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CASE REPORT

A Misdiagnosed Atypical Case of Diffuse Large B Cell Lymphoma Diagnosed by Computed Tomography Guided Spleen Biopsy

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SUMMARY

Background: **Lymphoma is a malignancy of hematopoietic and lymphoid tissues. Early diagnosis of lymphoma is very important and could save patients' lives. Nevertheless, the diagnosis of lymphoma could be difficult in the presence of complex manifestations and a lack of convincing laboratory findings. Here we report a case of large B cell lymphoma misdiagnosed as hemophagocytic syndrome during the hospitalization and treatment course.**
Methods and Results: **Retrospective review of patient's clinical data, differential diagnosis, and treatment were performed. Patient's disease course was followed and the final diagnosis, along with relevant discussions and summaries were documented.**
Conclusions: **This report may be helpful in the diagnosis of lymphoma with complex manifestations differentiated from hemophagocytic syndrome, and may facilitate early diagnosis and treatment.**
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KEY WORDS

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CASE REPORT

A 65-year-old male patient, presenting with repeated high fever (40°C), chills, and left elbow and wrist joint pain for 2 weeks, was admitted for hospitalization and treatment on the diagnosis of "fever of unknown origin". He did not report abdominal pain or diarrhea.
The patient complained of feeling unwell and showed 2.5 kg weight loss. The symptoms persisted after the taking levofloxacin plus cefotiam. He additionally denied having tuberculosis and a blood transfusion history.

The patient's skin was pale but with no jaundice. The body's superficial lymph nodes were impalpable. The liver and spleen were impalpable, and other signs of physical examination were normal.

The morphological examination of the bone marrow smear indicated a bone marrow hyperplasia with 15% granulocytes, 60.5% erythrocyte series, and the ratio of granulocytes: erythrocytes was 0.2, showing a mild reduction in granulocytes; however, the morphology was still roughly normal. It is notable that the lymphocytes accounted for 18%, with 8% atypical lymphocytes (Figure 1A). Phagocytic histiocytes were seen in bone marrow smear (Figure 1B). Bone marrow biopsy: the hematopoietic area accounted for 30%, with granulocyte to erythrocyte ratio of 2:1; scatter megakaryocytes were seen with normal morphology. Immunohistochemistry: CD31 expression positive in megakaryocytes; myeloperoxidase (MPO) staining positive in granulocytes; no metastatic tumor cells were seen. Hematology analysis of peripheral blood: the leukocyte count was normal with slightly increased levels of neutrophils; toxic granules and vacuolar degeneration were observed in some neutrophils. Atypical lymphocytes were observed. Flow cytometry result for immunophenotype: lymphocytes R2 = 15.92%, leukocytes R4 = 65.39%, immature cells R3 = 2.23% (indicating normal leukocyte population). Chromosome analysis (karyotyping): Five complex chromosomal aberration karyotypes were found in 20 metaphase cells. However, there were no other bone marrow or abnormal laboratory findings to support a diagnosis of myelodysplastic syndrome (MDS) or acute myeloid leukemia. Additional laboratory results are shown in Table 1.

Computed tomography (CT) scanning of the abdomen showed a mild hypersplenotrophy (2D 1 Distance: 5.19 cm, while normal value is < 4 cm, Figure 1C); No enlarged lymph nodes in the abdomen were seen. Lymph nodes of the bilateral neck, bilateral axillary fossa, and bilateral inguinal were visible.

The patient presented repeated chills and fever as the main symptoms, along with persistently elevated serum C-reactive protein and procalcitonin during the hospitalization. His high fever was still persistent after the taking of cefoperazone sodium plus sulbactam sodium, cefodizime sodium plus amikacin, and doxycycline antibiotics treatment, thus the antibiotics treatment was terminated. The patient's fever usually recurred in the afternoon and at night. In order to exclude an infection of tuberculosis, tuberculosis tests were ordered and the results were normal. In addition, the diagnostic anti-tuberculosis was administered as well, except during laboratory testing; however, the fever persisted, thus tuberculosis was excluded, and the associated treatment was terminated.

DISCUSSION

According to the diagnostic guidelines of hemophagocytic syndrome HLH-2004 [1], the patient was diagnosed with hemophagocytic syndrome. Thus, a treatment plan towards hemophagocytic syndrome for this patient was carried out as follows: VP-16 + Dexamethasone for a total of 5 weeks with variable doses. His condition improved after chemotherapy, and he was discharged. However, his fever recurred not long after discharge from the hospital. Along with chills and fever, the temperature persisted as high as 39.5°C every day, and he was re-admitted for hospitalization and further treatment.

At this point, a multi-disciplinary team (MDT) was formed to discuss the case, and the decision was made to perform the spleen biopsy for pathological diagnosis to exclude lymphoma, despite the risk of bleeding. The biopsy was performed under CT-scan positioning guidance.

Pathology reports of the biopsy indicated the patient's spleen and bone marrow were massively infiltrated by atypical lymphocytes, although the infiltration was milder in the bone marrow relative to the spleen (data not shown). Immunohistochemistry of the spleen and bone marrow biopsy showed positive for CD20 (Figure 1D and E). Gene rearrangement analysis results showed a clone rearrangement in IgH and IgK. Based on the above findings, the patient was eventually diagnosed with diffuse large B-cell lymphoma. He was subsequently treated with R-CHOP regimen (Rituximab 0.1 g day 0, Cyclophosphamide 0.6 g day 1, Doxorubicin 40 mg day 1, Vincristine 2 mg day 1, Prednisone Acetate tablets 60 mg day 1 to day 5). This regimen was halted and switched to GDP regimen due to the development of difficulties in breathing, oxygen saturation reduction, side effects from Rituximab. The GDP regimen consisted of: gemcitabine 1.6 g for day 1, dexamethasone 30 mg from day 1 to day 4, oxaliplatin 0.2 g from day 1 to day 3. The patient had a significant response to the GDP regimen, and he was discharged after 3 cycles of chemotherapy.

The patient returned for hospitalization only 1 week after previous discharge due to relapse of fever and chills. His condition worsened due to liver function damage and the condition was serious. He unfortunately passed away not long after.

Primary hemophagocytic syndrome is a familial autosomal recessive hereditary disease, while secondary hemophagocytic syndrome is the consequence of abnormal immune activation. For secondary hemophagocytic syndrome, malignancies including T cell lymphoma, leukemia, and precursor B-cell lymphoblastic leukemia are the most common causes in patients over 60 years of age, with the next most common causes being infection and autoimmune diseases [2,3]. For this patient, there was no evidence of infection, solid tumors (data not shown), or other malignancies, and the patient's persistent febrile condition made diagnosis difficult. Although

Table 1. Patient's laboratory test results (not described elsewhere).

Test	Result	Reference range
WBC count (* 10^9/L)	5.59	4.0 - 10.0 * 10^9/L
Neutrophil (%)	55.84	50 - 70%
Hemoglobin (g/L)	88	110 - 160 g/L
Platelet (* 10^9/L)	130	100 - 400 * 10^9/L
C-reactive protein (CRP, mg/L)	67.59	0 - 12 mg/L
Procalcitonin (PCT, µg/L)	0.84	0 - 0.05 µg/L
Blood cultures (3 sets)	bacteria negative, fungi negative, haemophilus negative (6 days culture)	negative
Mycoplasma and Chlamydia antibodies (IgM, IgG)	negative	negative
HIV antibody (S/CO)	negative	negative
Total Gram-negative bacteria lipopolysaccharide (pg/mL)	117.70	< 10 pg/ml
Widal test	negative	negative
Tuberculosis associated T cells test (T-SPOT and TB NK cells)	negative	negative
Triglyceride (TG, mmol/L)	2.57	< 1.7 mmol/L
Alanine aminotransferase, ALT (U/L)	76	0 - 50 U/L
γ-glutamyl-transpeptidase, γ-GT (U/L)	111	0 - 60 U/L
Lactate dehydrogenase (µ/L)	334	120 - 250 U/L
Serum ferritin (µg/L)	> 1,500	23.9 - 336.2 µg/L
Fibrinogen, FIB (g/L)	6.59	2 - 4 g/L
D-Dimer (µg/mL)	1.23	0.01 - 0.5 mg/L
Soluble CD25 (sIL-2R, U/mL)	7,278	223 - 710 U/mL
Rheumatoid factor (RF), Anti-Cyclic Citrullinated Peptide (anti-CCP), Anti-keratin antibodies (AKA)	negative	negative
Autoantibodies and anti-neutrophil antibodies	negative	negative
Anticardiolipin antibody, ACA	negative	negative
Anti double-stranded DNA antibody	negative	negative
Extractable nuclear antigen, ENA	negative	negative
Antineutrophil cytoplasmic antibodies, ANCA	negative	negative

the result of the CT scan indicated that the patient had splenomegaly, no evidence of tumor cells was found from either the triple bone marrow aspiration and biopsy or the bone marrow cell flow cytometry analysis. The result from the bone marrow aspiration found only 8% abnormal lymphocytes in the examination, which was considered normal. However, these results still did not exclude the possibility of lymphoproliferative disorders, as the negative result of tumor cells from the bone marrow biopsy and aspiration could have been due to a status of indolent lymphoma or small lesion tumor, thus further bone marrow examinations could have been considered when necessary.

The patient showed mild lymph node enlargement in the inguinal region via ultrasound during hospitalization, indicating a lymph node biopsy may be performed when necessary. The patient's spleen was enlarged via CT scan, indicating a possibility of tumor cell involvement and thus consideration for consultation from the division of interventional treatment to assess whether a spleen biopsy is necessary to confirm the diagnosis [4-6]. In this case, the patient presented recurrent febrile status, thus a spleen biopsy operation was performed under CT positioning guidance after the Multi-Disciplinary Team discussion, although the procedure carried the risk of spleen bleeding.

The lesson (experience) from this case provided indication that for a patient with fever of unknown origins, with enlargement of the spleen and lymph nodes, failure to respond to antibiotics and anti tuberculosis treatment,

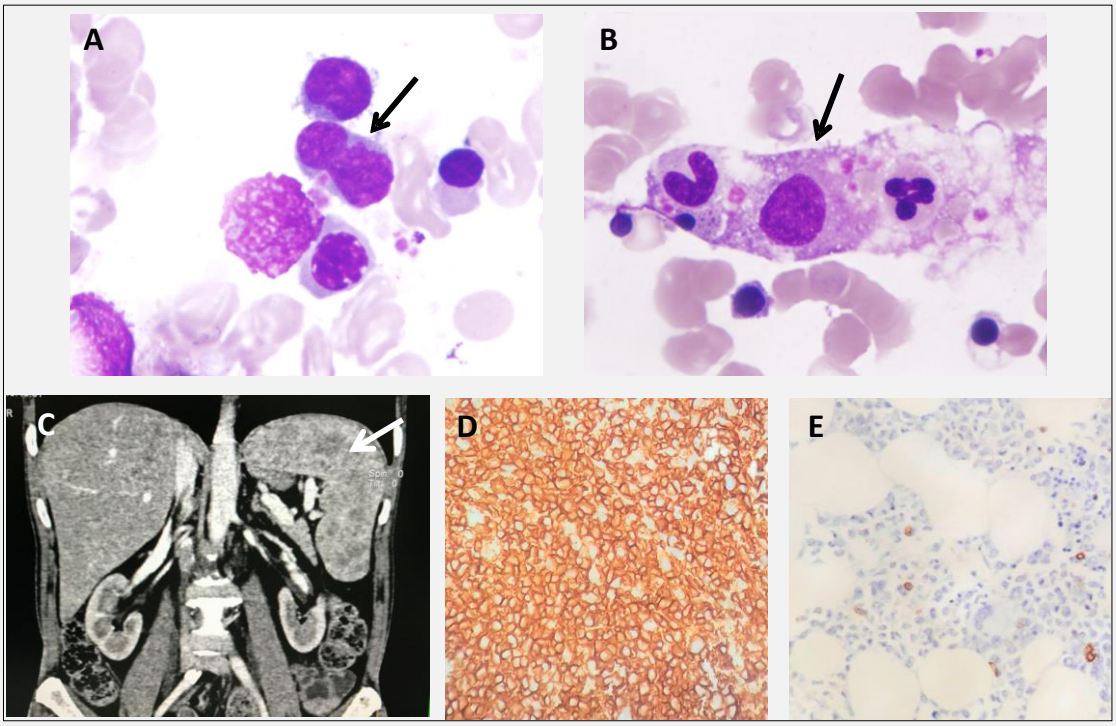

Figure 1. Atypical lymphocytes and phagocytic histiocyte in bone marrow (Wright-Giemsa, A, B), abdomen computed tomography imaging indicating of enlarged spleen (C, arrow pointed), and immunohistochemistry for CD20 of spleen and bone marrow biopsy (D, E).

normal testing results for autoimmune diseases, a lack of superficial lymph nodes enlargement, normal bone marrow aspiration morphology and biopsy examination, and normal flow cytometry of bone marrow cells, a spleen or lymph node biopsy for pathology diagnosis should be considered.

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Author Contributions:
Liejun Jiang performed the study on bone marrow examination, data collection and analysis; Qiang Wei and Endi Wang made the pathology diagnosis; Han Li and Cheng Peng managed the patient; Huayi Huang for conception and manuscript writing.

Declaration Interest:
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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