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【 CASE REPORT 】

Interleukin-6-producing Intravascular Large B-cell Lymphoma with Lymphadenopathy Mimicking the Histology of Multicentric Castleman Disease

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Abstract:
An inguinal lymph node biopsy of a woman with a one-month history of a progressive fever, fatigue, dyspnea, skin rash, and lymphadenopathy revealed a well-preserved basic structure, hyperplastic germinal centers, and an interfollicular region containing polyclonal plasma cell sheets, suggesting plasma cell-type multicentric Castleman disease (MCD). We initiated prednisolone and anti-interleukin (IL)-6 antibody (tocilizumab), without success. A biopsy specimen re-evaluation detected CD20-positive atypical large B cells infiltrating the small vessels within and around the lymph node and its capsule. We diagnosed her with intravascular large B-cell lymphoma (IVLBCL). Lymphoma cells were weakly positive for IL-6 by immunohistochemical staining. IL-6 from lymphoma cells may have caused the MCD-like presentation as a paraneoplastic etiology. Malignant lymphoma should be excluded before diagnosing MCD.

Key words: intravascular large B-cell lymphoma, multicentric Castleman disease, interleukin-6, paraneoplastic syndrome

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Introduction

Intravascular large B-cell lymphoma (IVLBCL) is a rare form of diffuse large B-cell lymphoma (DLBCL) that is characterized by the preferential intravascular growth of lymphoma cells and has a fatal clinical course due to its aggressive behavior (1). IVLBCL in Asian countries (the so-called as Asian variant) preferentially presents with a fever, hemophagocytic syndrome, and hypercytokinemia (2). Typical IVLBCL lacks lymphadenopathy, and its clinical features are not specific. The diagnosis of IVLBCL is thus very difficult to establish.

Castleman disease (CD) is a rare lymphoproliferative disorder with systemic inflammatory symptoms caused by cytokines produced by activated B cells (3). The cytokine interleukin (IL)-6 plays an important role in the pathogenesis of CD; it regulates the immune response, hematopoiesis, and acute inflammatory phase (4, 5). An elevated IL-6 level can lead to systemic manifestations, such as a fever, malaise, and laboratory abnormalities of anemia, thrombocytosis or thrombocytopenia, hypergammaglobulinemia, and C-reactive protein (CRP) elevation. CD is classified as unicentric CD (UCD) or multicentric CD (MCD) based on the localization of enlarged lymph nodes (6). Idiopathic MCD (iMCD), in whcih human herpes virus-8 (HHV-8) is negative, is common in Japan, in contrast to Western countries (7).

We herein report the first case of IVLBCL with clinical features and histology mimicking plasma cell-type MCD that may have been caused by the production of IL-6 by lymphoma cells. Our patient's case emphasizes that the careful exclusion of lymphoid malignancies is critical before diagnosing MCD.

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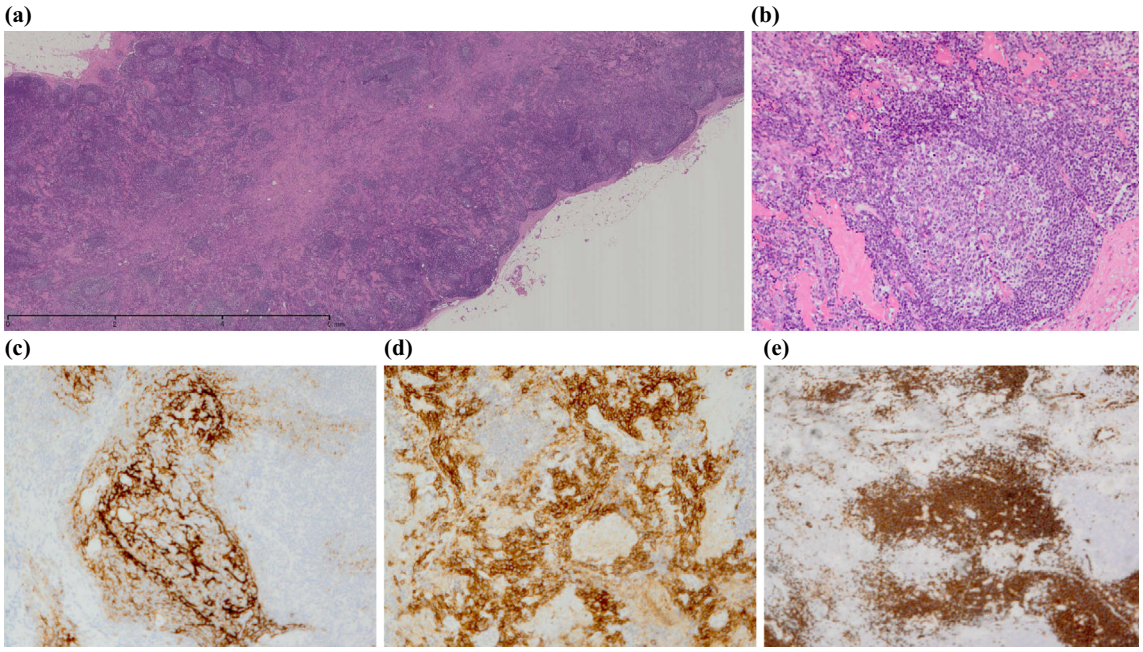

Figure 1. Pathological findings of the lymph node. The basic structure of the lymph node was well preserved (a), and the condition of the lymph nodules ranged from normal to hyperplastic (b). Proliferative dendritic small vessels and follicular dendritic cell were detected by CD23 staining (c). CD138-positive plasma cells were found in the interfollicular space (d). CD20-positive cells were observed in the interfollicular space but not in the main structure or central sinus of the lymph nodes (e). Original magnification: a, ×12.5; b, ×40; c, ×100; d, ×12.5, e, ×12.5.

Case Report

A 69-year-old Japanese woman was admitted to our hematology department due to anemia in August 2018. Her medical history was remarkable for dyslipidemia, gastroesophageal reflex disease, and a lumbar herniated disk.

On admission, she had a subfever, but physical examinations revealed no abnormal findings. The results of blood tests were remarkable for normocytic anemia (hemoglobin, 9.9 g/dL) and the elevation of lactate dehydrogenase (LDH) (461 IU/L: reference range 120-220 IU/L). The result of a Direct Coombs test was weakly positive, but haptoglobin remained within the normal range. Human immunodeficiency virus (HIV) antibody was negative. Whole-body computed tomography (CT) revealed mild splenomegaly but no adenopathy. Bone marrow (BM) was normocellular without dysplasia or the invasion of lymphoma cells. A karyotype analysis of bone marrow cells showed 46, XX in 20/20 metaphases. Based on these findings, the patient was subsequently followed at an outpatient clinic without treatment.

Six months later, the patient started experiencing malaise, difficulty breathing, and a fever. The findings of a physical examination were normal except for a brown skin rash on the left lower leg and splenomegaly. The hemoglobin level had dropped to 8.8 g/dL, and the serum LDH had risen to 791 U/L. Other abnormal laboratory data were as follows: IgG, 2,998 mg/dL (reference range 8,700-1,700 mg/dL); sIL-2R, 1,949 IU/mL (reference range 1,420-500 IU/mL); and IL-6, 41.6 pg/mL (reference range <4 pg/mL). Positron emission tomography (PET) revealed splenomegaly and lymph node swelling in the para-aortic (1.6 cm ×0.8 cm) and inguinal regions (2.0 cm ×1.4 cm). The maximum standardized uptake value (SUV_{max}) of both enlarged lymph nodes was under 2.9, suggesting low-grade lymphoma. A few atypical lymphoid cells were detected in a BM smear, but flow cytometry and a BM biopsy with immunohistochemical staining failed to demonstrate malignant lymphoma.

Immunoglobulin H (*IgH*) gene rearrangement was not detected, but a chromosomal analysis using bone marrow cells of G-banding showed 49, XX, trp(1)(q21q32), +add(3)(p13), −4, +7, +9, add(18)(q21.1), add(19)(q13.3), −21, +21mar in 1 of 50 metaphases. A skin biopsy of the patient's left lower leg showed polyclonal plasma cell infiltration, but we were unable to detect atypical lymphoid cells in the small vessels of the subcutaneous fat tissue. A left inguinal lymph node biopsy was also performed, and it revealed that (1) the basic structure of the lymph node was well preserved with hyperplastic germinal centers (Fig. 1a, b); (2) there was proliferation of dendritic small vessels, and the number of follicular dendritic cells was increased within germinal centers (Fig. 1c); and (3) polyclonal plasma cell proliferation was present in the interfollicular space (Fig. 1d). Latency-associated nuclear antigen-1 (LANA-1) was negative. CD20-positive cells were observed in the interfollicular space (Fig. 1e), but they did not infiltrate the main structure or central sinus of the lymph nodes, which was insufficient for

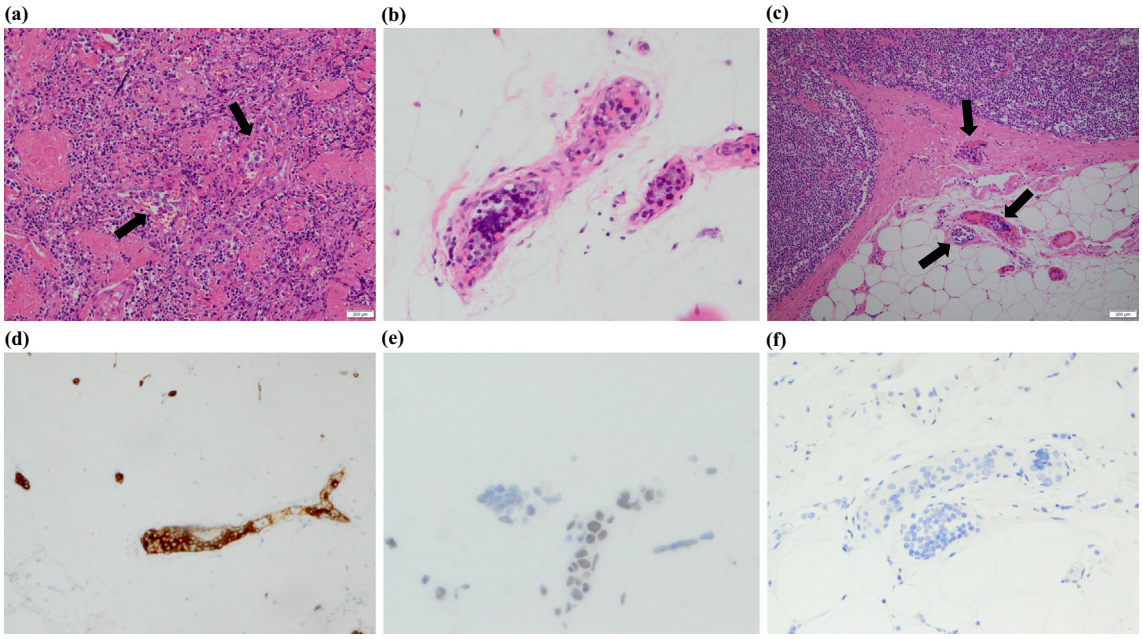

Figure 2. **Results of a second pathological evaluation of the lymph node. Atypical large lymph cells exclusively proliferated in the small vessels within (a) and around (b) the lymph node and its capsule (c) (arrows indicate atypical cells). On immunohistochemical staining, atypical cells were positive for CD20 (d) and weakly positive for IL-6 (e) but negative for PD-1 L (f). Original magnification: a-f, ×200.**

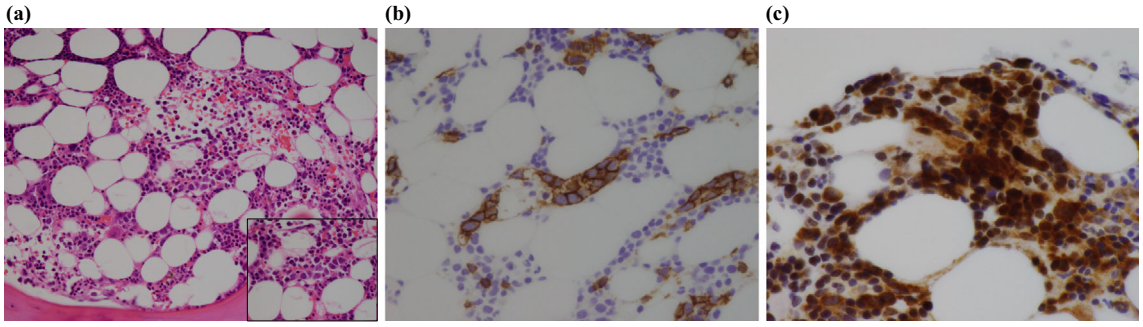

Figure 3. **Pathological findings of bone marrow before starting chemotherapy. Atypical large lymphoid cells had infiltrated the small vessels in the bone marrow (a). These cells were positive for CD20 (b) and IL-6 (c). Original magnification: a, ×200 (Black box: ×600); b, ×400; c, ×600.**

a diagnosis of malignant lymphoma.

Based on these findings, we diagnosed her with plasma cell-type MCD, and the patient was treated with prednisolone (PSL) 0.5 mg/kg and the anti-IL-6 antibody tocilizumab (TCZ) 8 mg/kg. However, her clinical condition continued to deteriorate, and she was hospitalized again one week after the start of the PSL/TCZ treatment due to progressive dyspnea and hypoxia. By that time, the results of the chromosomal analysis of the patient's lymph node had become available, showing the same abnormalities.

We therefore conducted a second evaluation of the pathological specimen and noted that atypical large lymphoid cells had exclusively proliferated in the small vessels within (Fig. 2a) and around (Fig. 2b) the lymph node and its capsule (Fig. 2c). Immunohistochemical staining showed that the atypical cells were positive for CD20 (Fig. 2d), CD79a, BCL-2, BCL-6, and multiple myeloma oncogene (MUM)-1 and negative for CD3, CD5, CD10, CD138, cyclinD1, Epstein-Barr virus encoded RNA (EBER), and latent nuclear antigen (LANA)-1. The atypical cells were also weakly positive for IL-6 (Fig. 2e) but negative for programmed cell death receptor 1 ligand 1 (PD-L1) (Fig. 2f). A repeat bone marrow examination revealed infiltration of atypical large lymphoid cells and hemophagocytosis. These atypical cells had invaded the small vessels (Fig. 3a) and were positive for CD20 (Fig. 3b) and IL-6 (Fig. 3c). We then diagnosed her with IVLBCL with a non-germinal center B-cell phenotype [non-germinal center B-cell-like (GCB) type].

The patient underwent eight cycles of R-CHOP (rituximab, cyclophosphamide, daunorubicin, vincristine, and PSL)

together with the intrathecal injection of hydrocortisone, methotrexate, and cytarabine. She achieved complete remission and was followed-up without relapse.

Discussion

We encountered a patient with IVLBCL with lymphadenopathy that histologically mimicked MCD. The patient was initially diagnosed with plasma cell-type MCD, but her symptoms worsened even after treatment with PSL and TCZ. In addition, chromosomal abnormalities were identified after we initiated the treatment for MCD. These observations prompted us to re-evaluate the initial lymph node biopsy specimen, which led us to the final diagnosis of IVLBCL.

The clinical characteristics of IVLBCL and those of MCD are strikingly similar (1, 8). A fever, night sweats, weight loss, and hepatosplenomegaly are common. Lymphadenopathy is a common initial presentation in MCD, whereas IVLBCL has no lymphadenopathy by its definition (1). Dyspnea is observed in both diseases with their pulmonary involvement. Nishimoto et al. reported that 18 of 28 Japanese patients with MCD had lung lesions, such as intestinal infiltration on CT (9). Similarly, one-third of IVLBCL patients present with dyspnea or hypoxia due to lymphoma cells' infiltration into the small vessels of the lung (10). Our patient presented with dyspnea before her diagnosis of IVLBCL. Although pathological examinations were not performed, we clinically judged that the pulmonary invasion of IVLBCL had caused the patient's dyspnea, as her lungs were clear on CT.

Anemia, thrombocytopenia, and hypoalbuminemia are frequently observed in both IVLBCL and MCD. Reflecting a hyperinflammatory state, the levels of plasma IL-6 and CRP are also high at the diagnosis of IVLBCL (11) and MCD (8). Because IVLBCL and MCD have similar clinical characteristics, clinicians must carefully distinguish between IVLBCL and MCD.

Several malignant lymphoma cases with MCD histology have been reported. Interfollicular Hodgkin lymphoma (HL) is the most frequently reported (12-15), followed by non-Hodgkin lymphoma (NHL) (15-18). In previous cases, concurrent MCD and lymphoma histology was observed. Larroche et al. reported the clinicopathological features of MCD and lymphoma in HIV-negative patients (15); they noted that NHL is more often associated with MCD, whereas HL is more often associated with UCD, and the diagnosis of NHL was made concurrently or within two years. However, to our knowledge, our patient's case is the first one of IVLBCL with MCD histology mimicking MCD.

We speculate that the MCD-like presentation in our patient's case was caused by IL-6 production by IVLBCL. The time from the diagnosis of MCD to that of IVLBCL was short for this patient, suggesting that the simultaneous presentation of two different diseases was unlikely. The patient's poor response to PSL and TCZ, the dramatic improvement of her clinical condition after chemotherapy for IVLBCL, and the finding that IL-6 was weakly positive on IVLBCL cells support our hypothesis. Although IL-6 was not measured after the diagnosis of MCD, it was speculated that the IL-6 level had normalized, based on her favorable clinical course after chemotherapy.

There are several reports regarding a high IL-6 plasma level in tumors (14,16,19,20), hemophagocytic syndrome (21, 22), and IVLBCL (11, 23) or IL-6 positivity on immunohistochemistry staining (14, 16, 19, 20, 24). These cases also support the possibility that paraneoplastically produced IL-6 can induce an MCD-like clinical presentation. Collectively, these findings led us to speculate that the paraneoplastic production of IL-6 might have caused clinical and pathological features mimicking those of MCD. The further accumulation of similar cases is needed in order to confirm this hypothesis.

We did not initially include IVLBCL in our patient's differential diagnosis as she had enlargement of multiple lymph nodes, which is not frequently observed in IVLBCL. However, only a few cases present with lymphadenopathy due to IVLBCL invasion into the lymph node (25), suggesting that careful evaluations are needed in order to distinguish IVLBCL from MCD. In our case, IVLBCL was not detected on a BM examination before clinical exacerbation. Regarding the early diagnosis of IVLBCL, we should have performed not only a skin biopsy on eruption but also a random skin biopsy, which has a higher sensitivity than a bone marrow biopsy (26). In addition, we should have focused on the LDH value, which we now consider the most important laboratory clue for distinguishing MCD and IVLBCL in this patient. LDH is high in all cases of IVLBCL (1, 11), but it is normal or low in MCD (27). When a high LDH level is detected in a patient with MCD, clinicians should look for potential underlying diseases, including malignant lymphoma. In our patient's case, the clinical exacerbation after treatment and the chromosomal abnormalities detected in the lymph node were also clues prompting us to reconsider our diagnosis. This emphasizes the importance of close and interactive discussions with pathologists in order to determine the accurate diagnosis.

In conclusion, we treated a patient with IVLBCL with lymphadenopathy mimicking MCD histology. We learned that (1) clinicians should carefully exclude malignant lymphoma in cases of MCD with elevated LDH and a poor response to treatment, and (2) IL-6 can induce lymphadenopathy mimicking MCD histology by a paraneoplastic mechanism. Clinicians should keep these diagnostic pitfalls in mind in order to avoid misdiagnoses and delays in initiating treatment.

The authors state that they have no Conflict of Interest (COI).

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