Hemophagocytic syndrome and neurological involvement in a case of intravascular large B-cell lymphoma

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Abstract
Intravascular large B-cell lymphoma (IVLBCL) is a rare form of non-Hodgkin’s lymphoma, and is divided into Western and Asian variants. The latter is rarely found to have neurological system involvement. In China, there have only been a few diagnosed cases of IVLBCL. Here, we present a Chinese case of Asian-variant IVLBCL with neurological symptoms. A 32-year-old Chinese man presented with bilateral lower limb numbness and persistent fever. He also complained of difficulties in urination and defecation. In addition, splenomegaly and pancytopenia were observed. We identified 3% dysplastic lymphocytes in his peripheral blood film, and his bone marrow biopsy led to a diagnosis of Asian-variant IVLBCL. Lumbar spine magnetic resonance imaging, which revealed an edematous spinal cord, further confirmed neurological involvement. The patient refused treatment from the time of diagnosis, and died 2 months after being discharged. IVLBCL is a highly aggressive but nonspecific clinical manifestation that is difficult to diagnose; therefore, a greater understanding of the disease is needed. The current first-line therapy involves R-CHOP combination therapy (cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab); however, the overall prognosis of IVLBCL remains poor.

Keywords
Intravascular large B-cell lymphoma, hemophagocytic syndrome, Asian variant, neurological symptoms, non-Hodgkin’s lymphoma, bilateral lower limb numbness

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Introduction

Intravascular large B-cell lymphoma (IVLBCL) is a rare form of non-Hodgkin’s lymphoma. In 2016, the World Health Organization (WHO) classification of lymphoid neoplasms categorized IVLBCL as an independent subset of diffuse large B-cell lymphomas. There are marked differences in the clinical presentation of IVLBCL between Asian and Western populations; thus, this disease is divided into Western and Asian variants. Western-variant IVLBCL typically presents with dermatological and neurological symptoms, whereas the Asian variant tends to present alongside hemophagocytic syndrome (HPS). Currently, case reports of Asian-type IVLBCL come predominantly from Japan. There have only been a few diagnosed cases of IVLBCL in China. The present case report aims to examine and discuss a case of Asian-variant IVLBCL presenting with neurological symptoms, and review the existing literature in the field.

Case presentation

A 32-year-old Chinese man was admitted to hospital in July 2018 with a 2-month history of bilateral lower limb numbness and persistent fever for 1 month. His symptoms had deteriorated over the previous month, manifesting as bilateral limb swelling, difficulty in walking, fatigue, and a maximum body temperature of 39°C. The patient also complained of difficulties in urination and defecation. No chills or rigors, cough, abdominal pain, or abdominal bloating were identified. From the onset of his symptoms, the patient experienced decreased appetite, poor sleep, and an unintentional weight loss of 3 kg.

On admission, physical examination revealed a body temperature of 39°C, pulse rate of 90 beats per minute, respiratory rate of 27 breaths per minute, and blood pressure of 90/50 mmHg. The patient had clear consciousness and an anemic appearance. General physical examination results were normal except for splenomegaly, which was palpable 2 cm below the costal margin and bilateral lower limbs, with concave edema. Neurological examination revealed muscle weakness in the lower limbs (Medical Research Council grade 4) and hyporeflexia in the lower limbs with absent calcaneal reflexes. Neuropathological signs and meningeal irritation signs were not noted. Sensation to pain on the right side below the first lumbar spinal vertebra was decreased.

The patient was anemic (hemoglobin, 84 g/L) and thrombocytopenic (platelets, 77 × 10^9/L). In addition, a serum biochemistry test revealed marked increases in lactate dehydrogenase (LDH; 1588 U/L), serum calcium (3.09 mmol/L), fibrinogen (1.42 g/L), and ferritin (1732 ng/L), as well as hypoproteinemia (albumin, 28.5 g/L). It is worth noting that there were also large increases in soluble interleukin-2 receptor alpha chain (sCD25, 13,213 pg/mL) and decreases in natural killer (NK) cell activity (12.93%). Hepatitis B, hepatitis C, human immunodeficiency virus, and syphilis serologies were negative. Cerebrospinal fluid analysis revealed the following: opening pressure 110 mmH2O, total protein 78.24 mg/dL, glucose 2.25 mmol/L, and 4 cells/µL (85% lymphocytes and 15% mononuclear cells). Abdominal computed tomography revealed splenomegaly. Lumbar spine magnetic resonance imaging demonstrated an edematous spinal cord in the fourth sacral vertebra, as well as in the second and third coccygeal vertebrae. The peripheral blood film was abnormal, with 3% dysplastic lymphocytes. Bone marrow aspiration showed 5% undifferentiated hyperplastic cells and classical hemophagocytosis. Cytogenetic analysis revealed an
aberrant karyotype: t(8; 14)(q24; q32). Bone marrow biopsy for immunohistochemistry confirmed IVLBCL; the neoplastic cells were positive for CD20, B-cell lymphoma 6 (Bcl-6), and Ki-67 (Figure 1). According to the hemophagocytic lymphohistiocytosis (HLH)-2004 study guidelines, at least five of the following eight diagnostic criteria must be fulfilled for diagnosis with IVLBCL: (1) fever, (2) splenomegaly, (3) cytopenia affecting ≥2 cell lines (hemoglobin < 90 g/L, and in infants < 100 g/L; platelet count < 100 × 10^9/L; neutrophils < 1.0 × 10^9/L), (4) hyperferritinaemia (>500 µg/L), (5) hypertriglyceridaemia (fasting triglycerides > 3.0 mmol/L) and/or hypofibrinogenemia (<1.5 g/L); (6) hemophagocytosis in the bone marrow, spleen, liver, or lymph nodes; (7) elevated levels of sCD25 (>2400 U/mL), and (8) low or absent NK cells. Thus, the patient was confirmed to have IVLBCL with HPS and neurological involvement.

We had provided the patient with symptomatic treatment, such as mecobalamin (0.5 mg), piperacillin, tazobactam (5 g q8H), intermission transfusion of red blood cell erythrocytes, and human albumin; however, the patient refused all treatments from the time of diagnosis. He died 2 months after being discharged. The biological evolution of the patient is shown in Table 1.

**Discussion**

IVLBCL was first reported by Pfleger and Tappeiner in 1959, and was originally named systemic vascular endotheliomatosis. In 2008, it was officially defined as IVLBCL in accordance with the WHO classification of lymphoid neoplasms, a subset of diffuse large B-cell lymphoma with a specialized intravascular (especially in capillaries) proliferative pattern. Its classification remained unchanged in the 2016 WHO classification of lymphoid neoplasms. IVLBCL is a rare and highly aggressive lymphoma; thus, the existing literature is limited to case reports and case series.

A global case series reported that the median patient age of IVLBCL was 64 ± 12.7 years, and that 51.1% of patients were men. The patient described in the present case was 32 years old, which is much younger than the average age of illness. Two recent case series within China reported an average age of onset of 56 and 58.5 years, suggesting a lower age of onset in China compared with other

**Figure 1.** Bone marrow biopsy pattern of the iliac bone. (a) Hematoxylin and eosin staining (40×). A few lymphoid cells can be observed in the small blood vessels of the bone marrow component, which are medium in size. (b) Immunohistochemical staining. A few scattered or focal CD20+ cells can be observed in the small vessels and sinus spaces.
countries. Ponzoni et al.\textsuperscript{8} proposed a possible pathophysiological mechanism for the intravascular localization of IVLBCL without metastasis; they suggested that IVLBCL lacks receptors to mediate its spread, such as the cell adhesion molecules intercellular adhesion molecule-1 (ICAM-1), CD25, and B1 integrin. Because neoplasms can infiltrate the capillaries of all kinds of organs, patients can present with a wide variety of non-specific symptoms. Common sites of infiltration include the central nervous system (CNS), skin, lungs, kidneys, endocrine organs, and other highly vascularized tissues.\textsuperscript{9}

Infiltration of hepatic sinusoids, bone marrow, and red pulp has also been reported.\textsuperscript{10} The Western-variant IVLBCL typically involves the skin and CNS,\textsuperscript{11} with common clinical findings including skin hyperpigmentation and nodules as well as neurological symptoms, such as impaired mental state, motor and sensory deficits, epilepsy, dementia, cauda equina syndrome, and spinal cord lesions.

Data on the Asian-variant IVLBCL have been predominantly reported in Japan. In 2007, a multicenter case report examining 96 patients with IVLBCL concluded that patients commonly presented with HPS (61%), anemia (66%), bone marrow involvement (75%), respiratory symptoms (34%), B symptoms (fever, night sweats, weight loss; 76%), hypalbuminemia (albumin < 30 g/L; 61%), thrombocytopenia (58%), and elevated LDH (98%). Only a few cases reported involvement of the CNS (27%) and skin (15%).\textsuperscript{2} The literature suggests that the higher occurrence of HPS in Asian-variant IVLBCL may be attributed to the higher expression of interleukin (IL)-6, IL-1\(\beta\), tumor necrosis factor alpha (TNF-\(\alpha\)), sCD25, and other cytokines.\textsuperscript{12}

Our patient demonstrated signs of fever, HPS, anemia, bone marrow involvement, thrombocytopenia, hypoproteinemia, and elevated LDH, in accordance with the Asian-variant IVLBCL criteria. However, the patient also demonstrated uncommon neurological signs within the Asian variant, such as bilateral lower limb numbness and urinary retention, indicating that his IVLBCL may be an intermediate version between the two variants. Recently, a case report described a 48-year-old woman who presented with HPS as well as pituitary

| Table 1. Biological evolution of the patient |
|---------------------------------------------|
| **2 months prior to admission** | Bilateral lower limb numbness. Lumbar spine magnetic resonance imaging revealed edematous spinal cord in the fourth sacral vertebra, as well as in the second and third coccygeal vertebrae. |
| **1 month prior to admission** | Symptoms deteriorated, manifesting as bilateral limb swelling, difficulty in walking, fatigue, and a maximum body temperature of 39\(\degree\)C. Leukocytes: \(4.81 \times 10^9\)/L, hemoglobin: 117 g/L, platelets: \(94 \times 10^9\)/L. |
| **2 weeks prior to admission** | New symptoms included difficulties in urination and defecation. Leukocytes: \(2.42 \times 10^9\)/L, hemoglobin: 82 g/L, platelets: \(77 \times 10^9\)/L. |
| **On admission to our hospital** | Leukocytes: \(4.08 \times 10^9\)/L, hemoglobin: 84 g/L, platelets: \(70 \times 10^9\)/L. Peripheral blood film was abnormal, with 3% dysplastic lymphocytes. |
| **1 week after admission** | We perfected the interleukin-2 receptor alpha chain (CD25) and natural killer cell activity tests and bone marrow aspiration. The patient was diagnosed with intravascular large B-cell lymphoma with hemophagocytic syndrome. |
gland and neurological involvement. She was being treated for seronegative rheumatoid arthritis. A diagnosis of IVLBCL was made based on her perisplenic vessels, while a liver and bone marrow biopsy were non-contributive. This patient was particularly rare because of the association between endocrine and neurological involvement in the context of HPS.

A case series of 13 IVLBCL patients at China West Hospital, Sichuan, China, found that 11 patients (86.6%) presented with fluctuating fever, eight (72.7%) showed bone marrow involvement, seven (53.8%) had splenomegaly, five (38.5%) had HPS, and one (7.7%) had CNS symptoms. In addition, a case series of 12 patients at the Peking Union Medical College Hospital, Beijing, China, identified six patients (50%) with HPS, three cases (25%) of bone marrow involvement, and two patients (16.7%) with central neurological deficits. The presentations of IVLBCL in China are typically of the Asian variant; however, the occurrence of HPS (29.4%–50%) is lower than that in the Japanese literature. This discrepancy may be caused by smaller sample sizes in Chinese reports, selection bias, or inexperience leading to undiagnosed HPS.

IVLBCL patients with secondary HPS tend to present more severely, but the impact of HPS on disease prognosis remains unknown. A large-scale retrospective study by the Japanese IVLBCL Research Group in 2008 did not indicate the presence of secondary HPS as a negative predictor of prognosis; however, a study in China reported a shorter survival rate for IVLBCL patients presenting with secondary HPS. Although CNS involvement is uncommon in the Asian variant, studies have reported a poorer prognosis for patients with CNS involvement; thus, neuroprotection should be emphasized in the management of IVLBCL. Shimada et al. concluded that CNS involvement, if present, usually manifests early in the disease, and once a relapse of CNS symptoms occurs, the 2-year survival rate is 12%. In contrast, isolated skin involvement leads to a more optimistic prognosis. However, a recent clinical study reported that overall survival does not differ according to CNS involvement.

A diagnosis of IVLBCL is mainly based on histopathology. The pathology of this disease is characterized by the infiltration and aggregation of neoplastic cells within small/medium vessels or capillaries. Dysplastic lymphocytes are characterized by hyperplastic nuclei, enhanced nucleoli, low cytoplasm, and visible mitosis. IVLBCL is typically a non-germinal center B-cell lymphoma (80%), and is characterized by the expression of CD79a (100%), CD20 (96%), multiple myeloma 1/interferon regulatory factor 4 (MUM-1/IRF4; 95%), Bcl-2 (91%), CD19 (85%), immunoglobulin κ light chain (71%), CD5 (38%), Bcl-6 (26%), CD10 (12%), and CD23 (4%). From a genetic perspective, IVLBCL originates from differentiating peripheral B lymphocytes and gene repetition at immunoglobulin heavy chain locations. In addition, chromosomal translocations such as t(11: 22)(q23; q11.2) and t(14; 18) are detected in some patients, although these mutations are not pathognomonic.

Because of the rarity of IVLBCL, its non-specific presenting symptoms, and the difficulty in its diagnosis, some diagnoses are made retrospectively using autopsies. Matsue et al. previously reported the usefulness of a random skin biopsy from normal-appearing skin for the early diagnosis of IVLBCL, which has high sensitivity and specificity. IVLBCL generally has a poor prognosis, with 1- and 3-year overall survival rates of 42.3% and 11.5%, respectively. It has naturally highly aggressive and infiltrative tumors and a poor response to chemotherapy. Furthermore, delays in
diagnosis are common because of a lack of understanding of the disease. There are currently no standardized treatment guidelines for IVLBCL; however, combination therapy with rituximab and chemotherapy has been shown to be better than traditional chemotherapy. The R-CHOP regimen (a combined treatment of cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab) remains the first-line treatment for IVLBCL, with a 2-year survival rate of 66%, which is much lower than that of other diffuse B-cell lymphomas. A recent case treated with R-CHOP demonstrated good recovery. Furthermore, a recent clinical trial (n = 38, median follow-up of 3.9 years, interquartile range: 1.5–5.5 years) treated previously untreated IVLBCL patients with R-CHOP, including high-dose methotrexate and intrathecal chemotherapy as CNS-oriented therapy, and reported that the 2-year progression-free survival rate was 76% (95% confidence interval: 58%–87%).

Recent studies have concluded that, once remission is achieved, autologous hematopoietic cell transplantation (auto-HSCT) can positively modify the prognosis of high-risk and relapsing patients. In a 2014 retrospective study in Japan, six patients received auto-HSCT post-remission following induction chemotherapy, and all patients were alive at their respective follow-ups (12–99 months later). Moreover, in 2016, data from the European Group for Bone and Marrow Transplantation showed that 11 patients received auto-HSCT following the R-CHOP regimen, of whom eight achieved complete remission. The 2-year survival rate was 91% and the progression-free survival rate was 81% over an average follow-up period of 51 months. However, the applicability of auto-HSCT is likely to be greatly limited in Western patients because of their more advanced age at diagnosis. Despite our patient being only 32 years of age, he refused all treatment from the time of diagnosis and died 2 months after being discharged.

**Conclusions**

IVLBCL is a rare form of diffuse large B-cell lymphoma, with a majority of cases occurring in the middle-aged to elderly age group. It is characterized by the proliferation of neoplastic cells in the lumen of small blood vessels. Because IVLBCL does not produce a mass or lymphadenopathy, its diagnosis is often difficult. Therefore, a greater understanding of the disease is necessary. IVLBCL is highly aggressive, and the overall prognosis of IVLBCL is very poor. The current first-line therapy involves R-CHOP combination therapy, which can increase remission and survival rates. Auto-HSCT post-remission may further improve the prognosis of these patients.

**Declaration of conflicting interest**

The authors declare that there is no conflict of interest.

**Ethics statement**

The study was approved by the medical ethics committee of Peking University People’s Hospital, and the patient provided verbal informed consent.

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