【 CASE REPORT 】

Osteosarcoma Manifesting Systemic Inflammation and Histological Features Mimicking Plasma Cell-type Castleman Disease

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Abstract:
   A 73-year-old man was referred to our hospital with a persistent fever, anemia, and a mass in the left pubic region. The findings of biopsy evaluations of the mass and a left inguinal lymph node were consistent with Castleman disease (CD) of plasma cell type. His serum interleukin 6 (IL-6) level was remarkably elevated, supporting the diagnosis of CD. However, imaging analyses revealed destruction of the pubic bone by the mass, which was atypical for CD. Therefore, another deeper biopsy was performed, which finally led to the diagnosis of IL-6-producing osteosarcoma. We conclude that clinicians should carefully exclude malignancies prior to making a CD diagnosis.

Key words: Castleman disease, osteosarcoma, interleukin 6, diagnosis

Introduction

   Castleman disease (CD) is a rare lymphoproliferative disorder with giant follicular lymphadenopathy, in which the increased interleukin 6 (IL-6) production in the affected lymph nodes causes systemic inflammatory manifestations, such as a fever, anemia, hypoalbuminemia, increased serum C-reactive protein (CRP), and polyclonal hypergammaglobu-rinemia (1, 2). CD is clinically classified as unicentric CD (UCD) and multicentric CD (MCD), depending on the distribution of the lesions. Histologically, it is classified into the hyaline-vascular type, plasma cell type, and mixed type (3, 4). However, infectious diseases, malignancies, and autoimmune diseases may also manifest systemic inflammation and lymphadenopathy similar to CD, and exclusion of these diseases is essential for the accurate diagnosis of CD,

although it is sometimes challenging (5, 6).
   We herein report a patient who was referred to our hospital with a tentative initial diagnosis of plasma cell type CD but was ultimately diagnosed with IL-6-producing osteosarcoma.

Case Report

   A 73-year-old Japanese man was referred to and admitted to Kanazawa Medical University Hospital with a persistent fever, anemia, and a mass in the left pubic region. Approximately 10 months before the admission, the patient had begun to experience pain in the left side of his pubic region, so he visited a local clinic. There, he was diagnosed with a fracture of the left pubic bone, which was treated conservatively at the clinic, but the pain persisted.
   Approximately two months before the admission, he com-

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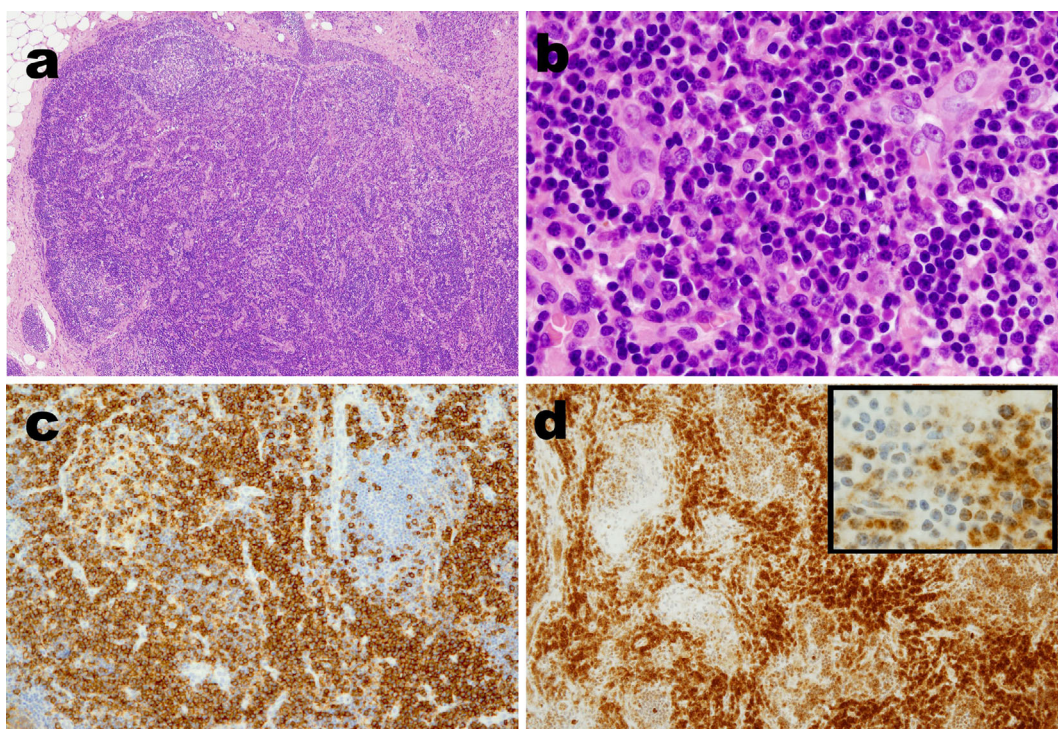
Figure 1. Sections of the left inguinal lymph node. (a, b) Hematoxylin and Eosin staining. (a) The primary structures of the lymph node were preserved, but the germinal centers were atrophic and obscure. (b) Remarkable proliferation of plasma cells was observed in the interfollicular spaces. (c, d) Immunohistochemical staining. (c) The plasma cells proliferating in the interfollicular spaces were positive for CD38. (d) The plasma cells were positive for interleukin-6, but the small lymphocytes were negative for interleukin-6 (inset). Original magnification; a, ×40; b, ×400; c and d, ×100; the inset of d, ×400.

plained of general malaise and appetite loss and visited another local hospital. There, a mass approximately 5 cm diameter at the left pubic bone and a swollen lymph node in the left inguinal region were detected by computed tomography (CT). ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) demonstrated a strong FDG uptake in the mass with a maximum standardized uptake value (SUV_{max}) of 15.2. A needle biopsy of the mass revealed proliferation of plasma cells, suggesting the possibility of a plasmacytoma or plasma cell-type CD. In order to make a diagnosis, the enlarged left inguinal lymph node (approximately 2 cm longest diameter) was excised. A histopathological examination revealed the primary structures of the lymph node to be preserved. However, the germinal centers were atrophic and obscure (Fig. 1a). Remarkable proliferation of CD38-positive plasma cells was observed in the interfollicular spaces (Fig. 1b, and c). *In situ* hybridization for the κ and λ light chains indicated that the plasma cells were polyclonal. An immunohistochemical examination clearly showed that the plasma cells were positive for IL-6 (Fig. 1d) and negative for human herpes virus type 8 (HHV-8). Based on these findings, along with the patient's clinical manifestations including a fever, anemia, hypoalbuminemia, and the increased serum IL-6 level (177 pg/mL: reference range, <4 pg/mL), he was diagnosed with plasma cell-type CD and referred to Kanazawa Medical University Hospital for treatment with tocilizumab, an anti-IL-6 receptor antibody.

On admission, his body temperature, blood pressure, and pulse rate were 38.7°C, 100/58 mmHg, and 89 beats/min, respectively. His heart and respiratory sounds were normal, his abdomen was soft and flat, and the liver and spleen were not palpable. A large, elastic, hard mass of approximately 10 cm diameter was palpable in the left pubic region, but no other superficial lymph nodes were palpable. Laboratory data revealed remarkable leukocytosis (15,100/μL) with neutrophil predominance, anemia (hemoglobin, 8.1 g/dL; MCV, 100.3 fL), borderline thrombocytosis (platelet count, 324× 10^3/μL), an elevated CRP level (16.7 mg/dL), hypoalbuminemia (1.7 g/dL), and polyclonal hypergammagloburinemia with an elevated IgG level (3,758 mg/dL). The serum aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, and alkaline phosphatase levels were 131 IU/L (reference range, 13-29 IU/L), 123 IU/L (reference range, 8-28 IU/L), 185 IU/L (reference range, 129-241 IU/L), and 1,404 IU/L (reference range, 115-359 IU/L), respectively. The anti-human immunodeficiency virus (HIV) antibody showed negative results.

CT demonstrated a large and vaguely lobulated mass approximately 7.5 cm in diameter located in the left pubic region, invading the left pubic bone and connected to another mass of approximately 2.5 cm present in the left abdominal wall (Fig. 2a and b). Magnetic resonance imaging (MRI) re-
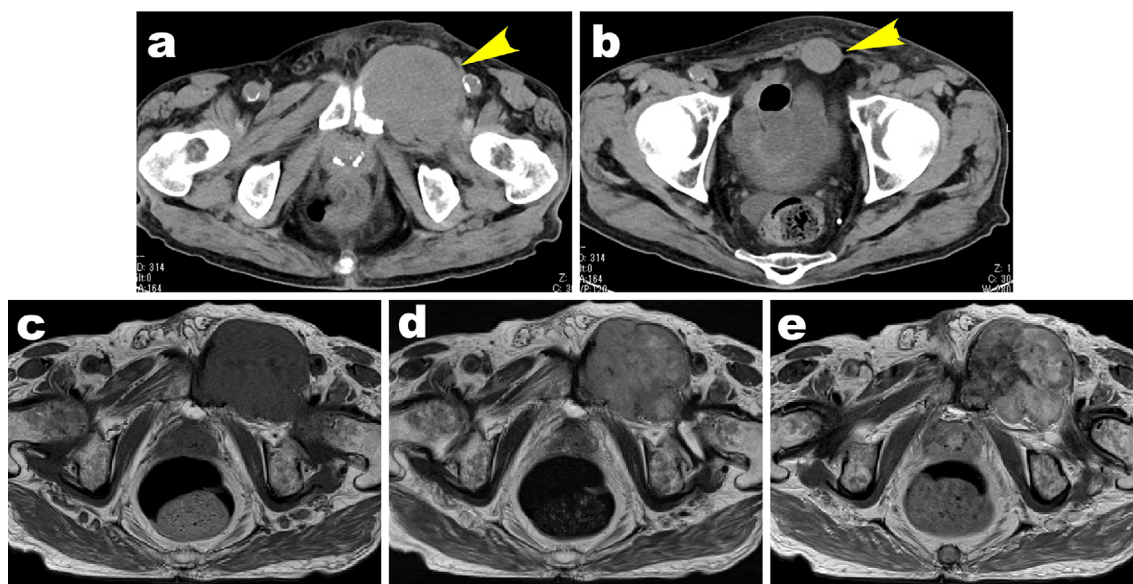
Figure 2. (a, b) Computed tomography (CT) images. (a) A large and vaguely lobulated mass of approximately 7.5 cm diameter located in the left pubic region (arrow head) was invading and destroying the left pubic bone. (b) Another mass approximately 2.5 cm in diameter in the left abdominal wall (arrow head) was connected to the main mass. (c-e) Magnetic resonance imaging findings. (c) The inside of the mass showed low intensity on T1-weighted imaging. (d) The inside of the mass showed fundamentally high intensity on T2-weighted imaging, although it was considerably heterogeneous. (e) The intensity of the mass on T1-weighted imaging was heterogeneously enhanced by gadolinium-diethylene-triaminepentaacetic acid.

vealed the inside of the main mass to be low intensity on T1-weighted imaging (Fig. 2c) but essentially high intensity with considerable heterogeneity on T2-weighted imaging (Fig. 2d). The main mass seemed to involve the left rectus muscle and left external obturator muscle. The intensity of the mass on T1-weighted imaging was heterogeneously enhanced by gadolinium-diethylene-triaminepentaacetic acid (Fig. 2e).

Although his clinical features were consistent with the diagnosis of CD, and the histology of the lymph node was consistent with plasma cell type CD, we were unsure about this diagnosis due to the presence of certain atypical findings. In particular, CT and MRI indicated destruction of the bone by the mass, which was quite unusual for CD. Therefore, instead of starting tocilizumab therapy, we performed another needle biopsy of a deeper portion of the main mass. Hematoxylin and eosin staining of the biopsy specimen revealed proliferation of atypical cells possessing large nuclei and prominent nucleoli on a background of eosinophilic matrix of the osteoid tissue (Fig. 3a and b). The morphology was consistent with the diagnosis of osteosarcoma. The tumor tissue was infiltrated by a considerable number of mature plasma cells (Fig. 3c). The tumor cells were positive for vimentin (Fig. 3d) and negative for cytokeratin AE1/3, CAM 5.2, desmin, CD34, αSMA, and S100p. The plasma cells were CD38-positive on immunohistochemical examinations (Fig. 3e). Both the tumor cells and plasma cells were positive for IL-6 (Fig. 3f). Based on these observations, the final diagnosis of IL-6-producing osteosarcoma was made. The

patient was treated with low-dose prednisolone, which helped alleviate his clinical symptoms, including his fever and anorexia. In order to receive intensive chemotherapy for his osteosarcoma, he was transferred to another hospital.

Discussion

In the 1950s, Benjamin Castleman described cases with solitary giant follicular lymphadenopathy, currently classified as UCD with hyaline-vascular type histology (1, 7). UCD is usually curable with complete surgical resection (3). Since the 1980s, a number of CD cases with generalized lymphadenopathy have been reported (8, 9), and based on these observations, Frizzera classified CD into two categories (UCD and MCD) depending on the distribution of the lesions (4, 10). The lymph nodes in UCD are usually large; according to a report by Talat et al., the mean diameter was 5.5±3.8 cm, which was larger than that of MCD (3.8±2.0 cm) (11). In cases of MCD, clinical symptoms of systemic inflammation and lymph node histology of plasma cell type are commonly observed. In a considerably large proportion of MCD cases in Western countries, the coexistence of Kaposi's sarcoma and HIV infection have been reported (12, 13). Furthermore, in 1995, Soulier et al. reported that HHV-8, also known as Kaposi's sarcoma-associated virus, was detected in the lymph nodes in such HIV-positive cases (14). In such cases, the HHV-8 genome encodes viral IL-6, which can stimulate the production of intrinsic IL-6 and cause systemic inflammation and lymphadenopathy (2).
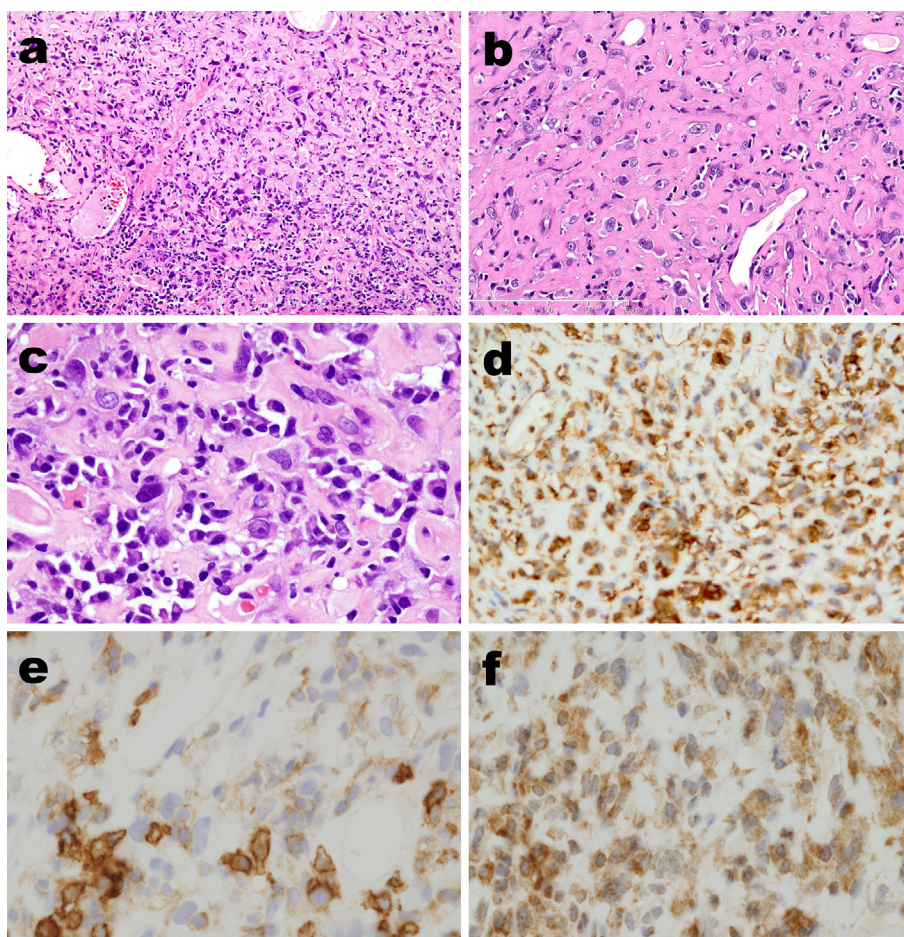
Figure 3. Sections of the deeper needle biopsy of the main mass. (a-c) Hematoxylin and Eosin staining; proliferation of atypical large cells with large nuclei and prominent nucleoli on a background of eosinophilic matrix of the osteoid tissue. Panel c shows that mature plasma cells had infiltrated the tissue (original magnification; a, ×100; b, ×200; c, ×400). (d-f) Immunohistochemical staining. (d) The neoplastic cells were positive for vimentin. (e) The infiltrated plasma cells were positive for CD38. (f) Both the neoplastic cells and plasma cells were positive for interleukin-6. Original magnification: a, ×100; b and d ×200; c, e and f, ×400.

In Japan, unlike in Western countries, most CD cases are HHV-8 negative idiopathic MCD (iMCD) (15, 16). Symptomatic iMCD cases are usually treated with the anti-IL-6 receptor antibody tocilizumab in Japan or the anti-IL-6 antibody siltuximab in the United States (17, 18).

In the present investigation, the primary tumor was located in the left pubic region, with a diameter of approximately 7.5 cm, which was unusually large for MCD but not unusual for UCD. Some enlarged lymph nodes were located near the main mass. The patient had systemic inflammatory symptoms, and his serum IL-6 levels were remarkably elevated. In the first two biopsies of the main mass and the neighboring lymph node, no suspected neoplasms were found, and the plasma cells proliferating in the lymph node were polyclonal and IL-6-positive. Based on these findings, we first assumed that the patient had plasma cell-type CD. However, some atypical findings were noted. First, the patient had macrocytic anemia, which was not characteristic of CD. CD usually manifests microcytic anemia due to the overproduction of hepcidin, the central regulator of systemic iron storage, induced by IL-6 (19). Second, the main tumor had apparently invaded and destroyed the pubic bone, which was quite strange for a CD-associated lesion. Third, the inside of the main mass was considerably heterogeneous on MRI, indicating hemorrhaging and necrosis; this finding was not typical for CD. Fourth, the SUV_{max} of the FDG uptake was unusually high for CD, which usually shows a mild to moderate uptake (SUV_{max}=2-8) (20-22). Furthermore, the diameter of the main mass was approximately 5 cm at 2 months prior to admission but grew to approximately 7.5 cm at the time of admission. This growing speed was unusual for CD. Therefore, we performed another biopsy of the deeper inner portion of the main mass, which ultimately led to the diagnosis of osteosarcoma. It has been reported that some bone tumors are difficult to diagnose even with large tissue samples and may require repeated biopsies or resection for the final diagnosis (23-25). Both the osteosarcoma cells in the main mass and the plasma cells in the neighboring lymph node were positive for IL-6 in immunohistochemistry. IL-6 appeared to have been primarily produced

by the neoplastic osteosarcoma cells, suggesting that plasma cells might produce IL-6 through paraneoplastic mechanisms.

Osteosarcoma is a high-grade malignant tumor characterized by tumor cells forming immature bone or osteoid. Osteosarcoma is largely a disease of the young, but it can also be found in older patients (26). To our knowledge, this is the first report of IL-6-producing osteosarcoma with CD-like manifestations. However, many cases of malignancies that were misdiagnosed as CD or transformed from CD had been reported in the literature; the most common misdiagnosis is in cases of follicular dendritic cell sarcoma, which can be associated with hyaline-vascular-type UCD (27, 28). Kikuchi et al. reported a case of IL-6-producing spindle cell sarcoma with paraneoplastic lymphadenopathy that had hyaline-vascular-type CD-like histology (29). Kraus et al. reported 10 cases of well-differentiated liposarcomas with an extensive lymphoplasmacytic infiltrate, mimicking the histology of plasma cell-type CD (30). While CD is rarely associated with carcinomas, the coexistence of hyaline-vascular-type CD and renal cell carcinoma has been occasionally reported (31-34). In such cases, IL-6 may play an essential role in the CD-like clinical manifestations.

In conclusion, we experienced a patient with IL-6-producing osteosarcoma whose diagnosis was quite challenging. Various diseases, such as chronic infectious diseases, malignancies, and autoimmune diseases, can manifest CD-like symptoms and the lymph node histology of both hyaline-vascular and plasma cell types due to the overproduction of IL-6. Clinicians should therefore carefully exclude such diseases before making a diagnosis of CD.

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

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