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Case Report

Case of hepatic Castleman's disease presenting as a malignancy: challenging diagnosis and literature review

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Abstract: Castleman's disease (CD) is a very rare lymphoproliferative disorder, first reported as a form of localized mediastinal lymphadenopathy. The pathogenesis of CD has not been fully elucidated, however, a defect in immune regulation has been suggested to cause excessive proliferation of lymphoplasma cells. To the best of our knowledge, 14 cases of hepatic CDs have been reported. The current study presents a rare case of localized hepatic CD with a review of the related literature. A 60-year-old asymptomatic woman underwent partial hepatectomy due to a hepatic mass incidentally found and presumed to be malignant. Grossly, the liver showed a well-defined pinkish yellow mass of 3.8 × 3.5 cm in size in segment 6/7. Microscopically, it was composed of follicular hyperplasia with extensive inter-follicular hyalinized vessels and numerous plasma cells, suggesting CD of the mixed hyaline vascular and plasma cell type. Based on this case and a review of the literature, preoperative diagnosis of CD at unusual sites is challenging and sometimes inaccurate. After undergoing surgical excision only, the patient was followed up over a nine-year period with no recurrence or progression to the more aggressive form.

Keywords: Castleman's disease, lymphadenopathy, follicular hyperplasia, hyalinized vessels, plasma cell

Introduction

Castleman's disease (CD), known as angiofollicular lymph node hyperplasia, is a rare heterogeneous group of benign lymphoproliferative disorders of unknown etiology, usually found in the mediastinum [1-3]. CD was first reported as a form of localized mediastinal lymphadenopathy by Castleman in 1954 [1]. Clinically, CD can be divided into two main groups, localized and multicentric forms, based on how much of the body it affects [2]. While localized CD is usually asymptomatic and frequently presents as solitary lymphadenopathy, the multicentric form is usually associated with systemic symptoms, such as recurrent lymphadenopathy, fever, and hepatosplenomegaly [2-5]. CD may be classified as hyaline vascular (HV), plasma cell (PC), plasmablastic, and mixed HV and PC types, according to histopathological characteristics [2, 4, 5]. CD can develop where a lymph system exists, such as the retroperitoneum and liver [2, 4-20]. Thus, preoperative diagnosis is sometimes difficult due to development at unusual sites. To the best of our knowledge, only 14 cases of hepatic CD have been reported. The current study reports a rare case of unicentric hepatic CD, mimicking hepatic malignancy, in an asymptomatic female patient with a review of related literature.

Case report

Clinical summary

A healthy female patient was referred for further evaluation of a hepatic mass incidentally found via an abdominal sonogram. At admission, this 60-year-old woman had no major health complaints or disease history except for intrapulmonary tuberculosis, diagnosed 20 years earlier. In addition, she had no significant abnormalities detected by blood tests. Tumor markers, such as CEA, CA19-9, and α-fetoprotein, were all within normal ranges and no hepatitis-associated viral markers were detected. The hepatic mass was strongly enhanced in the arterial phase. It persisted over the portal and delayed phases, except for a central area

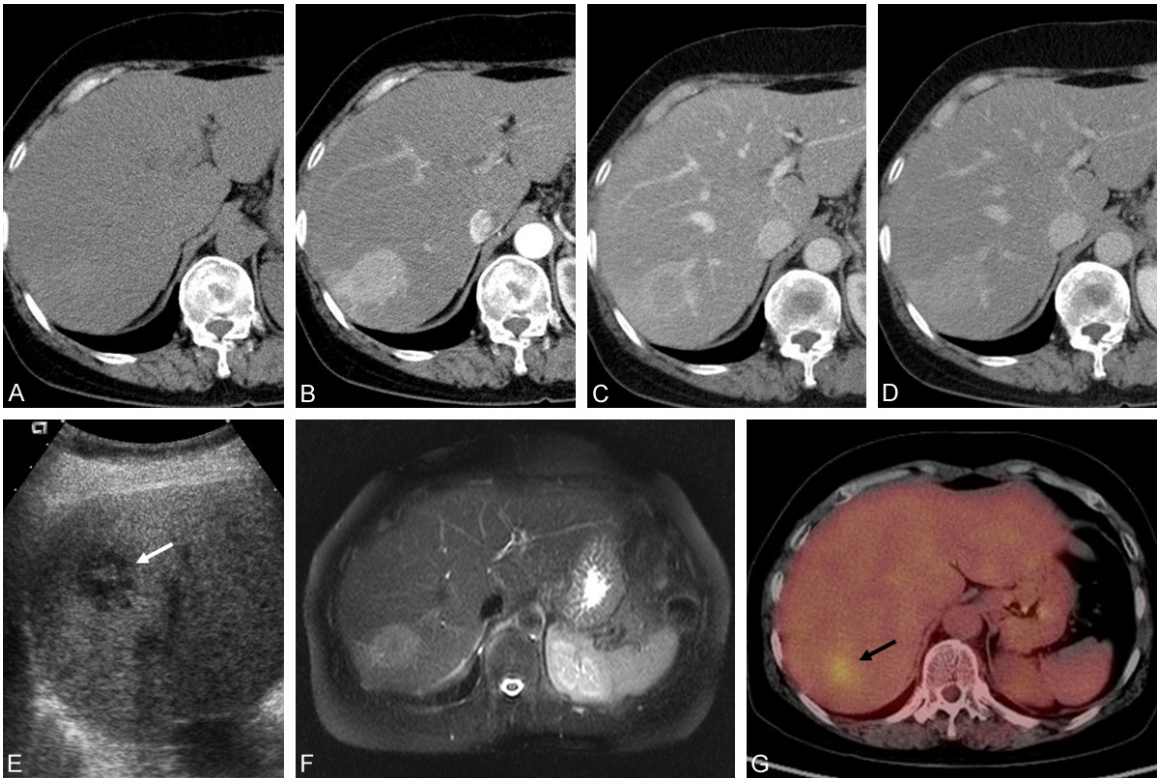

Figure 1. Radiological findings of hepatic Castleman's disease. A. A pre-contrast abdominal CT scan revealed a fatty liver without a definite tumor in the right lobe of the liver. B-D. Dynamic contrast-enhanced abdominal CT scans showed a strong homogeneously enhancing mass in the arterial phase with a persistent enhancement pattern in the portal and delayed phases, except for a central area of iso-attenuation in the portal phase. E. Abdominal ultrasonography identified a round hypoechoic mass with a central hyperechoic area in the right lobe of the steatotic liver (white arrow). F. Liver MRI revealed a high-signal intensity area with central low-signal intensity on a T2-weighted image. G. FDG-PET/CT showed a higher FDG uptake in the central area of the mass (black arrow).

of iso-attenuation according to abdominal computed tomography (CT) (**Figure 1A-D**). Abdominal ultrasonography showed a round central hyperechoic and peripheral hypoechoic mass in segment 6/7 as well as a mild fatty change (**Figure 1E**). This hepatic mass was also visible as a high signal intensity on T2-weighted images, observed through magnetic resonance imaging (MRI) (**Figure 1F**). Disseminated lymphadenopathy was not detected (**Figure 1G**).

Pathological findings

To evaluate the possibility of hepatic malignancy, needle biopsy was performed. The biopsy specimen showed heavy infiltration of mature lymphoplasma cells (**Figure 2A**) associated with a few atrophic bile ducts, which resembled lymphoepithelial lesions. The suspected diagnosis was extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma). Due to the potential presence of other hepatic malignancies, the patient underwent a partial hepatectomy. Upon gross examination, the liver showed a well-defined yellow to pinkish nodular mass with a central scar, measuring 3.8 × 3.5 cm in size (**Figure 2B**). Microscopic examination showed follicular hyperplasia with expansion of the paracortical mantle zone, accompanied by small germinal centers and an extensive interfollicular hyalinized interstitium, containing numerous hyalinized vessels with plasma cells as well as intracytoplasmic globules (**Figure 2C-E**). Neither atypical lymphoid cells nor granulomatous inflammation were identified on hematoxylin and eosin (H&E) staining. Immunohistochemical (IHC) analysis, using the primary antibodies of CD20, CD79a, CD3, CD5, CD21, CD23, CD15, CD30, Bcl-2, and IgG4, was performed to differentiate the possibilities of low-grade lymphoma or reactive lymphoid hyperplasia. The IHC staining procedure confirmed a wide distribution of mature B and T lympho-

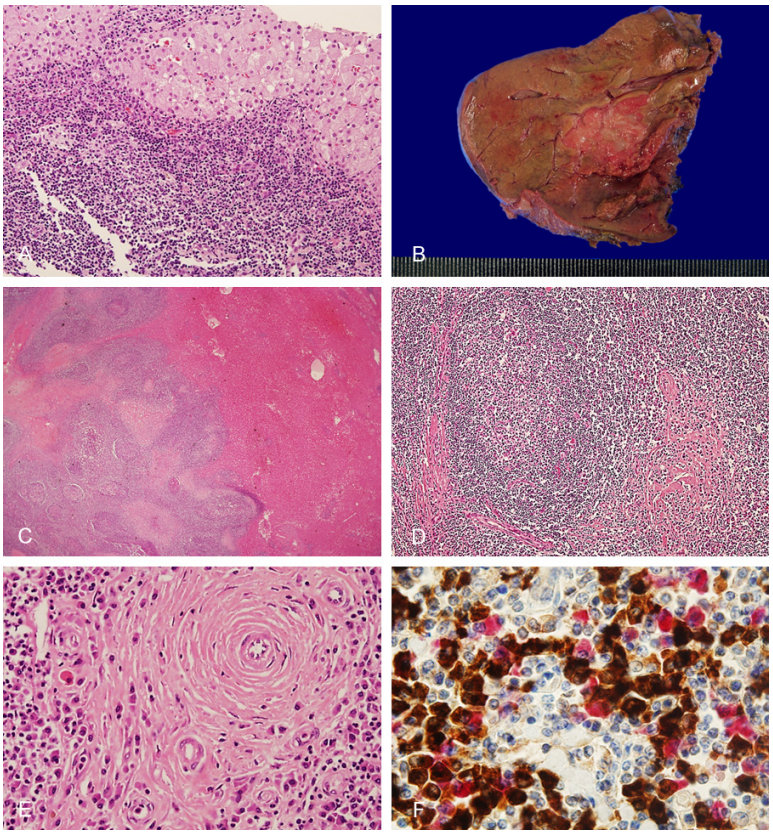

Figure 2. Histopathological findings of hepatic Castleman's disease. (A) Needle biopsy revealed a wide expansion of the portal areas with lymphoplasma cells (H&E, 200 ×). (B) The cut surface showed an ill-defined pinkish nodular mass with scar, 3.8 × 3.5 cm in size. (C-E) Microscopic examination revealed follicular hyperplasia with expansion of the paracortical mantle zone and interfollicular hyalinized interstitium as well as concentrically hyalinized vessels with infiltration of plasma cells (C: H&E, 12.5 ×; D: H&E, 100 ×; E: H&E, 200 ×). (F) Double immuno-histochemical staining showed polyclonal plasma cells with kappa (dark brown) and lambda (pink) light chains (400 ×).

cytes and follicular dendritic cells, while excluding malignant lymphoma (figures not shown). In addition, double IHC staining, using kappa and lambda light chains, identified a polyclonal population of plasma cells (**Figure 2F**). The sample was negative for human herpesvirus-8 (HHV-8), detected by nested PCR (1st primers: 5'-GAC TCT TCG CTG ATG AAC TGG-3' and 5'-AGC ACT CGC AGG GCA GTA CG-3'/2nd primers: 5'-AGC CGA AAG GAT TCC ACC AT-3' and 5'-TCC GTG TTG TCT ACG TCC AG-3') [21], and Epstein-Barr virus, detected by *in situ* hybridization (figure not shown). Based on clinicopathological features, the patient was diagnosed with solitary hepatic CD of the mixed HV and PC type. Nine years after her operation, the patient remained under follow-up care with no further treatment necessary and no signs of recurrence.

Discussion

CD can develop where lymphoid tissue is found. Hence, the preoperative diagnosis is often overlooked, especially when arising at unusual sites, such as the mesentery, axilla, pelvis, nasopharynx, retroperitoneum, and liver [4, 6-20, 22]. In the present case, histological findings of the preoperative biopsy detected heavy infiltration of lymphoplasma cells. This was the foci of follicular hyperplasia with expansion of the marginal zone in the surgical excision specimen and smudged small bile ducts around the portal areas, resembling lymphoepithelial lesions, a significant feature of MALT lymphoma. These findings eventually led to misdiagnoses of MALT lymphoma. Somdas [23] also reported a case of CD with an unusual neck mass. It was misdiagnosed as a lymphoma at the time of frozen diagnosis. Therefore, frozen or preoperative needle biopsies are not a useful tool for diagnosis of CD at unusual sites. This may be because the diagnosis of CD is not only based on histological features but also clinicopathological findings. Histologically, the HV type displays the hyperplasia of hyalinized lymphoid follicles with proliferation of vascular endothelial cells [4, 5, 18]. The PC type, more likely to cause symptoms and be multicentric, shows heavy infiltration of plasma cells into the interfollicular area. The plasmablastic type [2, 4], recognized recently as a subtype of the PC type, is usually multicentric, causing symptoms like those of the PC type. The mixed HV and PC type, as presented in the current case, shows histological features of both HV and PC types [2, 4]. CD can present clinically as a localized or, less often, a multicentric form. Localized CD has a benign and indolent course [7, 9, 12]. However, multicentric CD, generally associated with the PC type, can be associated with sys-

Table 1. Review of cases of hepatic Castleman's disease

Author (published year)	Age/ Sex	Clinical presentation	Size (cm)	Site	Locality	Treatment	Histologic Type
Rahmouni et al. (1992) [10]	48/F	No	5.0	Porta hepatis	Unicentric	Operation	HV
Peck et al. (1996) [11]	29/F	Abdominal pain	7.0	Porta hepatis	Unicentric	Operation	HV
Cirillo et al. (1998) [12]	43/F	No	7.9	Left lobe	Unicentric	Operation	Mixed HV-PC
Uzunlar et al. (2001) [13]	56/F	Chest pain	3.5	Porta hepatis	Unicentric	Operation	HV
Sato et al. (2006) [14]	26/F	No	4.5	Hepatoduodenal ligament	Unicentric	Operation	HV
Karami et al. (2010) [15]	5/F	Abdominal pain	3.7	Hepatic hilum	Unicentric	Operation	HV
Geramizadeh et al. (2012) [16]	41/F	No	3.0	Porta hepatis	Multicentric	Steroid	HV
Jang et al. (2012) [17]	40/F	Abdominal pain	3.0	Caudate lobe	Unicentric	Operation	HV
Miyoshi et al. (2013) [18]	70/F	No	1.5	Segment 6	Unicentric	Operation	HV
Dong et al. (2014) [19]	57/F	No	3.3	Caudate lobe	Unicentric	Operation	HV
Ueki et al. (2017) [20]	26/F	Anemia	10.0	Right lobe	Multicentric	Steroid	PC
Maundura et al. (2017) [4]	64/F	No	1.4	Segment 4a	Unicentric	Operation	HV
Present case	60/F	No	3.8	Segment 6/7	Unicentric	Operation	Mixed HV-PC

HV, hyaline vascular; PC, plasma cell.

temic inflammatory symptoms, such as hepatosplenomegaly, malaise, fever, night sweats, and weight loss [8, 12, 24]. In the literature to date, 14 cases of hepatic CD have been reported [4, 8-20]. However, only 12 cases could be fully reviewed in the present study (**Table 1**). Based on reviews of these reports, mean tumor size was 4.4 cm in maximum diameter and predominant features were female, localized form, and HV type. Radiological images, in all but one of these cases, showed hepatic neoplasm or malignancy.

The pathogenesis of CD has not been completely clarified. However, a defect in immune regulation initiated by viral infections has been assumed, resulting in excessive proliferation of B lymphocytes and plasma cells [4, 24, 25]. Several studies have suggested that HHV-8 plays an important role in the pathogenesis of multicentric CD and Kaposi's sarcoma, regardless of whether the patient is infected with HIV [2, 21, 24]. HHV-8 could lead to hypersecretion of immune mediators, particularly IL-6, resulting in the induction of hyperplasia of the lymphoid follicles and proliferation of endothelial cells [2, 18]. However, in the present case, nested PCR for HHV-8 failed to detect HHV-8-encoded RNA.

Histopathological findings of heavy infiltration of plasma cells have been found to overlap with those of IgG4-related disease (IGG4-RD), demonstrating a pathological link between these diseases [26-28]. For these reasons, clinicians should routinely examine serum IgG4 levels in patients with CD. In the present case, heavy infiltration of plasma cells surrounded the follicles. However, neither expression of IgG4 (+) plasma cells on the IHC stain nor high serum levels of IgG4 were detected. Therefore, IgG4-RD was ruled out as a final diagnosis or the underlying disease.

Radiographically, CD is usually indistinguishable from other mediastinal masses, including both neoplasia and inflammation [2, 10, 12]. Based on radiological findings, the patient was suspected of having malignant hypervascular hepatic tumors, including hepatocellular carcinoma, cholangiocarcinoma, and metastatic tumors, as well as benign hypervascular tumors, such as hemangioma, adenoma, and focal nodular hyperplasia. The hepatic mass showed enhanced accumulation with a standardized uptake value (SUV) of 3.24 on FDG-PET/CT. Miyoshi et al. [18] reported that the mean SUV of CD could range from 3.2 to 8.9 (mean 4.9) and this value was close to that of low-grade lymphoma.

Treatment of CD differs between localized and multicentric forms. In cases of the HV type with a single lesion, radical treatment with surgical resection, alone, is likely to be successful with a good prognosis [17, 29], as shown in the present case. Recurrences have rarely been reported. They are mainly reported in cases when the excision was incomplete [12, 21]. No curative therapy exists for the multicentric form. Although steroid therapy and radiotherapy have been attempted [2, 30], the degree of efficien-

cy remains controversial. Recent studies to elucidate the biological basis of the disease, particularly the crucial role of HHV-8 and IL-6, have led to development of potential targeted therapies agents, such as cytotoxic chemotherapy compounds, immunoregulators, and antiviral agents [3, 24].

In conclusion, CD can arise anywhere a lymph system exists. Preoperative diagnosis of CD at unusual sites is very difficult and may be inaccurate when the biopsy is obtained from limited specimens, such as frozen or small tissues. In the present case, surgical resection was useful for both diagnosis and treatment since malignancy was not excluded by radiological findings. This study involved a long-term follow-up case of unicentric hepatic CD of the mixed HV and PC type. After surgical excision, the patient was monitored for nine years, suffering no recurrence or progression to the more aggressive form.

Disclosure of conflict of interest

None.

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