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Case Report

Concurrent hepatocellular adenoma and Castleman disease in mesocolonic fat

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Castleman disease is a rare lymphoproliferative disorder of unknown etiology. It can be present in localized type or multicentric type. We reported a case with hyaline vascular type of Castleman disease found in mesocolon with presence of unusual dysplastic dendritic cells and spindle cells and synchronous hepatocelluar adenoma in liver. We reviewed the literature about the etiology and how to survey about the biological nature of dysplastic dendritic cells and spindle cells and association about Castleman disease and hepatocellular adenoma and gave our suggestions for treatment and differential diagnosis and subsequent clinical survey.

Keywords: Castleman disease, follicular dendritic sarcoma, hepatocellular adenoma.

1. Introduction

We present a patient with concurrent hepatocellular adenoma and Castleman disease in mesocolon. Dysplastic follicular dendritic cells and marked stromal spindle cell proliferation are found in pathological finding. We review the literature about the significance of dysplastic follicular dendritic cells and stromal cell proliferation and the association with follicular dendritic sarcoma. At the same time, we found it is very rare about the concurrency of hepatocellular adenoma and Castleman disease. We found may be interleukin-6 singnal pathway would be a link about the two disease. In addition, we also suggest a key point for differential diagnosis for pathologist and treatment and follow-up plan for clinicians

2. Case report

A 53-year-old male was admitted to the hospital due to recurrent episodes of abdominal pain and persistent diarrhea spanning a duration of 7 years. The patient's medical history revealed that seven years prior to his current presentation, an abdominal computed tomography (CT) scan had identified a liver tumor measuring 2.4 cm, accompanied by an intra-abdominal tumor. Subsequent regular monitoring of the patient revealed a gradual enlargement of the liver tumor, which increased in size to 3.7 cm at its largest dimension. Remarkably, despite these developments, results from laboratory tests including blood analysis (Hb: 14.1; platelet: 296000/ul; WBC count: 6340/ul; RBC count: 476x104/ul) and assessments of liver function (AST: 18 IU/L; ALT: 22 IU/L; ALP: 89 IU/L; total bilirubin: 0.6 mg/dl) consistently remained within the normal range. The tumor marker for hepatocellular carcinoma (alpha fetoprotein: 3.1 ng/ml) was also within normal limits. A preoperative MRI survey revealed a hypervascular liver tumor during the arterial phase, suggestive of focal nodular hyperplasia. Although the preoperative clinical suspicion of hepatocellular carcinoma combined with intra-abdominal seeding couldn't be definitively ruled out, surgical exploration was undertaken.

Following hepatic segmentectomy and right hemicolectomy, a mesocolonic mass measuring

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approximately 6.0 x 5.5 x 4.0 cm was identified within the ascending colon, alongside a liver tumor in segment 6 measuring 3.5 x 3.0 x 1.5 cm. Microscopically, sections from the mesocolonic mass revealed focal spindle cell hyperplasia, stromal hyalinization, dendritic cell hyperplasia and dysplasia (depicted in Figures 1b, 1d, and 2a). Additional observations included focal atrophy of the atrophic germinal center and hyalinization of the vascular wall (as shown in Figure 1c), myofibroblasitc proliferation and rich lymphoplasmacytic cells infiltrate. The potential pathological diagnosis considered for the colonic mass encompass IgG4-related lymphadenopathy, mycobacterial lymphadenopathy, inflammatory myofibroblastic tumor, and Castleman disease of hyaline type with focal malignant changes or Caslteman disease of plasma cell type. Within the liver sections, a characteristic pathological pattern consistent with hepatocellular adenoma was observed, featuring regenerated hepatocytes without a portal tract. This included a dilated central vein, sinusoidal dilatation, and numerous blood-filled cystic spaces (as illustrated in Figure 1a). The hepatocytes exhibited no significant cytological atypia and were organized in thin or mildly thickened cell plates, ranging from 1 to 2 cells in thickness.

Immunohistochemical staining of the liver displayed a patch pattern of glutamine synthase, with hepatocytes testing negative for glypican-3, CD34, and beta-catenin, confirming the diagnosis of hepatocellular adenoma. Within the atypical follicular dendritic cells of the mesocolonic mass, immunohistochemical staining revealed positivity for CD21 (as depicted in Figures 1d, 2a, and 2c), CD23, and D2-40, while p53 was negative. Similarly, immunohistochemical staining of the stromal spindle cells demonstrated positivity for smooth muscle actin (illustrated in Figures 1d and 2d), fascin, and D2-40. In-depth testing, including Epstein–Barr virus encoding region (EBER) in situ hybridization, acid-fast staining, human herpesvirus-8 (HHV8), IgG4, CD30, and ALK, yielded negative results for both the atypical follicular dendritic cells and stromal myofibroblastic cells. Moreover, immunohistochemical staining of kappa and lambda light chains of plasmacytic cells indicated the absence of light-chain restriction and rule out the possibility of plasma myeloma. Subsequently, the presence of mycobacterial infection,

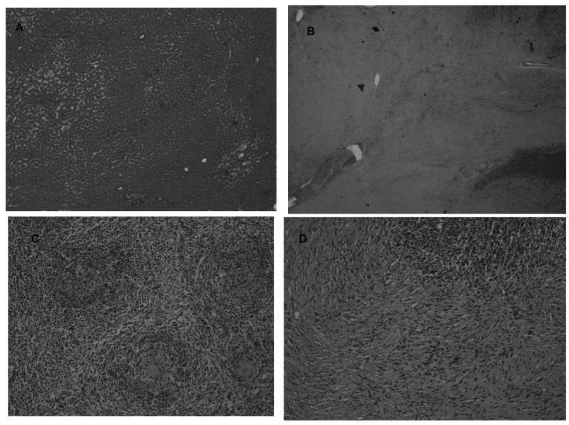


Figure 1. a: hepatocellular adenoma without interlobular bile duct and thin or only mildly thickened cell plates, 1 - 2 cells thick. (40X, H&E stain).
b. Castleman disease characterized with atrophic germinal center and marked stromal spindle cell proliferation (40X, H&E stain).
c. Atretic germinal centers traversed by sclerotic penetrating vessels and hyalinization (200X, H&E stain).
d. Marked stromal spindle cell proliferation (200X, H&E stain).

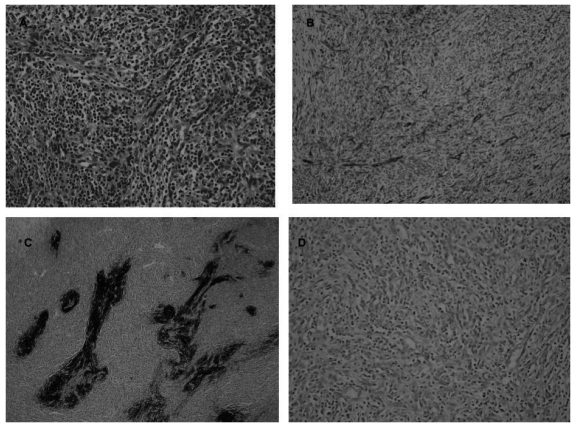


Figure 2. a: dysplastic follicular dendritic cells adminxed with stromal spindle cell proliferation (400X, H&E stain).
b. Immunohistochemical stain of CD31 reveals increased vascularity.
c. Immunohistochemical stain of CD21 highlights follicular dendritic cells.
d. Immunohistochemical stain of smooth muscle actin highlights stromal spindle cells.

human herpesvirus-8 (HHV8), and Epstein–Barr virus infection has been definitively excluded. The potential diagnoses of IgG4-related lymphadenopathy, inflammatory myofibroblastic tumor, and plasma cell myeloma have also been definitively ruled out.

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Additionally, the absence of p53 staining has led to the exclusion of malignant transformation in the follicular dendritic cells.

3. Discussion

Castleman disease is a rare lymphoproliferative disorder of unknown etiology, including unicentric Castleman disease and multicenetric Castleman disease. Pathologically, it is divided into three types, hyaline- vascular type, plasma cell type and mixed type. Generally, patients with unicentric type always present mass-associated symptoms or are asymptomatic and have no radiological characteristic features. Laboratory data of unicentric Castleman disease is usually unremarkable(1). The most common sites are the abdominal cavity and the mediastinum (2). Surgical resection stands as the primary therapeutic option. Histologically, the hyaline vascular type is the most common, accounting for 65% of all cases. Pathologically, it manifests as large follicles featuring small regressed germinal centers enveloped by an expanded mantle zone, hyaline vascular lesions, vascular proliferation, and hyperplasia of follicular dendritic cells. In our case, the presence of dendritic cell dysplasia and pronounced stromal spindle cell hyperplasia raised significant concerns. It is worth noting that follicular dendritic sarcoma can potentially stem from hyaline vascular castleman Disease(3). Notably, the appearance of dysplastic dendritic cells in the hyaline vascular castleman disease may suggest a progression towards follicular dendritic sarcoma. This linkage is supported by Nagy et al.'s discovery of shared somatic mutations in chromatin modifiers between the hyaline vascular Castleman disease and follicular dendritic cell sarcoma(4).

Singh et al. have proposed an insightful diagnostic tool involving p53 expression in stromal spindle cells to differentiate between reactive and neoplastic spindle cells (5). Furthermore, their research has revealed that progenitor cells of follicular dendritic cells possess the capacity to give rise to other mesenchymal and stromal cell populations, such as reticular and myoid cells. These cell populations exhibit certain morphological, immunophenotypic, and biological similarities with follicular dendritic cells (5). Recognizing the importance of predicting the biological behavior of dendritic cells and hyperplastic stromal cells in assessing the risk of subsequent development of follicular dendritic cell sarcoma, we conducted immunohistochemical staining for p53. Fortunately, our findings indicated a negative expression of p53.

Furthermore, it is essential to acknowledge that Epstein–Barr virus infection, human immunodeficiency virus (HIV) infection, mycobacterial infection, and IgG4-related disease can present pathologically with Castleman-like features. Consequently, establishing a precise differential diagnosis plays a pivotal role in guiding postoperative decisions.

Initially, we recommended that clinicians conduct a serum study to assess for human immunodeficiency virus (HIV) infection. Subsequently, we performed EBER in situ hybridization to exclude Epstein-Barr virus infection, acid-fast staining to eliminate the possibility of mycobacterial infection, and an immunohistochemical stain for IgG4 to rule out IgG4-related lymphadenopathy. A negative immunohistochemical result for herpesvirus-8 effectively ruled out Castleman disease of the plasma cell type.

Given the negative results from EBER in situ hybridization, acid-fast staining, IgG4 immunohistochemistry, and p53 immunohistochemical staining, we considered the likelihood of malignant transformation of dysplastic dendritic cells to be low, with mycobacterial lymphadenopathy also being definitively ruled out. We have proposed a comprehensive flowchart for predicting the malignant potential of hyaline vascular Castleman disease (Figure 3). Moreover, when considering a preoperative biopsy, the pathological differential diagnosis should encompass low-grade lymphomas, such as follicular lymphoma, marginal zone lymphoma, and mantle cell lymphoma, especially when dealing with lymphocyte-rich specimens. Conversely, in cases with a substantial vascular component, it is crucial to eliminate the possibilities of hemangioepithelioma and Kaposi sarcoma. Furthermore, when dealing with specimens rich in stromal cells, a thorough assessment of the nature of spindle cells is imperative. Potential differentials to rule out include myofibroblastoma, fibrosarcoma, and spindle cell neoplasms with lymphoid involvement (6). In cases where specimens

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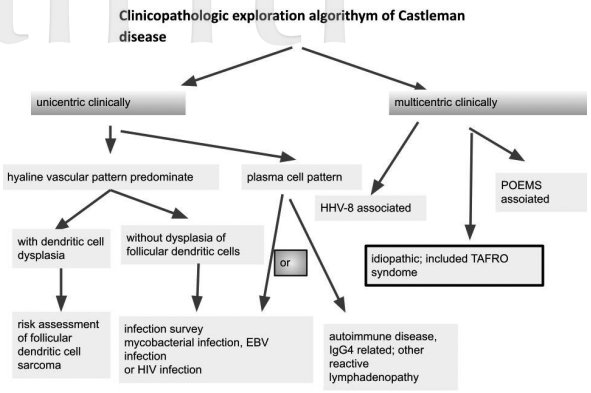


Figure 3. Clinicopathologic exploration algorithm of Castleman disease. POEMS: Polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes; HHV-8: human herpesvirus-8; TAFRO: thrombocytopenia, anasarca, fever, reticulin fibrosis, and organomegaly; HIV: human immunodeficiency virus. EBV: Epstein–Barr virus. HHV8: Human herpesvirus 8

are abundant in lymphocytes, plasma cells, and stromal cells, it is essential to consider autoimmune and infectious lymphadenopathy, which encompasses conditions like mycobacterial infection and HIV-associated lymphadenopathy.

In summary, we believe that in order to diagnose Castleman disease through preoperative biopsy specimen, it is essential to first rule out the aforementioned diseases and conduct various blood tests to exclude tumors and infections, ensuring an accurate diagnosis. For cases of unresectable unicentric Castleman disease, once tissue confirmation has been obtained, considering preoperative neoadjuvant radiotherapy, immunotherapy, anti-angiogenesis treatment, or embolization therapy can be favorable for reducing tumor size(7).

In our particular case, the patient presented with both hepatocellular adenoma and Castleman disease. To the best of our knowledge, this is only the second documented instance in the literature. De Vito et al. previously reported a case involving synchronous hepatocellular adenoma and Castleman disease of the unicentric plasma cell type, which was associated with AA amyloid deposition in the liver (8). Additionally, Jang et al. reported a case where hepatocellular carcinoma developed subsequent to hepatocellular adenoma and Castleman disease (9). Both of these cases prompted speculation about the interleukin-6 signaling pathway potentially explaining the concurrent occurrence. This hypothesis arises from the observation that multicentric Castleman disease or large unicentric Castleman disease can benefit from interleukin-6 antibody treatment(7). Notably, interleukin-6 also plays a pivotal role in liver regeneration and liver carcinogenesis (10). Therefore, we deemed it necessary to investigate this relationship further.

In conclusion, unicentric Castleman disease typically exhibits a biologically benign nature; however, it is imperative to assess the risk of potential progression to FDC carcinoma. This assessment should focus on key indicators, such as clonal proliferation of spindle cells or dysplastic dendritic cells. Furthermore, conducting comprehensive infection surveys, both pathologically and clinically, is essential to differentiate Castleman-like patterns from mycobacterial and viral infections that can manifest similarly. In the context of biopsy specimens displaying Castleman-like features, consideration should also be given to infectious lymphadenopathy, as it can mimic low-grade lymphoma, autoimmune diseases, IgG4-related diseases, and plasma cell neoplasms. Lastly, the relationship between hepatocellular neoplasms and Castleman disease remains an enigma, necessitating further research and exploration to gain a deeper understanding.

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