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CASE REPORT

Retroperitoneal hyaline-vascular variant Castleman Disease in a patient with iron-deficiency anemia and sinus bradycardia: a case report

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Abstract

Objective Castleman disease, also known as giant lymph node hyperplasia, involves lesions in the lymph nodes usually located in the chest_ENREF_1, particularly in the mediastinum. Meanwhile, sinus bradycardia is a sinus rhythm slower than 60 beats per min, and it can occur in both healthy and sick individuals. However, the comorbidity of these two disorders has not been previously reported. In this paper, we report a case of a 46-year-old woman who presented with persistent sinus bradycardia and iron-deficiency anemia. Diagnostic work-up revealed hepatosplenomegaly and a giant mass near the splenic hilum. The mass was removed surgically; after which, the patient's bradycardia resolved immediately, while her anemia was corrected after subsequent chemotherapy. Pathological examination revealed lymph nodes with benign lesions, and the patient was diagnosed with hyaline-vascular variant of Castleman disease. This is the first documented case of sinus bradycardia associated with Castleman disease. In this paper, we describe the case characteristics, discuss the possible pathogenesis, and consider the appropriate treatment of symptomatic sinus bradycardia accompanying Castleman disease.

Key words: Castleman disease; sinus bradycardia; iron-deficiency anemia

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Castleman disease is a rare, non-neoplastic lymphoproliferative disorder first described in 1954 [1-3]. It can be either unicentric or multicentric, depending on whether the lymphoproliferation occurs at a single site or multiple sites [1–3]. The incidences of Castleman disease are similar in men and women [4–5], and although it can occur at any age, unicentric disease is more common in younger patients. Castleman disease usually develops in the chest [6-8] and rarely in the abdomen [6], but it can occur in any body area with lymph nodes [6]. Mass lesions associated with Castleman disease have been reported in the pelvic and retroperitoneal regions, mesentery, and the porta hepatis [6, 9–10]. The most common site in adults is the thorax (approximately 60% of cases), followed by the neck (14%), abdomen (11%), and axilla (4%) [8, 11].

Sinus bradycardia is a sinus rhythm slower than 60 beats per min (bpm) and may occur even in healthy individuals, particularly athletes and the elderly. Disease states such as increased intracranial pressure, hyperkalemia, and hypothyroidism may also cause sinus bradycardia.

Reports of Castleman disease are relatively common, particularly in relation to the mechanisms and type of disease. However, sinus bradycardia caused by Castleman disease is very rare. In this paper, we report a patient with both conditions and discuss the possible pathogenesis of sinus bradycardia in the setting of Castleman disease.

Case report

A 46-year-old woman was admitted to the Surgery Department of our hospital in June 2015 for weakness. Imaging data indicated a retroperitoneal tumor near the splenic hilum. The patient had been diagnosed with iron-deficiency anemia several years earlier and had remained

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anemic despite oral iron supplementation. Diagnostic work-up revealed persistent sinus bradycardia and mild hepatosplenomegaly.

Echocardiography (ECG) indicated a heart rate of 40–50 bpm. Endocrinology tests showed normal levels of free T3, free T4, and thyroid-stimulating hormone. Other laboratory analyses revealed serum hemoglobin of 6.6 g/dL; red blood cell deposition, 23.3%; average red blood cell volume, 63.1 fL (1L=1015 fL); average hemoglobin content, 17.9 pg; average hemoglobin concentration, 283 g/L; leukocyte count, 4.99×10^9/L; thrombocyte count, 532.0×10^9/L; high-sensitivity C-reactive protein, 201 mg/mL; erythrocyte sedimentation rate, 93 mm/h; serum iron, 5.19 μmol/L; ferritin, 1210.7 μg/L, transferrin, 2.35 g/L; soluble transferrin receptor, 20.35 mg/L; albumin, 25.8 g/L; globulin, 47.1 g/L; alanine aminotransferase, 18 U/L; aspartate aminotransferase, 17 U/L; alkaline phosphatase, 315 U/L; and gamma-glutamyltransferase, 94 U/L. Serum protein analysis showed increased levels of immunoglobulins A and G. Results of routine urinalysis were normal. Serological analysis for infectious diseases detected hepatitis B surface antibody and core antibody. The fecalysis results for common parasites were normal. Contrast-enhanced abdominal computed tomography revealed liver hemangioma, multiple swollen retroperitoneal lymph nodes, splenomegaly, and an upper left abdominal retroperitoneal mass, leading to a suspicion of Castleman disease (Fig. 1).

Abdominal ultrasound showed liver hemangioma and gallbladder cholestasis. Dynamic electrocardiography revealed sinus rhythm with a minimum heart rate of 40 bpm and a maximum of 90 bpm (average, 61 bpm) and 30 occasional multisource atrial premature beats. Abdominal magnetic resonance imaging showed a retroperitoneal mass, indicating a possible small intestinal stromal tumor. Because of suspected gastrointestinal bleeding indicated by low hemoglobin, the patient underwent ECG monitoring and blood transfusion. ECG monitoring showed persistent sinus bradycardia with 40–50 bpm. Laparotomy was performed on June 10, 2015 and revealed a mass (5 × 3 × 4 cm) with a complete capsule located on the small mesenteric margin near the splenic hilum. After removal of the mass, her ECG normalized, and her heart rate increased to > 60 bpm. Her serum hemoglobin concentration increased to > 9.0 g/dL and to >11 g/dL 1 month later, without transfusion or iron supplementation. Pathological examination of the surgical specimen revealed benign lymph node lesions, consistent with Castleman disease, hyaline-vascular variant (Fig. 2 and 3). Postoperative recovery was uneventful, and the patient was discharged 8 days after surgery without complications, with referral to an oncology clinic for postoperative adjuvant therapy.

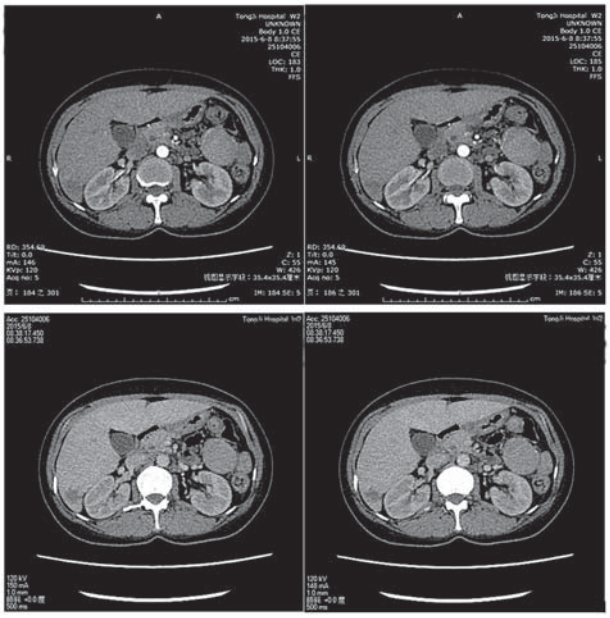

Fig. 1 CT images showing a retroperitoneal mass in the upper left abdomen, near the splenic hilum.

Discussion

This patient was initially diagnosed with a tumor of the pancreas or small intestine, but intraoperative examination ruled out both of these. Retroperitoneal multiple lymph node enlargement together with pathological results of the surgical specimen confirmed retroperitoneal Castleman disease, hyaline-vascular variant, and we attributed both her anemia and sinus bradycardia to this condition. The patient's anemia may have been anemia of inflammation associated with iron malabsorption largely due to Castleman disease [1–3]. In this disease, the inflammatory cytokine interleukin-6 (IL-6) can induce high levels of hepcidin, which impairs the release of iron from macrophages into the plasma and promotes the degradation of ferroportin secreted by hepatocytes [1, 12–13]. IL-6 thus plays a critical role in the pathogenesis and symptomatology of Castleman disease [14].

The hyaline-vascular variant accounts for 80–90% of cases of Castleman disease, whereas the plasma-cell and mixed variants are less common [1]. The condition can be unicentric or multicentric, depending on whether the lesion occurs in only one or several areas in the body [1-3]. The plasma-cell variant is more common in patients with multicentric Castleman disease, whereas the hyaline-vascular variant is more common in unicentric disease [1]. Multicentric disease is more severe and is often accompanied by systemic symptoms, such as fatigue, fever, night sweats, weight loss,and so on; and these patients also have hepatosplenomegaly and enlarged

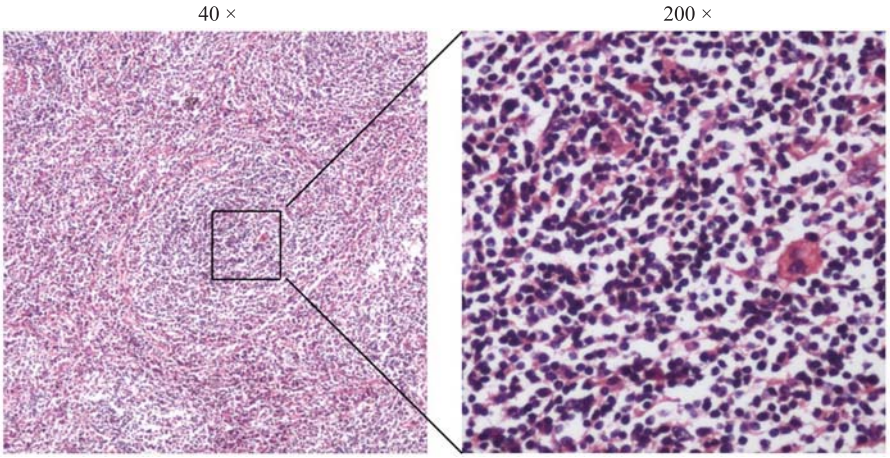

Fig. 2 Hyaline deposits were present within the germinal center. The germinal center of the follicles were partially lymphocyte depleted and some of the follicular dendritic cells were mildly atypital. A follicle penetrated by a sclerotic blood vessel, hyaline vascular lesion was in the follicle.

central lymph node [14–15]. Common laboratory results include anemia, low albumin, blood sedimentation abnormalities, and high immunoglobulin levels [14, 16]. However, the pathogenesis of Castleman disease is unclear, although dysregulated IL-6 production by affected lymph nodes may be responsible for its systemic manifestations [17]. Studies have shown an association with human herpes virus 8 (HHV-8, also called Kaposi sarcoma-associated herpes virus) [14, 17–19], and IL-6, which is increased by HHV-8, induces the expression of vascular endothelial growth factor, leading to vascular proliferation in the enlarged lymph nodes [6, 14, 20]. Human immunodeficiency virus is also associated with Castleman disease [17, 21, 22]. Moreover, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin abnormality syndrome as well as amyloidosis, renal insufficiency, and increased risk of lymphoma may also be associated with the disease [2, 8].

Sinus bradycardia is a relatively common condition, but its occurrence along with Castleman disease is very rare.

In theory, the heart rhythm of a patient with anemia should be faster; however, it was characterized by sinus bradycardia in our patient, suggesting the existence of a mechanism slowing her heart rate. The maintenance of a normal sinus rate several days after surgery indicated that the improved rate was not caused by intraoperative medication used to increase the heart rate. The immediate disappearance of the patient's bradycardia after removal of the mass suggested that her sinus bradycardia was caused by her Castleman disease, via either a chemical or physical mechanism or both. Although the exact mechanism remains unknown, sinus bradycardia may be caused by single or multiple genetic mutations. For example, mutations in the *HCN4* gene encoding the hyperpolarization-activated cyclic nucleotide-gated potassium channel 4 are associated with various rhythm disorders, specifically sinus bradycardia [23–27], and the sodium channel gene *SCN5A* may also be associated with sinus bradycardia [28–29]. Several studies have reported an

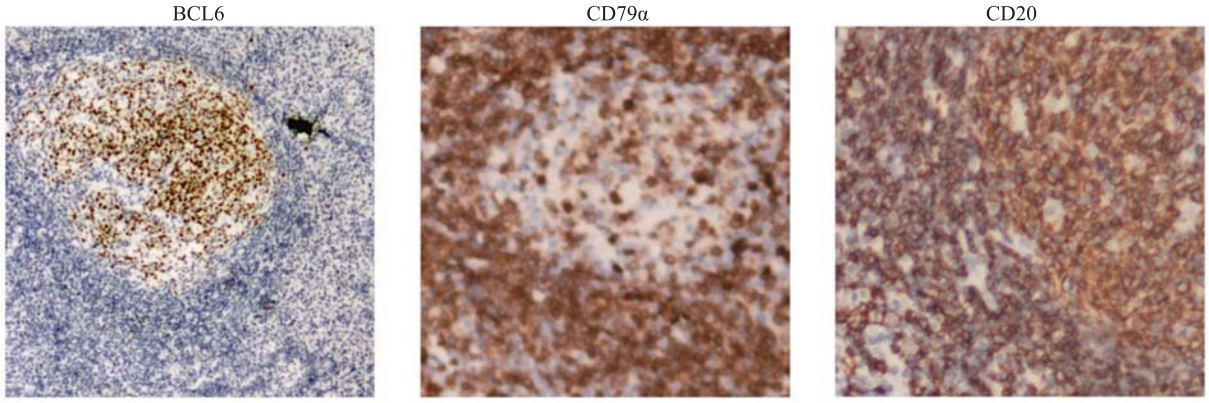

Fig. 3 CD20 immunostain highlights the germinal center cells mostly. BCL6 immunostain highlights the germinal center cells, but the mantle zoon is negative. CD79α immunostain highlights the mental zoon mostly.

association between loss-of-function mutations in *HCN4* and sinus bradycardia [23, 30]. *NKX2.5* and *SHOX2* have also been shown to maintain the condition of sinoatrial node cells [31], which may represent another mechanism whereby Castleman disease may lead to sinus bradycardia. Furthermore, the tumor mass may stimulate the vagus nerve directly. The mechanisms responsible for the other clinical manifestations attributed to Castleman disease are also unknown, except for its capability to cause iron-deficiency anemia.

The optimal treatment for Castleman disease is unclear; surgical removal is considered as the standard therapy in patients with unicentric masses [17, 32–35]. Meanwhile, although multicentric disease is often refractory to treatment, humanized anti-IL-6 antibody therapy may be transiently effective [17].

The current case was unusual in presenting with multicentric hyaline-vascular variant Castleman disease because this variant is more commonly associated with isolated, asymptomatic lymphadenopathy [5]. Furthermore, Castleman disease usually occurs in the chest [6–8], and the abdomen is rarely affected. However, the current patient had retroperitoneal disease and also presented with sinus bradycardia, which may have been caused by the Castleman disease.

This report describes a patient with Castleman disease and asymptomatic sinus bradycardia, which should thus be considered as a possible comorbidity. This case also highlights the potential of surgery to cure both unicentric Castleman disease and concomitant symptomatic sinus bradycardia in these patients without the need for a cardiac pacemaker.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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