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Letter to the Editors

Unicentric Castleman disease, hyaline vascular variant, stromal rich, with increased plasma cells and a high level of serum IL-6: Raising the diagnostic and therapeutic issues

Letter to the Editor,

Castleman disease (CD) is a rare hematolymphoid disorder, first described by Benjamin Castleman in 1956 [1]. The clinical presentation of patients with CD can be subdivided into unicentric (U) or multicentric (M). Histologically, most cases of UCD present as a single lesion without systemic symptoms and display morphologic features usually can be classified as hyaline vascular or plasma cell variants [2,3]. Most cases of MCD present with systemic symptoms and histologically show features of plasma cell variant with polytypic plasmacytosis and elevated levels of interleukin 6 (IL-6), a cytokine involved in chronic inflammation and autoimmunity. MCD is commonly associated with human herpes virus 8 (HHV-8) infection. MCD positive for HHV-8 is associated with human immunodeficiency virus (HIV) infection. Those patients without HHV-8 infections are considered as having idiopathic CD [4]. The diagnosis of CD can be challenging and cases be confused with low-grade B-cell lymphoma such as marginal zone lymphoma (MZL), particularly in needle biopsy specimens.

The therapy for patients with CD is variable and depends, in part, on the disease being unicentric or multicentric. Patients with UCD and hyaline vascular variant are often treated with surgical excision alone. For patients with idiopathic MCD, an international consortium recently proposed a systematic approach for diagnosis and treatment. The optimal management of therapy for patients with UCD presenting with systemic symptoms is uncertain. Herein we report a case of UCD presenting with systemic symptoms and increased serum IL-6 level.

A 35-year-old woman without significant past medical history, was admitted to another hospital complaining of abdominal discomfort, fatigue, low-grade fever, and decreased appetite. Physical examination was unremarkable. Laboratory evaluation showed a complete blood count (CBC) and metabolic panel within normal ranges. Computed tomography (CT) scan of the abdomen and pelvis without contrast showed a 5.7 × 4.7 × 6.2 cm retroperitoneal mass; a core incisional biopsy of the mass was reported as an atypical lymphoid infiltrate, suggestive of a low-grade B-cell lymphoma. The serum IL-6 level was 275 pg/mL (normal range, 0–16 pg/mL). The patient was treated with rituximab with symptomatic improvement, but had stable disease on repeated CT scan. One year after completion of treatment the patient's symptoms recurred and she was referred to our institution. The physical examination was unremarkable. Laboratory findings included white blood cell (WBC) 8.9 × 10^9/L (normal range, 4–11 × 10^9/L), hemoglobin (Hgb) 8.7 g/dL (normal range, 12.0–16.0 g/dL), mean corpuscular volume (MCV) 78 fL, and platelet count 579 × 10^9/L (normal range, 150–440 × 10^9/L); a metabolic profile including serum lactic dehydrogenase was normal. The serum IL-6 level was 68 pg/mL. A positron emission tomography–computed tomography (PET-CT) scan was performed and showed an enhancing retroperitoneal pelvic mass, 5.2 × 4.0 cm with maximum SUV of 12.13, and mesenteric/retroperitoneal lymphadenopathy (Fig. 1). A needle biopsy of the main mass showed a diffuse infiltrate of small mature lymphocytes, which on immunohistochemistry were predominantly B lymphocytes. Surgical excision was recommended. Staging bone marrow biopsy was negative for lymphoma involvement.

Histologic sections of the mass excision showed a diffuse infiltrate with interstitial and perivascular fibrosis. Scattered remnants of lymphoid follicles with involuted, lymphocyte-depleyed germinal centers were noted. The interfollicular regions showed a mixture of small lymphocytes, scattered spindle cells, increased small blood vessel proliferation (Fig. 2, A, 200×), and areas with many mature plasma cells. Residual lymph node with small follicles displaying a predominance of follicular dendritic cells and scant small lymphocytes and marked interfollicular plasmacytosis were noted at the periphery of the mass (Fig. 2, B, 200× and B insert, 400×).

Immunohistochemical studies showed that the spindle cells were positive for CD35 (Fig. 2, C, 100×) and EGFR (Fig. 2, D, 400×). CD117, S-100 protein, and HHV-8 were negative. There were multiple foci of TdT-positive small lymphocytes in the interfollicular and perifollicular regions. The small lymphoid follicles were positive for CD20 and BCL-6. Numerous small, mature plasma cells were polytypic for immunoglobulin kappa and lambda light chains (Fig. 2, E and F, 100×). IgG4 highlighted rare plasma cells. In situ hybridization for Epstein-Barr virus encoded RNA (EBER1) was negative. The histological and immunohistochemical features support the diagnosis of CD, but the lesion was difficult to further classify. We believe the features best support hyaline vascular variant, stroma-rich, but there were also areas with increased mature plasma cells as are seen usually in the plasma cell variant CD. Two weeks after excision, the patient's symptoms, the previously identified lymphadenopathies resolved, and serum IL-6 became undetectable.

CD can mimic low grade malignant lymphomas clinically and histologically, as was the case in this patient, particularly in small needle biopsy specimens that may not be representative. Specifically, the patient we report received rituximab for an initial diagnosis of low-grade B-cell lymphoma. Subsequent progression led to surgical excision of the mass 1 year later followed by complete remission. Neoadjuvant therapy is recommended for un-resectable or for incompletely resected cases of UCD [5,6]. Rituximab is the most commonly used agent for this purpose, but the patient we report was primarily refractory. The patient had unusual clinicopathologic features for UCD and the high serum level of IL-6, raised the question as to whether tocilizumab, siltuximab or other agents targeting IL-6 receptor were indicated in this patient. The use of these agents is well established in idiopathic MCD, achieving high response rates and favorable outcomes.

In contrast with MCD, IL-6 levels are not typically monitored in patients with UCD. The patient we report presented with an elevated serum IL-6 level that became undetectable after resection of the lesion

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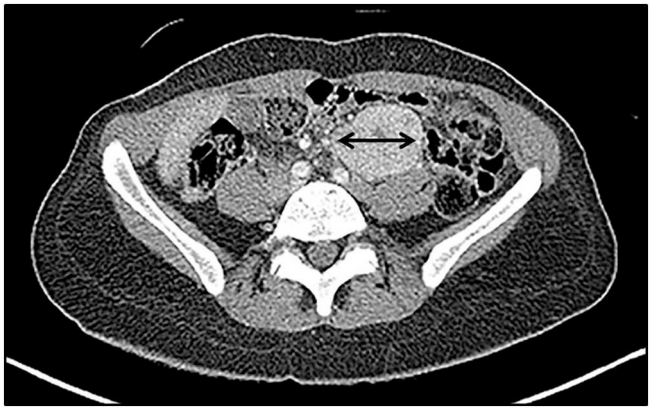

Fig. 1. PET CT scan: An enhancing fluoro-deoxyglucose (FDG) avid mass, 5.2 × 4.0 cm, is seen in the left common iliac lymph node.

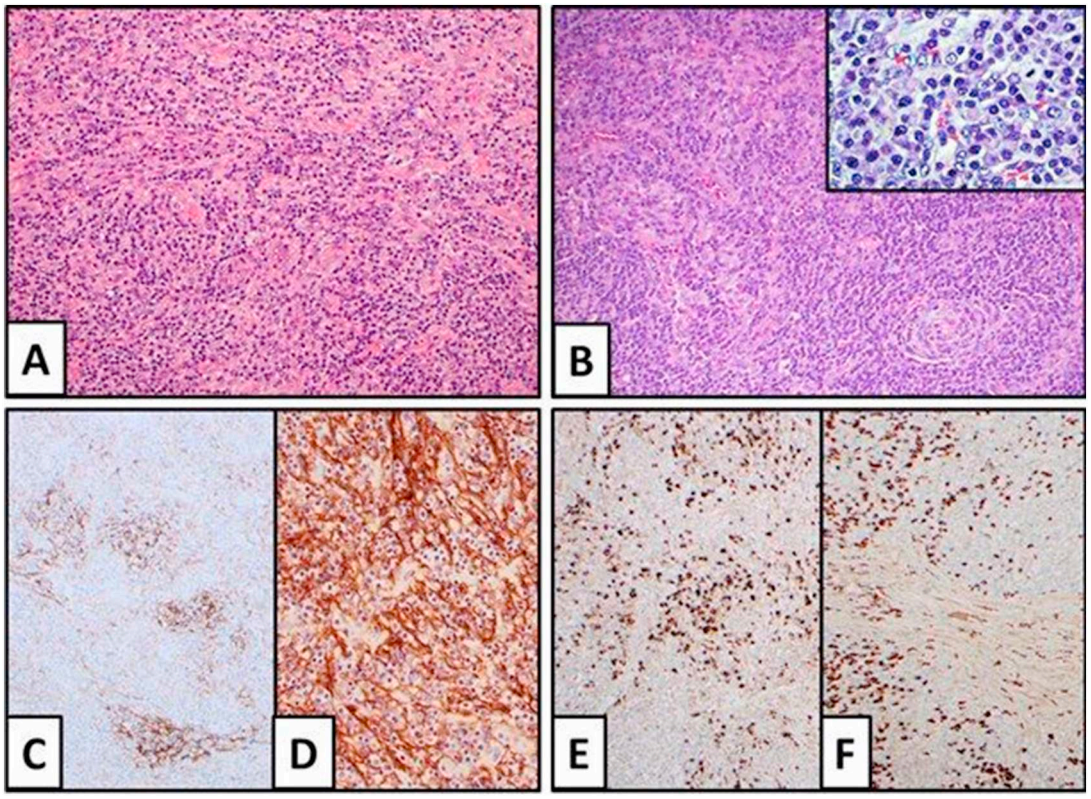

Fig. 2. Microscopically the mass is composed of fibroblasts, fibrosis, many small lymphocytes and mature plasma cells (A, H&E, 200×). Residual lymph node with features of Castleman disease characterized by areas with small follicles, lymphocyte-depleted germinal centers and marked interfollicular plasmacytosis (B, H&E, 200× and B insert, 400×). Immunohistochemical stains show reactivity for CD35 (C, 100×) and EGFR (D, 400×) in the spindle cells. Numerous small, mature plasma cells were polytypic for immunoglobulin kappa and lambda light chains (E and F, 100×).

and thus the IL-6 level was a biomarker for response to therapy in this patient. The presence of elevated serum IL-6 levels is thought to be unusual in patients with UCD. Most patients with UCD have hyaline vascular variant CD and the major driver dysregulation of vascular endothelial growth factor (VEGF). In contrast, dysregulation of IL-6 is more common n plasma cell variant. The IL-6 association is well shown in two separate experiments involving transgenic mice that constitutively expressed murine IL-6 [7] and viral IL-6 (vIL-6) [8]. vIL-6 is a viral homolog of human IL-6, encoded by HHV-8, that does not require the cellular IL-6 receptor for binding to the ubiquitously expressed gp130 receptor subunit and subsequent JAK-STAT signaling. In these two studies, mice developed CD-like syndrome: splenomegaly, multifocal lymphadenopathy, hypergammaglobulinemia, and plasmacytosis. However, in the second study, where a murine IL-6 knockout model was used, the stimulation with vIL-6 failed to induce the development of CD signs, supporting the idea that endogenous IL-6 plays a vital role. This finding could substantiate the role of viral infection in the etiology of CD, especially the plasma cell variant.

In conclusion, we present a patient with UCD in whom the clinical and pathologic features showed mixed features of hyaline-vascular and plasma cell variant. The morphologic features support the stroma-rich hyaline vascular variant, but there were many plasma cells in some areas as seen in plasma cell variant. The elevated serum IL-6 levels are more common in patients with MCD which almost always shows features of plasma cell variant. Serum IL-6 is usually not monitored in patients with UCD, but this patient's experience suggests that monitoring serum IL-6 levels may be helpful for diagnosis and follow up of residual disease.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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