g/L)	PLT ($\times10^9$/L)	Scr (μmol/L)	
1	5.59	88	200	167	
40	5.48	70	109	112	
60	6.96	65	212	140	
75	10.85	54	69	311	Dexamethasone 5 mg iv on day 75, 80 and 85.
80	13	86	75	232	
85	6.5	76	77	136	
100	5.66	73	125	118	

The test results before August 14 were compiled from the examination reports of the patients in other hospitals before admission. WBC, white blood cells. Hb, hemoglobin. PLT, platelet counts. Scr, serum creatinine.

inhalation, doxycycline combined with levofloxacin for anti-infection, and PPI, her intermittent fever persisted. Hence, she was transferred to the central hospital for further examination. The PET-CT showed splenomegaly with mildly increased glucose metabolism (thickness: 5 cm, SUV max: 2.6); and diffuse mild metabolic changes in both renal parenchyma. The differential diagnoses considered in this patient were as follows: fever of unknown origin, hemophagocytic syndrome, acute kidney injury, severe anemia, hypoproteinemia, hyperlipidemia, and splenomegaly. After admission, despite giving intermittent infusions of albumin, plasma, red cell suspensions, and antibiotics, the patient's fever persisted. However, glucocorticoid therapy helped (**Table 1**). Since the cause of the fever was unclear, the patient was admitted to our hospital three months later.

Physical examination

The patient's body temperature was 37.2°C. The breath sounds of both lungs were coarse, and no obvious dry or wet rales were heard. The mitral valve sound was audible and had a mild systolic murmur. The liver and spleen were not under the ribs. There was no obvious rash on the whole body. Additionally, no petechiae or ecchymosis were noted on the skin and the mucous membranes. Pitting edema was seen in both lower extremities in the front of the tibia.

Laboratory tests

Blood routine revealed the following: WBC: 5.66*10^9/L, N: 65%, PLT: 125*10^9/L; Hb: 73 g/L. The liver function was normal, Scr: 118 umol/L, TG: 3.58 mmol/L, 24 h urine protein quantification: 3.58 g, EBV/CMV-DNA negative, bacterial culture of blood: negative, autoimmune antibody: negative, C3/C4: normal.

Auxiliary examination

B-ultrasound revealed a liver cyst, possible nephropathy in both kidneys, and a small cyst in the right kidney. The chest CT showed increased markings in both lungs and mild interstitial changes with exudation.

Disease progression

After admission, glucocorticoids were stopped. This resulted in a gradual increase in the patient's body temperature and a noticeable decrease in the hemoglobin levels and platelet counts within three days (**Figure 1**). After performing the bone puncture, the patient was treated with dexamethasone. The patient's bone marrow smear showed that the proportion of mononuclear tissue macrophages and hemophagocytic cells was increased (accounting for 2.5%). In addition, a small number of immature lymphocytes and tortuous lymphocytes were seen. Furthermore, abnormal cells were not found by bone marrow flow cytometry. After adding dexamethasone, the patient's temperature and anemia noticeably improved, and the creatinine level also decreased (**Figure 1A**, **1D**). As she had hypertension, hypoalbuminemia, proteinuria, and edema in both lower extremities, a nephrotic syndrome was considered the probable clinical presentation. Despite initiating glucocorticoid therapy, the patient's 24 h urine total protein continued to increase

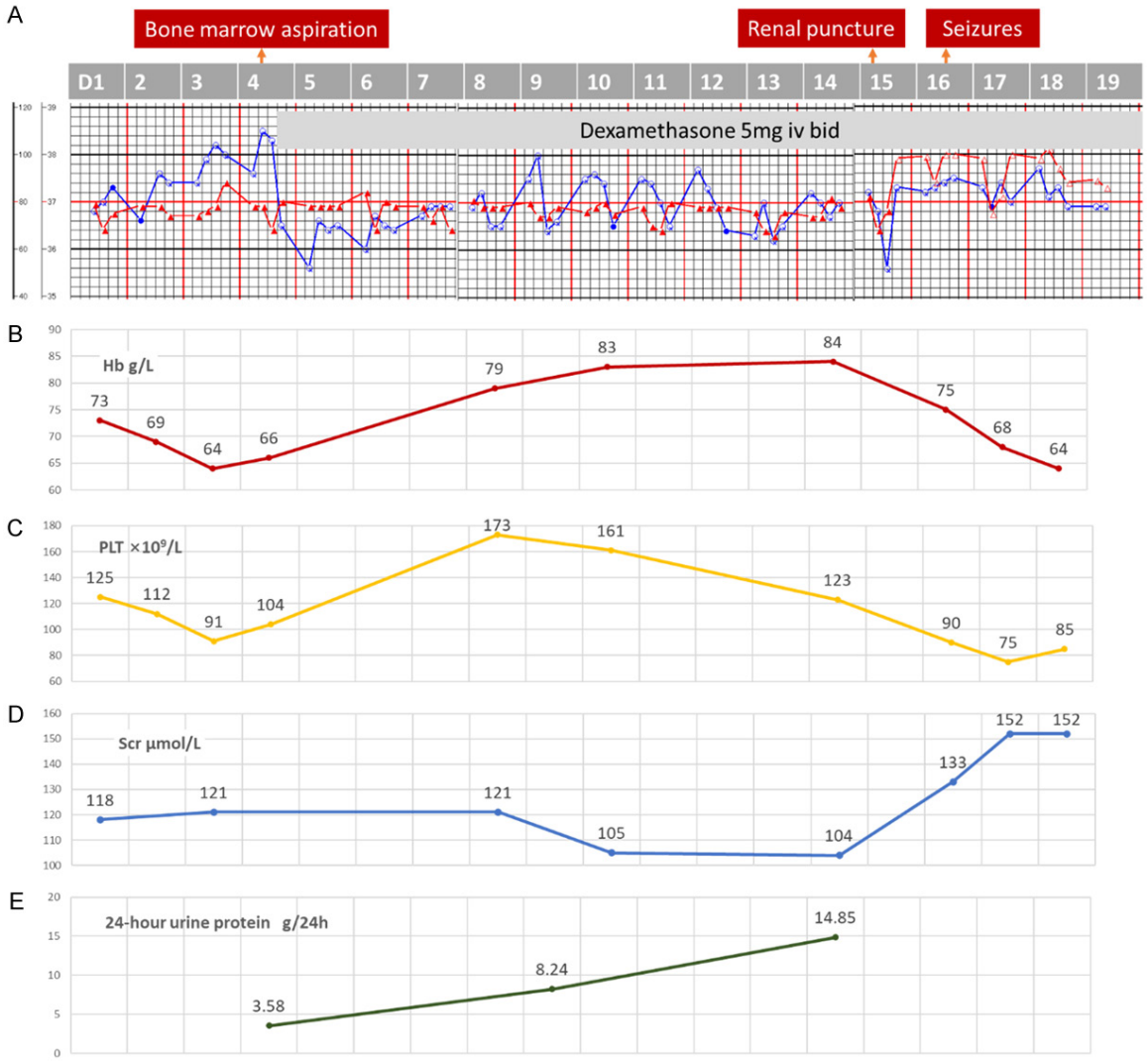

Figure 1. The patient's body temperature, treatment process, and some laboratory indicators after admission. A. The white numbers on the grey indicate the days after admission. The blue line represents body temperature. The red line represents the heart rate. B. Hemoglobin results of the routine blood test. Hb, Hemoglobin. C. Platelet counts of blood routine test. PLT, platelet count. D. Serum creatinine results. Scr, serum creatinine. E. Results of the 24-hour urine protein test.

(**Figure 1E**). Also, the specific indicators of membranous nephropathy, like PLA2R and TSHD7A, were both negative. Therefore, a renal core biopsy was performed. While awaiting the report, the patient experienced two major seizures for which an intramuscular injection of diazepam 10 mg was given. The head CT and MRI, lumbar puncture, and cerebrospinal fluid examination revealed the following picture: sugar: 5.43 mmol/L, protein: 0.18 g/L, and white cells: $2*10^6$/L. The brainstem MR enhancement showed the possibility of new brainstem infarction (**Figure 2**). Simultaneously, her hemoglobin and platelet count markedly decreased, whereas the creatinine level increased rapidly (**Figure 1B**, **1C**, **1E**). A repeated chest CT showed a progression in the pulmonary infection as compared to previous reports. Considering the patient's moderate dose of corticosteroids, caspofungin combined with meropenem was given to prevent infection. At this time, the results of the renal puncture reported that many CD20-positive cells were present in the glomerulus and some in the peritubular capillaries. Therefore, the patient was diagnosed with intravascular large B-cell lym-

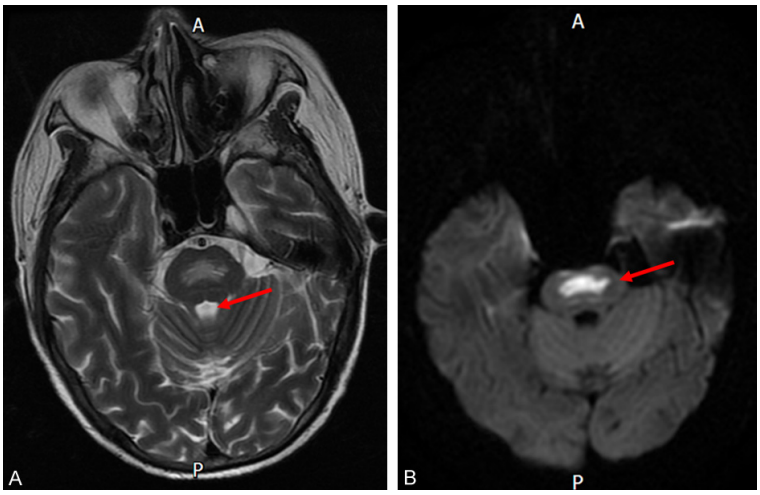

Figure 2. The brain MR showed patchy abnormal signal in the brain stem after the patient had epilepsy. A. T2W FLAIR image. B. DWI image (red arrow).

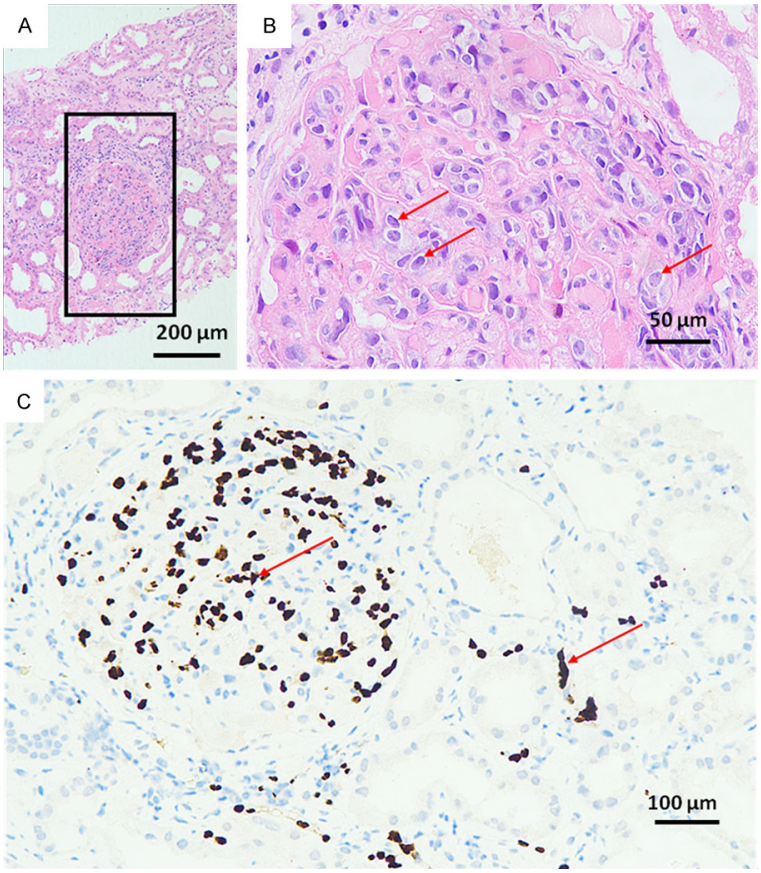

Figure 3. Biopsy and pathologic examination of the kidney show that the density of cells in the glomerulus was significantly increased, and macronuclear cells were seen in the capillary loops and mesangial areas, with obvious nucleoli, and a moderate amount of cytoplasm. A: H&E, Large B-cell infiltration was seen in the peritubular interstitium. (Original magnification ×100, scale bar: 200 μm). B: High magnification shows scattered large B-cell infiltration in the glomerulus. (Original magnification ×400, scale bar: 50 μm). C: Immunohistochemistry shows a PAX5-positive cells infiltrate scattered in the glomerulus and the peritubular interstitium. (Original magnification ×400, scale bar: 100 μm).

phoma, a non-GCB subtype based on the histology of kidney biopsy (**Figure 3**). The patient was transferred to the Division of Hematology for chemotherapy. After treatment, her condition was relatively stable.

Discussion

Intravascular large B-cell lymphoma (IVLBCL) is a rare extranodal large B-cell lymphoma characterized by the selective growth of lymphoma cells within the lumen of small blood vessels [1]. Since it was first reported in 1959, over 300 cases have been reported worldwide. Moreover, a literature search might reveal fewer than 1,000 cases so far. Renal ILBL is even rarer. In IVLBCL, the kidney is involved in approximately 2%-13% of cases. A wide range of clinical presentations might be observed from mild proteinuria to nephrotic syndrome with or without acute kidney injury, kidney enlargement, or a kidney mass [2]. According to the 2008 WHO classification, it has been independently classified as diffuse large B-cell lymphoma [1].

IVLBCL mostly affects older adults. A total of 80% of patients with IVLBCL are over 60 years old. The incidence is higher in men than women [3]. IVLBCL shows a variety of clinical symptoms, including a single symptom of unexplained persistent fever, pain, or organ damage or failure [4], involving any organ. IVLBCL also makes early diagnosis difficult. Only 26% of patients are diagnosed with the disease before the pathologic examination. Approximately, 55-85% of patients present with systemic group B

symptoms, as well as fever, night sweats, and weight loss. Around 45% of patients also had undiagnosed fever. The disease is clinically divided into two types based on clinical manifestations and organ involvement. In western patients, the disease is mainly called the European type or the classic type. In this type, neurological and dermatological symptoms are the most common. In Asian patients, hemophagocytic syndrome, fever, anemia, thrombocytopenia, hepatosplenomegaly, and bone marrow involvement are more common. Hence, this is also called the hemophagocytic type or Asian type [5].

The diagnosis of intravascular large B-cell lymphoma relies on pathology. Different organs are involved in different symptoms. However, the common point is that tumor cells are mainly distributed in small and medium blood vessels, especially capillaries, which do not easily form masses and cannot be found easily clinically. After obtaining an appropriate biopsy sample, making an accurate diagnosis is not difficult as large tumor cells are found in the lumens of small blood vessels or the sinusoids of organs. Immunohistochemical staining for CD-20 and CD34 is particularly useful for diagnosis, as staining helps identify tumor cells in blood vessels or sinusoids [6].

In patients with IVLBCL, CHOP and CHOP-like regimens are still the main treatment methods. Rituximab can noticeably alter the progression of IVLBCL [7]. In patients who have not undergone rituximab treatment, IVLBCL has an extremely poor prognosis due to the difficulty of diagnosis, involvement of multiple organs, and a delay in diagnosis made at stage IV. Despite improved outcomes, relapse is seen in a substantial proportion of patients, especially in those with central nervous system manifestations [8]. Presently, plentiful experience in the treatment of IVLBCL with new drugs is not available. Although a few treatments are available, the success rate is very low. Interestingly, autopsy cases of disseminated IVLBCL showed strong expression of programmed death ligand 1 (PD-L1) on tumor lymphocytes. This finding may have important therapeutic implications [5]. However, the prognosis for the hemophagocytic population remains very poor.

To summarize, it is not easy to diagnose the rare disease of IVLBL. A patient with a fever of unknown origin had abnormal renal function, proteinuria, and hypoalbuminemia. Thus, the nephrotic syndrome was considered the clinical manifestation. In such patients, when tracing the cause of fever, the cause of renal insufficiency should also be searched. In combined hemophagocytic syndrome, choosing the appropriate timing of renal biopsy and finally obtaining the pathologic evidence was the most notable aspect of this case. IVLBL is quite rare, and its clinical manifestations are very diverse, often including symptoms related to organ dysfunction caused by vascular occlusion which could involve any organ. For patients with fever of unknown origin combined with proteinuria and abnormal renal function, especially patients with the hemophagocytic syndrome, IVLBL should be one of the differential diagnoses.

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Disclosure of conflict of interest

None.

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