

## Case Report

# Elevated level of serum antinuclear antibody and hemophagocytic syndrome in Asian-variant intravascular large B-cell lymphoma: a case report with its diagnostic pitfalls

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**Abstract:** Intravascular large B-cell lymphoma (IVLBCL) is a rare and aggressive subtype of extranodal large B-cell lymphoma, characterized by preferential growth of neoplastic lymphoma cells within the lumina of small blood vessels. Clinical diagnosis of IVLBCL is challenging because of heterogeneous clinical presentation. Herein, we describe a case of Asian-variant IVLBCL with serum antinuclear antibody (ANA) elevation and hemophagocytic syndrome. The patient was a 74-year-old female who presented with persistent general fatigue, fever, night sweats, bilateral leg edema and dyspnea on exertion. Initially, some type of autoimmune disease was suspected because laboratory test showed ANA elevation. Positron emission tomography with CT (PET-CT) revealed splenomegaly and diffuse FDG uptake in bone marrow. Bone marrow aspiration showed hemophagocytosis, and clinical findings fulfilled the diagnostic criteria for hemophagocytic syndrome. A random skin biopsy demonstrated CD20-positive, atypical large lymphoid cells within vessels in the subcutaneous tissue, leading to a final diagnosis of Asian-variant IVLBCL. IVLBCL often presents as a disseminated disease, mimicking autoimmune disease. However, laboratory findings on autoimmune antibody have not been described in most previous cases of IVLBCL. It is very important to consider IVLBCL as a differential diagnosis in patients with uncertain autoimmune disease-like clinical presentations, including serum ANA elevation.

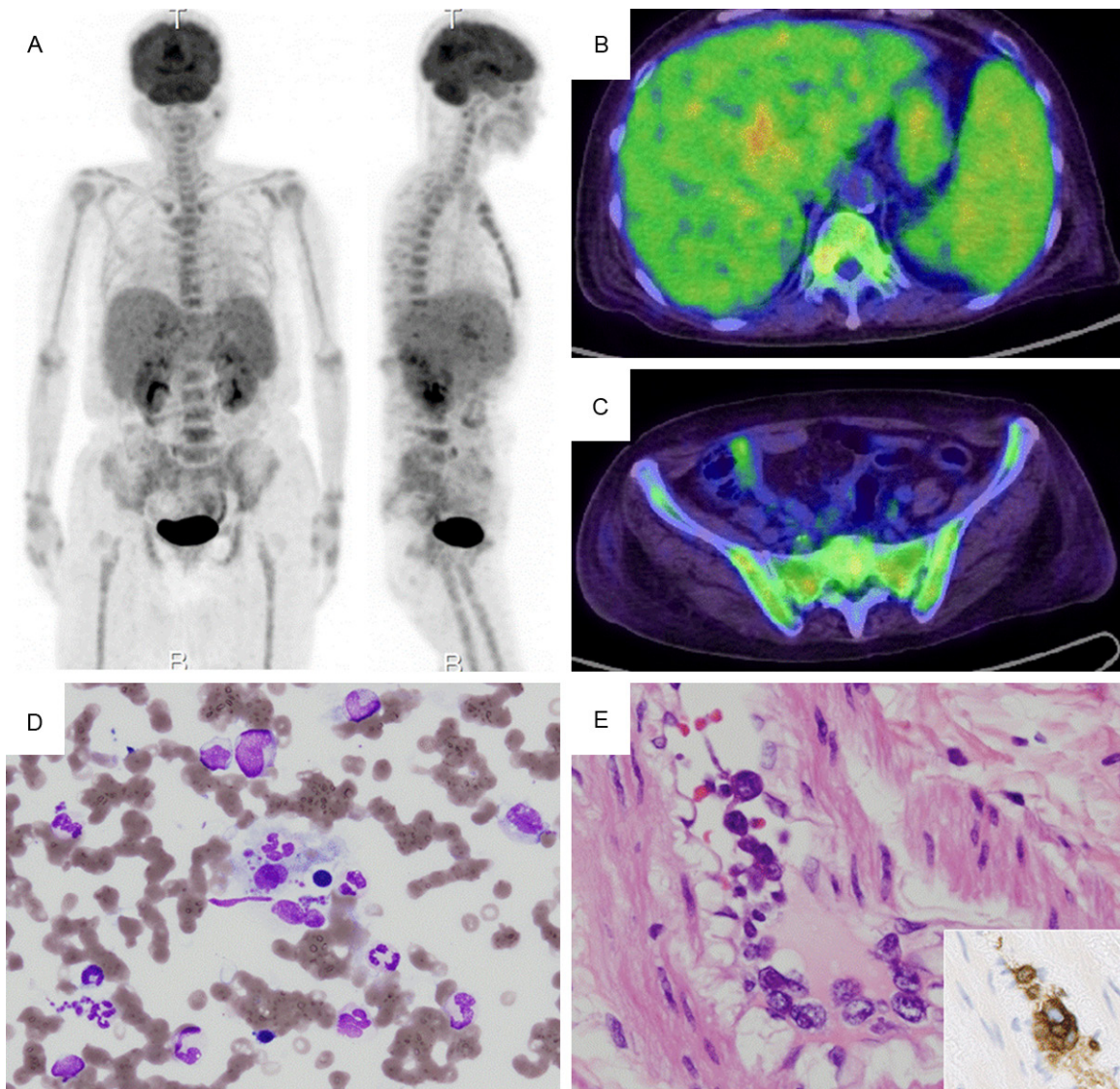
**Keywords:** Intravascular large B-cell lymphoma, Asian variant, antinuclear antibody, hemophagocytic syndrome

## Introduction

Intravascular large B-cell lymphoma (IVLBCL), a rare and aggressive subtype of extranodal large B-cell lymphoma, is characterized by selective growth of neoplastic lymphoma cells within the lumina of vessels, particularly capillaries and postcapillary venules, without an obvious extravascular tumor mass or detectable circulating lymphoma cells in the peripheral blood [1]. Although different organs can be affected, leading to a varied presentation of IVLBCL, two major patterns of the disease have been recognized. The Western form is characterized by symptoms related to the main organ involved, predominantly neurological or cutaneous, often in conjunction with B symptoms, including fever, weight loss, and night sweats. In contrast,

the Asian variant preferentially shows multiorgan failure, hepatosplenomegaly, pancytopenia, hemophagocytic syndrome, and B symptoms [1].

Despite rapidly fatal malignancy, it is difficult to make an accurate diagnosis in the early stage of the disease, because the clinical manifestations of this systemic lymphoma are extremely variable, and most of the signs and symptoms are nonspecific with relation to the preferentially involved organs. A definitive diagnosis of IVLBCL is often unobtainable until the postmortem period when diagnosed at autopsy [2]. Laboratory findings are nonspecific, but many patients display a pathologic hemogram, with anemia in almost 65% of patients. Increased serum lactate dehydrogenase (LDH) and  $\beta_2$ -



**Figure 1.** Positron emission tomography with CT (PET-CT) images and microscopic findings of bone marrow aspiration and random skin biopsy. Maximum intensity projection of FDG-PET (A) and PET-CT (B, C) demonstrated splenomegaly with significant FDG uptake. Increased FDG uptake was also observed diffusely in bone marrow, including the vertebrae, the sternum, and the sacrum. Bone marrow aspiration revealed hemophagocytosis (D). In random skin biopsy specimens, some small vessels in subcutaneous tissue were observed, which included atypical large lymphoid cells. The atypical cells showed selective growth within the lumina of vessels without infiltration around the vessels. High magnification demonstrated atypical large nuclei with 1 or more prominent nucleoli (E). These cells were positive for CD20 immunostaining (E, inset).

microglobulin levels are observed in  $\geq 80\%$  of patients [3].

IVLBCL often presents as a disseminated disease, mimicking a systemic disease, including autoimmune disease. However, laboratory findings on autoimmune antibody have not been described in most previous case reports of IVLBCL. Herein, we describe a case of Asian-variant IVLBCL that was diagnostically challeng-

ing because of serum antinuclear antibody (ANA) elevation and other symptoms resembling those of autoimmune disease.

#### Case report

A 74-year-old Japanese female with an unremarkable medical history was admitted to another hospital with persistent general fatigue, fever, a 2-month history of night sweats,

and recently appearing bilateral leg edema and dyspnea on exertion. She was referred to our hospital for detailed examination because laboratory findings showed anemia, hypoproteinemia, electrolyte imbalance, and serum ANA elevation, despite unremarkable findings on computed tomography (CT) scanning. Physical examination on admission showed fever (up to 38-39°C), with no evidence of skin lesions or lymphadenopathy. Laboratory testing showed anemia (hemoglobin 9.4 g/dL); thrombocytopenia (94 k/mm<sup>3</sup>); elevated LDH (873 U/L); C-reactive protein (7.65 mg/dL);  $\beta_2$ -microglobulin (4.2 mg/L); ferritin (1,451.5 ng/mL); soluble interleukin-2 receptor (sIL-2R) (6,257 U/mL); and ANA (1:1280, homogeneous pattern, no subtype found). Other more specific autoantibodies, including anti-double-stranded DNA, anti-single-stranded DNA (ssDNA), anti-RNP, anti-Sm, anti-SSA, anti-SSB, anti-smooth muscle, anti-mitochondrial M2, anti-CCP, anti-neutrophil cytoplasmic (ANC), and anti-Scl-70 antibodies, were all negative. Extensive screenings for bacteria, fungi, and viruses were negative. For whole body examination, positron emission tomography with CT (PET-CT) was performed, which revealed splenomegaly and diffuse FDG uptake in bone marrow (**Figure 1A-C**).

Bone marrow aspiration was subsequently performed, which revealed hemophagocytosis (**Figure 1D**). Atypical lymphoid cells were not obvious on this examination. The patient's clinical findings fulfilled the diagnostic criteria for hemophagocytic syndrome (fever  $\geq 38.5^\circ\text{C}$ ; peripheral blood cytopenia with at least 2 lineages; hemophagocytosis; ferritin  $> 500$  ng/mL; and elevated sIL-2R, 2 standard deviations above age-adjusted, laboratory-specific norms) [4]. As a differential diagnosis, IVLBCL was considered because of hemophagocytosis, sIL-2R elevation, and no detectable lymphadenopathy.

A random skin biopsy was strongly recommended, to which the patient consented. Biopsy specimens obtained from abdominal and bilateral femoral skin showed a few atypical, large lymphoid cells, which had round-to-oval nuclei with 1 or more prominent nucleoli within a few vessels in the subcutis (**Figure 1E**). Immunohistochemical stains demonstrated that the atypical cells were positive for CD20 (**Figure 1E**, inset) and BCL-2. A subset of the atypical cells was negative for CD3 and CD10 and

expressed CD5. Ki-67 immunostaining showed a distinctive nuclear reaction involving most of the atypical cells. Flow cytometry studies were also carried out on a portion of the biopsy specimens, but showed no evidence of a monoclonal B-cell population. These findings were diagnostic of IVLBCL.

Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) systemic chemotherapy was administered, but it could not be continued because of the side effects and the patient's deteriorating general status. She died approximately 8 months after the reported onset of symptoms.

## Discussion

Early and accurate diagnosis of IVLBCL is frequently challenging because of its rarity and its diverse clinical presentation. The most common symptom is fever, followed by cutaneous symptoms and central nervous system presentations. Similar to the present case, fatigue, edema, and dyspnea are frequently observed [5]. The current patient was initially suspected to have some type of autoimmune disease because of high serum ANA elevation and symptoms in accordance with classical autoimmune manifestations, such as fever, fatigue, bilateral leg edema, and pleural and peritoneal effusions.

In fact, malignant lymphoma frequently demonstrates positivity (39-84%) for one or more autoimmune antibodies [8, 9], and serum ANA elevation is also observed. A high titer of ANA is seen in connective tissue diseases, and ANA positivity is also found in 10-15% of healthy people over the age of 65 years [10].

In previous studies, serum ANA elevation has been detected in 4.7-21% of cases of non-Hodgkin's lymphoma (NHL) [8, 9, 11, 12]. Guyomard et al. found that ANA positivity was significantly higher in patients with NHL (19.0%) compared to that in the control groups (5.6%) [11]. They also showed that the frequency of ANA was especially high in follicular and mantle cell lymphoma [11]. Taken together, B-cell lymphoma is more likely to show serum ANA elevation than is T-cell lymphoma.

Most previous studies and case reports of IVLBCL have not focused on serum ANA elevation, and its prevalence is still unclear. However,

It is suspected that serum ANA elevation in IVLBCL is not so rare a phenomenon, especially in the Asian variant. To our knowledge, only a few cases of IVLBCL with ANA positivity have been previously reported [6, 7]. One typical case of IVLBCL was reported in a Western country, and 4 cases were found in a series of the Asian variant of IVLBCL (4/25 cases) [6]. More specific autoantibodies can be observed in patients with malignant lymphoma, although it is unclear whether IVLBCL can show positivity for them. In a quantitative analysis, Bilici et al. reported that the mean levels of anti-Jo-1, anti-ssDNA, c-ANCA, and RF were significantly higher in cases of diffuse large B-cell lymphoma (DLBCL) compared to those in patients with non-DLBCL [9].

Hemophagocytic syndrome is a characteristic manifestation of Asian-variant IVLBCL. However, it is also known as a relatively rare complication in autoimmune diseases. Fukaya et al. demonstrated that 30/1,014 (3.0%) cases of autoimmune disease fulfilled the criteria for hemophagocytic syndrome [13]. According to their study, the underlying diseases were systemic lupus erythematosus (SLE, 18/350 cases); rheumatoid arthritis (RA, 2/136 cases); polymyositis/dermatomyositis complex (PM/DM, 2/98 cases); systemic sclerosis (SSc, 2/88 cases); vasculitis syndrome (1/91 cases); primary Sjögren syndrome (SS, 2/37 cases); and adult-onset Still's disease (3/26 cases). These clinical findings can be confusing for clinicians in the diagnosis of cases of malignant lymphoma with symptoms of an autoimmune disease, and the diagnosis becomes even more difficult in cases of IVLBCL, because lymph nodes are typically spared, and there are no detectable tumors that appear different from other kinds of classic lymphomas.

It is known that autoimmune diseases and lymphocytic malignancies are bidirectionally related. Lymphomas develop more frequently in the course of autoimmune diseases, and signs and symptoms of autoimmune diseases occur in the course of lymphomas [14]. Serum ANA elevation frequently appears during treatment for lymphoma, and it is assumed that there is a relationship between these autoantibodies and antitumor immunity [9, 12]. Some authors have postulated that specific treatment of lymphoma induces cellular lysis and leads to produc-

tion of different autoantibodies [12]. In addition, several studies have shown that there is an increased risk of lymphoma subsequent to autoimmune conditions, including RA, SS, and SLE [11, 12]. Altintas et al. described 2 cases of DLBCL with SS showing anti-SSA and -SSB positivity, and they concluded that the presence of positive anti-SSA and -SSB was a marker for the development of SS in patients with NHL [12].

In conclusion, serum elevation of autoantibody is not specific to autoimmune diseases, but is frequently observed in malignant lymphomas, including IVLBCL. This can be more problematic in cases of IVLBCL than in those of conventional malignant lymphomas, because IVLBCL is an unusual type of lymphoma with no lymph node involvement and no specific symptoms or laboratory findings. Awareness of this is crucial to avert misdiagnosis and potentially deleterious management decisions.

#### Disclosure of conflict of interest

None.

#### Abbreviations

ANA, antinuclear antibody; ANC, anti-neutrophil cytoplasmic; CT, computed tomography; IVLBCL, intravascular large B-cell lymphoma; LDH, lactate dehydrogenase; NHL, non-Hodgkin's lymphoma; PET, positron emission tomography; PM/DM, polymyositis/dermatomyositis complex; RA, rheumatoid arthritis; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; SLE, systemic lupus erythematosus; sIL-2R, soluble interleukin-2 receptor; SS, Sjögren syndrome; SSc, systemic sclerosis; ssDNA, single-stranded DNA.

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