CASE REPORT

Hyaline-Vascular Type Castleman's Disease, Sarcoidosis, and Crohns Disease

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Abstract Sarcoidosis and Crohns disease have been associated with increased long term risk of lymphoproliferative disorders, including lymphomas. Newly developed lymphadenopathy in a patient with these disorders should prompt pathological evaluation. Castleman's disease is a lymphoproliferative disorder characterized by enlarged hyperplastic lymph nodes with regressed follicles surrounded by expanded mantle zones of small lymphocytes, and interfollicular vascular proliferation in the hyaline-vascular type. Similar to sarcoidosis and Crohns disease, its etiology is incompletely understood, although immune dysregulation, genetic factors and infectious and environmental factors are thought to play a role in all three diseases. Interleukin-6 is a possible pathological common factor between these three disease processed. Unicentric, hyaline-vascular type Castleman's disease can be treated successfully with complete surgical resection. We report a patient with long history of sarcoidosis and Crohns disease with newly developed lymphadenopathy which was found to be due to Castleman's disease.

Keywords Castleman's disease · Sarcoidosis · Crohns disease · Surgical resection

Introduction

Castleman's disease is an unusual lymphoproliferative disorder that may mimic lymphoma clinically and pathologically. It is classified clinically as localized and multicentric types, and pathologically as hyaline-vascular and plasma cell type, and human herpes virus-8 (HHV-8)-associated plasmablastic multicentric Castleman's disease. The etiology remains unclear although immune dysregulation, genetic factors and infection may play a role in pathogenesis [1]. A similar pathophysiological picture is seen in sarcoidosis and Crohns disease. Newly developed lymphadenopathy with night sweats in a patient with a long history of Crohns disease and sarcoidosis treated with immunosuppressive therapy is concerning for lymphoma. We report a patient with Crohns disease and sarcoidosis with lymphadenopathy who developed Unicentric, hyaline-vascular type Castleman's disease. This is the first report describing such association among these three disorders. The pathologic features, pathogenesis and clinical management of Castleman's disease are discussed.

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Case Report

A 51 year-old woman with history of sarcoidosis presented to our institution for surgical evaluation for ileal strictures secondary to Crohns disease. She had been diagnosed with sarcoidosis 2 years prior to presentation after routine chest X-ray demonstrated mediastinal and hilar lymphadenopathy. No significant pulmonary parenchymal involvement was

noted on high resolution CT. Spirometry showed mild obstructive pattern although she was asymptomatic. Biopsy of the mediastinal lymph nodes demonstrated non-necrotizing epithelioid granulomas, focal giant cells with Schaumann bodies with negative AFB and Giemsa staining for mycobacterial and fungal organisms. Punch biopsy of the multiple erythematous indurated plaques on her right lower extremity revealed numerous foci of granulomatous inflammation extending into the subcutis. She was diagnosed with Crohns disease 15 years prior after she developed 18–20 episodes of daily diarrhea. Colonoscopic evaluation at that time revealed transmural inflammation and multiple crypt abscesses. She was initially managed with high dose prednisone, received azathioprine for 5 years, and had been receiving 4-weekly infliximab starting a year before presentation. She continued to have bloody stools, obstructive symptoms, abdominal pain and iron deficiency anemia despite the infliximab. MRI enterography showed multifocal wall thickening and luminal narrowing within the ileum with associated mild pseudo-sacculation. Outside medical records revealed a retroperitoneal mass noted on CT abdomen pelvis performed 3 years ago; this had remained stable on current imaging performed at our institution. Apart from non resolved GI symptoms, she complained of night sweats. She did not endorse fevers or recent weight changes. Medication included monthly infliximab infusions, hydroxychloroquine, fluticasone–salmeterol inhaler, and as needed ibuprofen and loperamide for joint pain and diarrhea respectively.

Her exam was notable for an obese female in no apparent distress. General and systemic examination did not reveal other abnormalities. Laboratory analysis revealed white cell count $6.4 \times 10^9/L$, hemoglobin 113 g/L, and platelet count $246 \times 10^9/L$. Anemia was attributed to chronic gastrointestinal blood loss (serum iron 27 mcg/dL (normal 37–145), serum ferritin 56 ng/mL (normal 13–150). Renal and liver function was preserved, with alkaline phosphatase (ALP) level of 126 IU/L (normal 35–104). Serum albumen was 3.9 g/dL (normal 3.5–5.2).

She underwent uncomplicated laparoscopic small bowel stricturoplasty and enterectomy, as well resection of the retroperitoneal mass, which did not involve any large vessel and spared the ureters. A lymphomatous process was suspected given her history of immunosuppression and 'B' symptoms. Surgical pathology showed small bowel segment (38 cm) with stricturing, non-granulomatous patchy chronic active enteritis with ulceration and pseudopolyp formation, and no evidence of dysplasia.

The retroperitoneal mass consisted of a partially encapsulated lobulated lymph node structure measuring $5.7 \times 3.5 \times 2.0$ cm with a pink-tan, fleshy lobulated cut surface. Morphological and immunophenotypic analyses

(Figs. 1, 2) showed an overall architecturally preserved lymph node with numerous regressed CD10(+) germinal centers that resided in CD21(+) follicular dendritic cell meshworks, and ringed by expanded mantle zone IgD(+)/TCL-1(+)/CD20 (+) small B lymphocytes. Hyalinized vessels penetrating germinal centers were noted (Fig. 1). The interfollicular areas showed varying degrees of sclerosis and thickened vessels. There was no significant increase in CD138(+) or IgG4(+) plasma cells. A diagnosis of Castleman disease was suspected based on these pathological findings. Further testing for HIV 1- and 2 antibodies, blood HHV-8 PCR, Hepatitis B and C serology and Quantiferon tuberculosis tests were negative. No monoclonal gammopathy was noted. She had no evidence of organomegaly, endocrinopathy or neuropathy.

Since she did not have other foci of involvement clinically and imaging (no effusions, organomegaly, palpable or radiological masses elsewhere), a diagnosis of Unicentric Castleman's disease was made. The original surgical specimen had clean margins and the surgical resection was considered a definitive curative procedure. Her night sweats resolved after this. She is doing well 18 months later at last follow-up.

Discussion

Castleman's disease (CD) is a lymphoproliferative disorder characterized by enlarged hyperplastic lymph nodes with various pathologic features [1, 2]. It is classified clinically as unicentric and multicentric types. Unicentric disease is more common, benign and limited to one lymph node area. Multicentric disease on the other hand is a systemic process, often associated with infection (HIV, HHV-8), malignancy (lymphomas and Kaposi sarcoma) and plasma cell disorders (POEMS syndrome and amyloidosis).

Similar to sarcoidosis and Crohns disease, the pathogenesis of CD is incompletely understood [3]. Very few reports document an association between sarcoidosis and CD [4, 5], Crohns disease and CD [6, 7], and CD with other gastrointestinal autoimmune disorders such as celiac disease [8] and ulcerative colitis [9]. Immune dysregulation (autoimmunity and immune deficiency), genetic and environmental factors including infectious agents may play roles in pathogenesis of these three disorders, sarcoidosis, Crohn disease and CD. IL-6 is a cytokine released by macrophages, fibroblasts and lymphocytes and leads to B- and T-lymphocyte proliferation and neutrophil chemotaxis. Overproduction of IL-6 has been associated with CD, Crohn's disease and sarcoidosis [10–12]. Tocilizumab and siltuximab, anti-IL-6 antagonists have demonstrated their efficacy in treating multicentric CD [13, 14].

Fig. 1 Hyaline-vascular variant of Castleman's disease, histopathology. **a** Regressed germinal center with expanded mantle zones of small lymphocytes forming concentric rings. **b** Regressed germinal center with penetrating blood vessels (*arrows*)

Fig. 2 Hyaline-vascular variant of Castleman's disease, immunohistochemistry. **a** TCL-1 highlights expanded mantle zone B cells around regressed germinal centers. **b** IgD highlights expanded mantle zone B cells around regressed germinal centers

Our patient had a long history of Crohns disease and sarcoidosis treated with multiple immunomodulatory medications, including steroids, azathioprine and infliximab. It is unclear why the retroperitoneal mass was not evaluated earlier. While the retroperitoneal mass was initially seen on imaging even before infliximab was initiated, it is likely that immunodeficiency and the altered immunogenic milieu associated with sarcoidosis and Crohns disease may contribute to development of the CD. This is the first report, to the best of our knowledge, detailing the occurrence of CD in a patient with Crohns disease and sarcoidosis.

Patients with unicentric CD typically have asymptomatic lymphadenopathy of one area, discovered on physical exam or imaging. Lesions had a median size of 5.5 cm in the largest reported CD cohort [15]. Our patient had a similarly sized specimen. Although the thorax and mediastinum are more common sites of involvement, the retroperitoneum accounts for a significant number of cases [15]. Systemic symptoms are uncommon in the hyaline vascular subtype, but more common in the plasma cell subtype and multicentric CD. Our patient did report night sweats but no fevers or weight loss. It is unclear if this was due to sarcoidosis or CD. Resolution of night sweats after

surgical resection points to it being due to CD. Patients with multicentric CD often develop edema, body effusions, organomegaly, neuropathy and skin rash.

Laboratory evaluation is usually unremarkable in Unicentric CD although multicentric CD is often associated with anemia, thrombocytopenia, elevated inflammatory biomarkers, hypoalbuminemia and polyclonal hypergammaglobulinemia. Our patient did have iron deficiency anemia but it was likely related to chronic GI blood loss. Tests such as HIV, HHV-8, hepatitis viral serologies, serum protein electrophoresis and quantitative immunoglobulin can help to rule out associated conditions.

Pathological evaluation of the lymph node(s) is essential for the diagnosis of CD. Large population based studies from Sweden have demonstrated an increased risk of non-Hodgkin lymphoma in patients with sarcoidosis and Crohns disease [16, 17]. Newly developed lymphadenopathy during the course of chronic sarcoidosis should be investigated promptly in order to rule out concomitant lymphoma [18]. We were concerned about malignancy in our patient. She had a large sized retroperitoneal mass and night sweats with chronic Crohns disease and sarcoidosis managed with various immunosuppressive therapies.

Pathologically CD is classified as hyaline-vascular and plasma cell type, and human herpes virus-8-associated plasmablastic multicentric Castleman's disease. The most common hyaline vascular type (representing approximately 90 % of Unicentric CD) is characterized by regressed germinal centers surrounded by a mantle zone of small lymphocytes in a concentric pattern, imparting onion-skinning appearance. The germinal center is often atrophic and hyalinized [2] with variable degree of proliferation of CD21(+) follicular dendritic cells. Sinuses are usually absent [2]. Our patient had those characteristic findings (Figs. 1, 2) and no evidence of lymphoma. The less common plasma cell type is characterized by hyperplastic germinal centers and plasma cells [19] whereas HHV-8-associated multicentric CD is characterized by scattered HHV-8(+) large lymphoid cells (plasmablasts) in the mantle zone. These histopathological changes are thought to represent exaggerated immune responses to antigens. The pathological differential diagnosis of CD includes malignancy (lymphoma, and plasmacytoma), inflammatory conditions (reactive follicular hyperplasia, rheumatoid arthritis), and infection (Toxoplasma or HIV).

Our patient had hilar/mediastinal and cutaneous sarcoidosis (plaque sarcoidosis), and a radiographically diagnosed retroperitoneal mass. She had lymphadenopathy in the thorax, that biopsy was typical of sarcoidosis. Granulomatous inflammation practically rules out CD [19]. The management of Unicentric and multicentric CD is completely different and it is important to characterize extent of disease before management can be initiated.

Although no randomized trials have compared treatment modalities given the rarity of this disorder, complete surgical resection is the current standard of care for Unicentric hyaline-vascular type CD. Outcome is generally excellent [15, 20]. Management of multicentric CD is more complex and involves managing concurrent infections (HIV with ART) along with rituximab, anti IL-6 agents, cytotoxic and radiation therapy [21].

To summarize, Castleman's Disease is a rare lymphoproliferative disorder. It may occur in patients with sarcoidosis and Crohn's disease, especially those who have received immunosuppressive therapy. These three diseases may be well linked and associated with underlying immune dysregulation. Suspicious masses in patients with sarcoidosis should be biopsied to rule out lymphoma and obtain accurate diagnosis. Unicentric hyaline-vascular type Castleman's disease can be managed successfully with complete surgical resection.

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Conflict of Interest AG, BA, HZ, WC, SH and HVN declare that they have no conflict of interest.

Informed consent Informed consent was obtained from all individual participants included in the study.

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