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Case Report

Castleman's disease combined with choledocholithiasis: a case report and review of literature

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Abstract: Castleman's disease (CD) is a rare lymphoproliferative disease with unclear pathogenesis. CD is divided into unicentric and multicentric according to clinical classification, and is usually successfully treated with surgical resection alone. CD is also classified into hyaline vascular, plasma cell, or mixed cell type according to histopathological type. CD can occur in any part of the lymphatic tissue, but most occur in mediastinal lymph node, followed by the neck, armpit, and abdominal lymph nodes. Here, we have reported a case of Castleman disease which was accidently discovered during the operation of common bile duct calculi. The histological presentation of the lymph nodes was corresponded to the plasma cell type of CD. To our knowledge, there is no report about the plasma cell type of Castleman's disease coexistence with common bile duct calculi. Finally we also review the literature.

Keywords: Castleman's disease, lymph node hyperplasia, common bile duct calculi, plasma cell type

Introduction

Castleman's disease (CD) is a relatively rare lymphoproliferative disorder and features enlarged hyperplastic lymph nodes. The disease was initially presented by Castleman and colleagues in 1956 with unclear etiology [1]. CD is divided into unicentric and multicentric according to the range of lymph nodes involved. Unicentric type of CD involves a single site and presents without classical symptoms except a slow growing mass, while multicentric type of CD is associated with multiple lymph nodes and manifests systemic symptoms such as fever, malaise, weight loss, anemia, hypoalbuminemia, and generalized lymphadenopathy [2]. Based on the histological manifestation, the CD is categorized into hyaline vascular, plasma cell and mixed cell type [3]. It's reported that the hyaline vascular type was the most common type, in about 76% to 91% of CD cases, and the plasma cell type just represents about 9% to 24% of CD cases. The mixed cell type is rarely reported [4, 5]. The plasma cell type is more common in the multicentric type of CD which frequently presents with constitutional symptoms and the hyaline vascular type is most often found in asymptomatic unicentric type of CD.

Here, we described a case of unicentric type of CD. The histopathologic presentation of the lymph nodes corresponds to the plasmacytic variety of CD. To our knowledge, this is the first report of unicentric type of CD concomitant with common bile duct calculi.

Case report

A 59-year-old Asian female patient was admitted to our hospital with the chief complaint of right upper-quadrant abdominal pain for 3 days. The character of the pain was colic, intermittent and accompanied by waist pain. She also presented with nausea and vomiting. After admission for 2 days, the patient had jaundice accompanied by itchy skin. Her medical history was relevant only for hypertension. There was no significant surgical history, family history, and personal history. Laboratory Data: Patient's HGb, total count, differential count, red blood

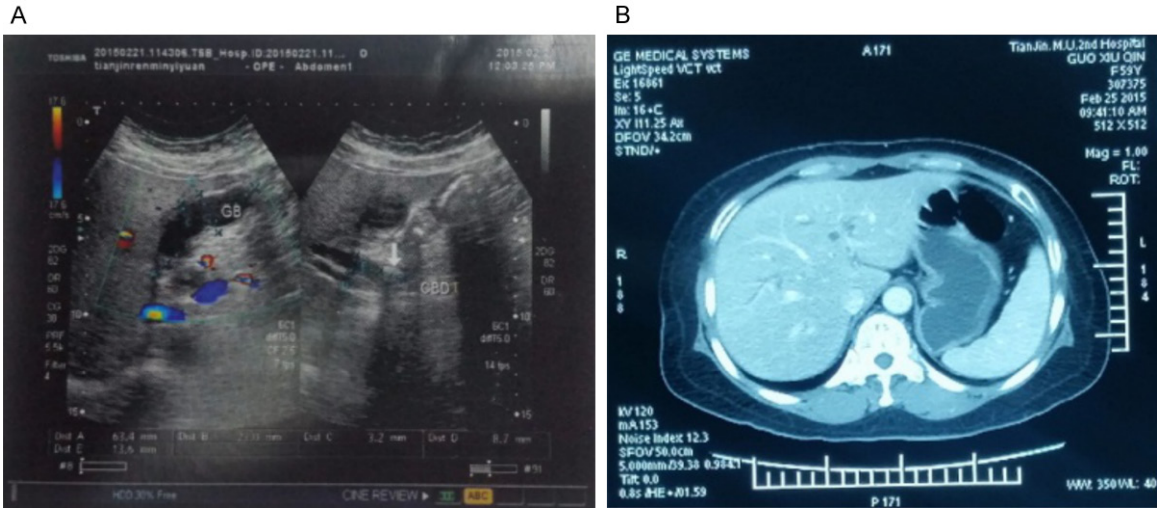

Figure 1. A: The abdominal ultrasound revealed common bile duct calculi, choledochal mild dilation, and cholecystitis. B: Abdominal computed tomography revealed distal common bile duct stenosis, and intra- and extrahepatic bile duct dilation, but no obvious lymph node.

cell count and platelet count were normal. Her liver function tests were abnormal (AST 453.8 U/L, ALT 306.7 U/L) and renal function tests were within normal limits. Serum sugar and electrolytes were also normal. Serum tumor markers CA-199, CEA, AFP, and CA72-4 were normal, serum HIV-Ab was negative.

The abdominal ultrasound revealed cholecystitis and common bile duct calculi with a diameter of 14 mm. The gallbladder size was normal with gallbladder wall thickening. There was no obvious abnormal echo in the cavity (**Figure 1A**). Abdominal computed tomography (CT) shows the common bile duct broadening and wall thickening. No enlarged lymph nodes were noted around the inferior vena cava and abdominal aorta. There was no evidence of any abnormalities in other organs (**Figure 1B**).

The patient was taken to the operating room for a common bile duct exploration. Intraoperatively a neoplasm was found at the bottom of the common bile duct. It was a fixed, hard, low vascular mass with dense adhesions to the common bile duct lumen and severe surrounding inflammatory edema, making complete resection impossible. The mass was cut off with a part of common bile duct and the specimen was sent for intraoperative frozen histopathologic examination. Final frozen diagnosis of the mass revealed chronic inflammation. After excision of the mass, a side-to-side Roux-en-y choledochojejunostomy was performed. Below the hepatoduodenal ligament and above the pylorus there were swollen lymph nodes about 20 mm in diameter and this was also excised. The specimen was sent for histopathologic examination.

The pathologic manifestation of the enlarged lymph node revealed angiofollicular hyperplasia accompanied by plenty of hyperplasic plasma cells infiltration in the follicular and interfollicular region, with mildly hyalinized blood vessel hyperplasia perforating the follicles (**Figure 2A** and **2B**). The immunohistochemical staining showed the plasma cells were positive for CD138 (**Figure 2C**). Additionally, immunohistochemical staining with Kappa and Lambda were positive, which means the hyperplasic plasma cells were polyclonal (**Figure 2D** and **2E**). Through the immunohistochemical staining with CD34, the hyperplastic small blood vessels penetrating into the lymph follicle were marked out (**Figure 2F**). The immunohistochemical staining with CD3, CD20 and CD21 represented T lymphocytes, B lymphocytes, and dendritic cells respectively. The results showed all the T lymphocytes, B lymphocytes, and dendritic cells coexisting and there were no malignancy-associated changes (**Figure 3A-C**). Meanwhile, the immunohistochemical staining with Cyclin-D1 was negative. Cyclin-D1 gets overexpressed in mantle cell lymphoma, thus we ruled out mantle cell lymphoma (**Figure 3D**).

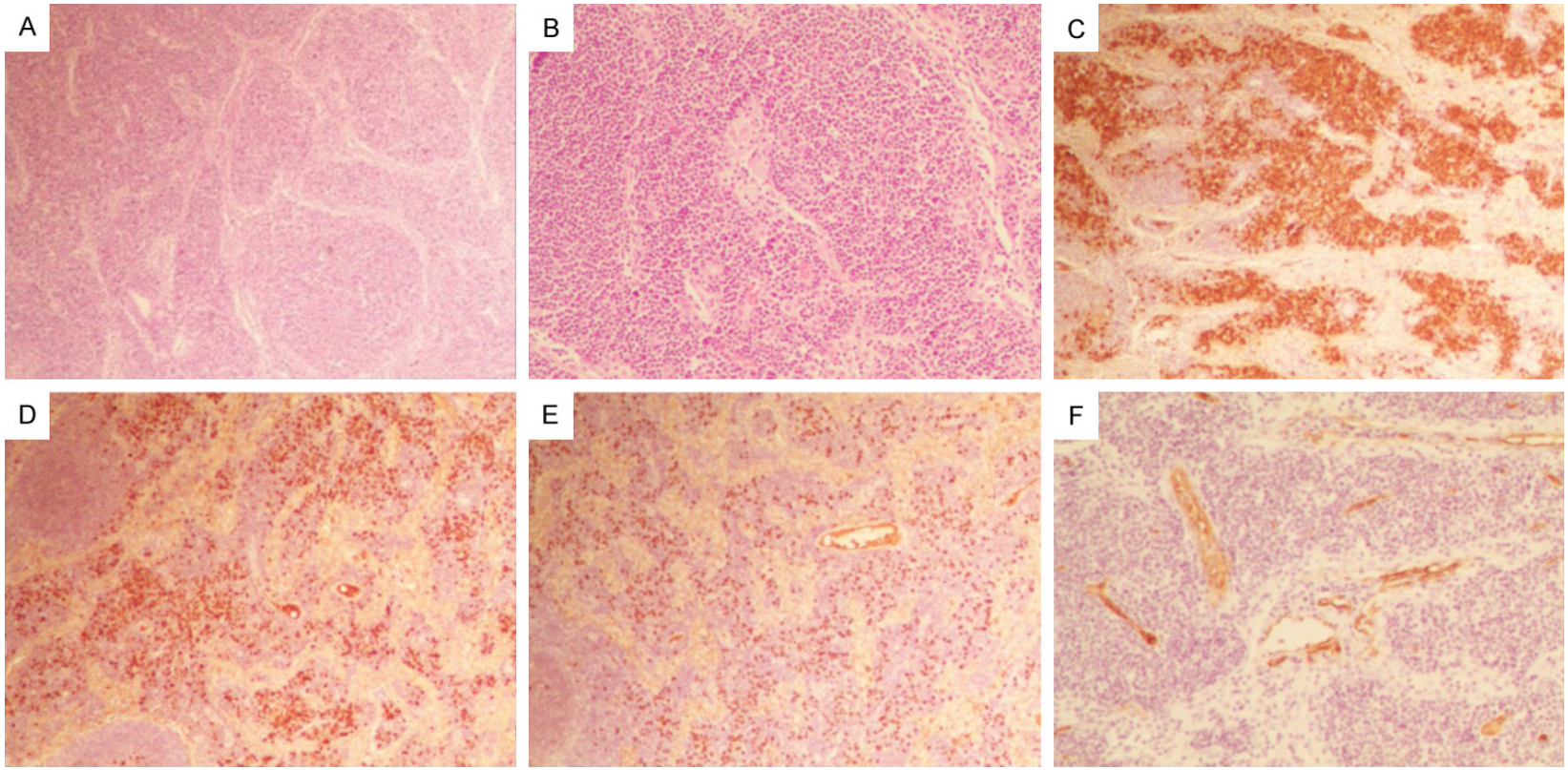

Figure 2. Microscopic images of the lymph node. (A and B) The enlarged lymph node presented with angiofollicular hyperplasia, accompanied by many plasma cells and mildly hyalinized blood vessels with hyperplasia which perforated the follicles (Hematoxylin-eosin stain, original magnification ×40 for A, original magnification ×100 for B). (C) The immunohistochemical staining with CD138 to mark the plasma cells was positive. (D and E) Immunohistochemical staining with kappa (D) and lambda (E) was positive, which revealed that the hyperplastic plasma cells found in the follicular and interfollicular region were polyclonal. (F) Immunohistochemical staining with CD34 was positive, which marked the hyperplastic small blood vessels penetrating into the lymph follicle. (C-F original magnification ×40).

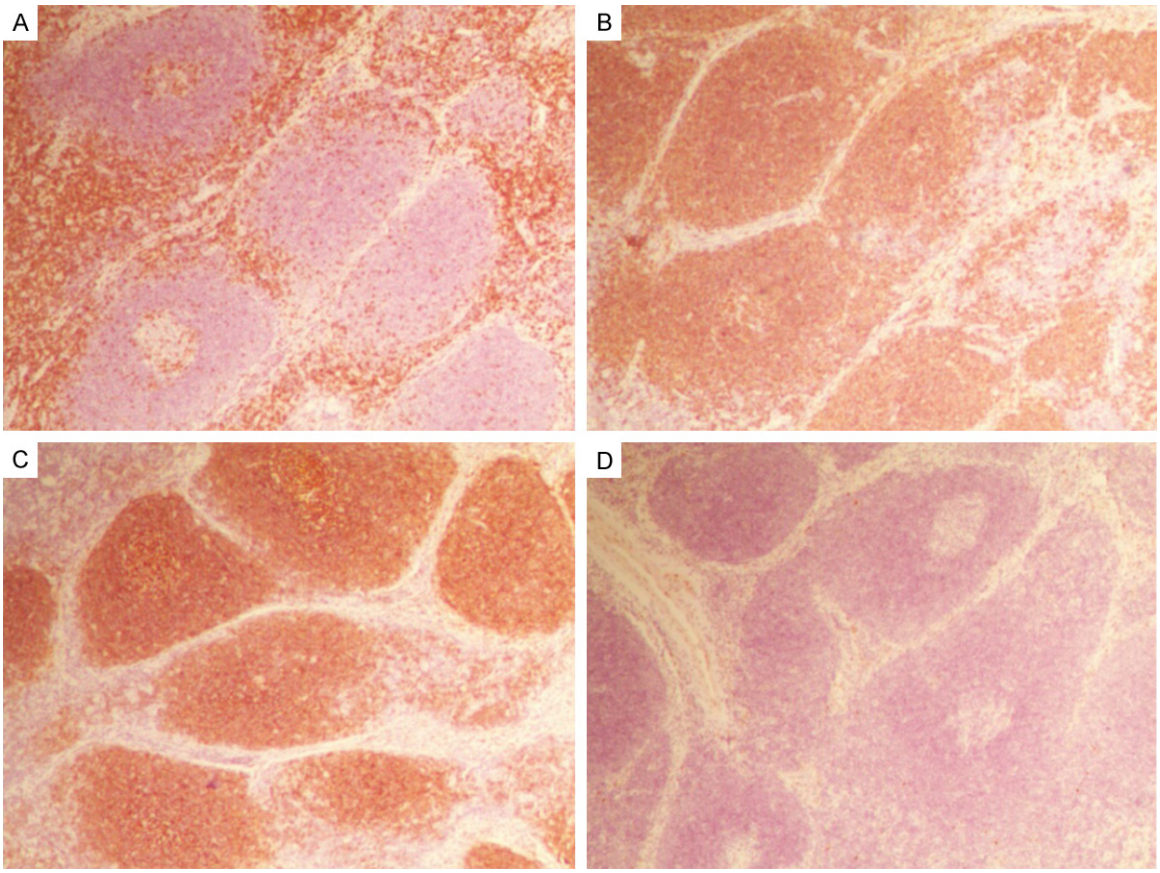

Figure 3. Microscopic images of the lymph node. (A-C) Immunohistochemical staining with CD3 (A), CD20 (B) and CD21 (C) represented T lymphocytes, (B) lymphocytes, and dendritic cells respectively. (D) Immunohistochemical staining with Cyclin-D1 was negative. (A-D original magnification ×40).

Taken together, the features of pathologic examination and inmmunochemical findings were consistent with early appearance of plasma cell type of CD. Based on this, the diagnosis of plasmacytic type of Castleman's disease was given.

After surgery, no adjuvant treatment like monoclonal antibodies or radiotherapy was given and the patient continued to do well at her 12th month postoperative visit. There was no pathologic or radiographic evidence to suggest multicentricity.

Discussion

Since first identified by Castleman and colleagues [1], Castleman's disease has attracted extensive scientists' attention but still is poorly understood. Castleman's disease lacks typical clinical symptoms and the etiology is unclear. It's difficult to diagnose and usually found by accident. In this case report, Castleman's disease was accidently discovered during the operation of common bile duct calculi without clinical symptoms.

Although the etiology of Castleman's disease is unclear, some studies have demonstrated that viruses such as human herpes virus 8 (HHV-8), HIV, and Epstein-Barr virus infection may be implicated in the occurrence of CD [6-8]. Soulier et al. reported frequent coincidence of HHV-8 in 31 patients with multicentric type of CD [9]. A recent report suggested that HHV-8 infection in an HIV patient caused an improvement in immune status, thus causing multicentric type of CD [8]. Lachant et al. reported 2 patients with the acquired immunodeficiency syndrome (AIDS) who developed multicentric type of CD followed by Kaposi sarcoma [10]. Similarly, Powles et al. demonstrated that older HIV-positive individuals with well-preserved immune function, are more likely to acquire a multicentric type of CD [6]. HIV-associated multicentric type of CD is diagnosed late and is associated

with high mortality [11]. Also, EBV may have a potential role in angiogenesis of Castleman disease, thus accelerating the occurrence of CD [7, 12]. Furthermore, dysregulation or dysplasia of follicular dendritic cells and inflammatory mediators (especially interleukin-6) have been incriminated, mainly in the multicentric type of the disease [13, 14]. Other than that, some other cell factors such as vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR) have also been reported in the development of some cases. Nishiet et al. found the level of VEGF in sera and supernatants of cultured lymph nodes in two plasma cell type of CD patients to be higher than in normal controls. Immunohistochemical analysis showed a high expression level of VEGF in plasma cells of the interfollicular region [15]. In addition, a recent study demonstrated EGFR is up-regulated in follicular dendritic cells and surrounding perifollicular fibroblastic reticular cells, therefore it is expressed more strongly in the hyaline vascular type of CD compared to the plasma cell type of CD [16, 17].

As of now, establishing the diagnosis of CD requires histopathologic examination through substantial tissue biopsies. We have mentioned the basic histological subtypes of CD included the hyaline vascular variety, plasma cell type, and mixed type. The hyaline vascular variety presents dense capillary proliferation and small lymphocyte predominant infiltrates surrounding a regressed germinal centre in an onion ring-like arrangement. In addition, the regressed germinal center may become hyalinized and contain follicular dendritic cells. The plasma cell type is characterized by massive accumulation of mature polyclonal plasma cells surrounding the hyperplastic germinal center and infiltrating in the interfollicular region [2]. Here, we confirmed this case according to the pathologic characteristics of the lymph node biopsy. The pathologic diagnosis showed angiofollicular lymph node hyperplasia accompanied with plenty of plasma cell infiltration. The results of immunohistochemical staining with Kappa and Lambda found that the plasma cells in the interfollicular region were polyclonal. Immunohistochemical staining with CD34 marked the hyperplastic small blood vessels penetrating into the lymph follicle. Otherwise, the immunohistochemical staining with CD3, CD20 and CD21 were positive which suggested that the T lymphocytes, B lymphocytes, and dendritic cells were coexisting and there were no malignancy associated changes. Since immunohistochemical staining with Cyclin-D1 was negative, it rules out mantle cell lymphoma. Based on this, the diagnosis of plasmacytic type of Castleman's disease was given.

The therapy and prognosis of CD differs between unicentric type of CD and multicentric type of CD. For unicentric type of CD, since the position is localized, complete surgical excision of the affected lymph node is feasible and affords a high cure rate [17, 18]. If complete resection of the mass is technically difficult, radiotherapy could be a valuable alternative [19]. In our report, the CD was accidently discovered during the choledochojejunostomy and there were no other symptoms except the presentation of common bile duct calculi. The enlarged lymph nodes were completely resected. We did no adjuvant treatment such as monoclonal antibodies or radiotherapy and the patient continued to do well at her 8th month postoperative visit. In regard to multicentric type of CD, the management is more complicated. Several therapeutic options, such as antiviral agents, immunomodulators, targeted CD20 or IL-6 therapy have been employed in multicentric type of CD patients [20-23] whose prognosis is less favorable. With a better understanding of the underlying pathologic mechanism of multicentric type of CD, new therapeutic approaches are under development.

Conclusion

We describe a rare case of unicentric type of CD, accidently discovered during choledochojejunostomy for common bile duct calculi. Lymph node biopsy showed it is belonged to plasma cell type. We managed it by surgical resection, and the prognosis is good after 12-month follow up. To our knowledge, this is the first report about CD accompanied by common bile duct calculi, a new contribution to the study of CD.

Disclosure of conflict of interest

None.

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