J Med Sci 2023;43 (6):292-295
DOI: 10.4103/jmedsci.jmedsci_249_22

CASE REPORT

Finding a Needle in the Haystack: A Hidden Follicular Lymphoma

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The classical morphological features of follicular lymphoma (FL) are well-recognized. However, identifying some morphological variants, such as FL with hyaline-vascular Castleman disease (HVCD) like features (FL-HVCD), is challenging. Hence, we report a 57-year-old male with FL-HVCD who presented with nontender swelling of the bilateral lower limbs, caused by enlarged intra-abdominal lymph nodes with venous compression. The excised lymph nodes showed onionskin-like mantle zones and hyalinized blood vessels, which was consisted with HVCD. Oral medications were prescribed; however, the patient was lost to follow-up after 6 months and was readmitted with anemia, thrombocytopenia, and leukocytosis 3 years later. A bone marrow biopsy was done, and the patient was diagnosed as having overt FL with bone marrow involvement. Physicians should be careful if HCVD patients present with systemic symptoms or generalized lymphadenopathy. Excluding the possibility of lymphoma is necessary because the different treatment strategy and prognosis from HVCD.

Key words: Follicular lymphoma, hyaline-vascular Castleman disease, unicentric Castleman disease

INTRODUCTION

Although follicular lymphoma (FL) with hyaline-vascular Castleman disease (HVCD) like features (FL-HVCD) was first described in 1994,[1] this rare morphologic variant of lymphoma has been reported in fewer than 20 patients since then.[2-7] FL-HVCD is one of the most underrecognized variants of FL due to its rare occurrence. Hence, we report the case of a patient who was initially diagnosed with HVCD by lymph node biopsy but was confirmed to have overt FL with bone marrow involvement through a bone marrow biopsy 3 years later.

CASE REPORT

A 57-year-old man with a medical history of hypertension and type 2 diabetes mellitus presented with nontender swelling of the bilateral lower limbs for 3 months. On admission, physical examination revealed Grade III pitting edema of the bilateral lower limbs and palpable, movable, and nontender masses in the bilateral inguinal regions. Laboratory studies did not reveal any abnormalities, including abnormal blood cell profiles, liver function, renal function, and lactate dehydrogenase levels. Contrast-enhanced computed tomography of the lower limbs demonstrated subcutaneous lymphedema with no evidence of deep-vein thrombosis. However, enlarged confluent lymph nodes in the retroperitoneal and pelvic regions with vessel compression were identified [Figure 1a]. Histology of the excisional biopsy of inguinal lymph nodes showed variable-sized lymphoid follicles with interfollicular increased vascularity and some penetrating blood vessels into follicles [Figure 2a]. The areas of the germinal center were immunoreactive for Bcl-6, CD20, and CD10 [Figure 2b], but negative for Bcl-2 [Figure 2c]. Based on these characteristics, the patient was diagnosed with Castleman disease (CD). Oral chlorambucil was then administered. Following discharge, the patient's clinical symptoms gradually improved after 3 months of treatment. However, 6 months after treatment, the patient was lost to follow-up.

Received: November 12, 2022; Accepted: December 10, 2022; Published: February 03, 2023
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How to cite this article: Lin HY, Peng YJ, Wu YY, Chang PY. Finding a needle in the haystack: A hidden follicular lymphoma. J Med Sci 2023;43:292-5.

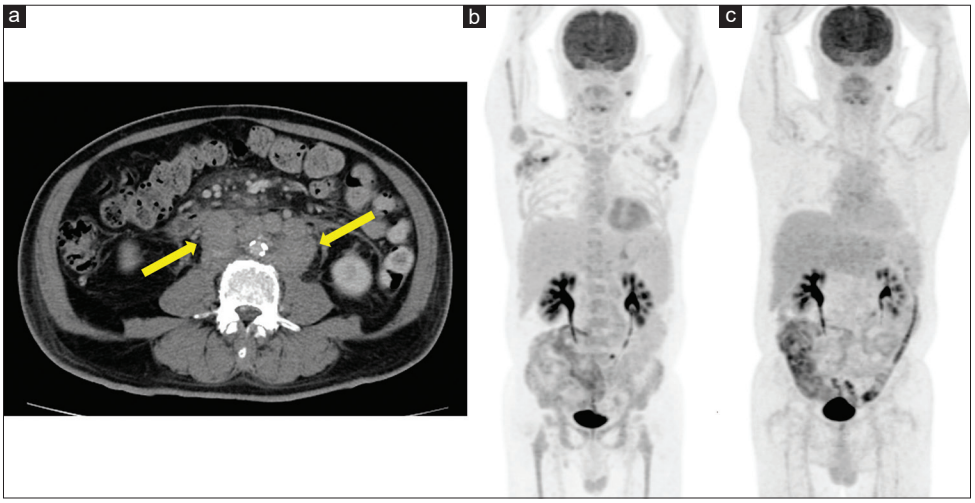

Figure 1: Image work-up of the patient. (a) Contrast-enhanced computed tomography of the abdomen showed retroperitoneal lymphadenopathies (yellow arrow). (b) PET scan showed multiple FDG-avid lesions over neck, axillary, intra-abdominal lymphadenopathies and entire skeleton (c) PET scan showed a good metabolic remission after the completion of R-COP treatment. PET: Positron emission tomography, R-COP: Rituximab, vincristine, cyclophosphamide, and prednisolone

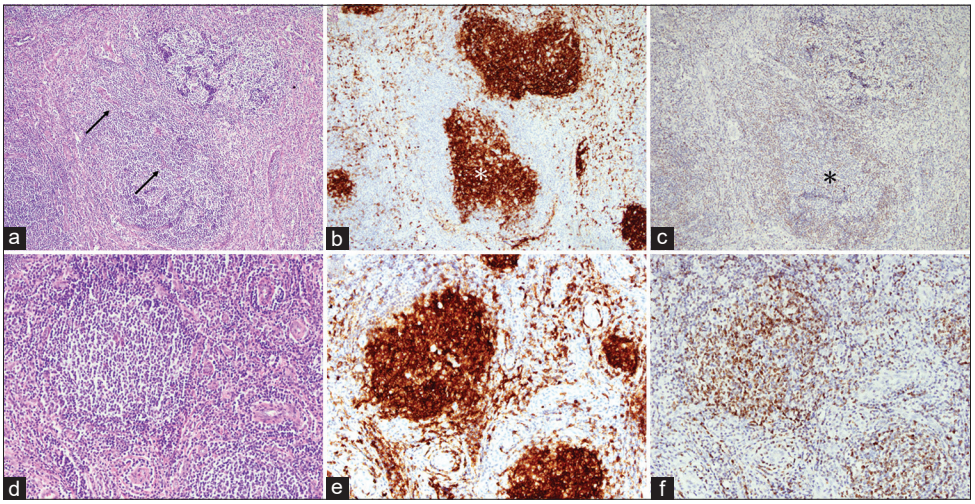

Figure 2: Histopathological and immunohistochemical findings for inguinal lymph nodes on the first admission and readmission after 3 years. (a-c) Castleman disease on first admission. The enlarged lymphoid follicles had penetrative blood vessels (arrows) (a, H and E, ×100). The areas of germinal center (✲) are immunoreactive for CD10 (b, ×100), but not for Bcl-2 (c, ×100). (d-f) Follicular lymphoma after 3 years. The homogenous nodules lacking tangible-body macrophages and mantle zones (d, H and E, ×100). Vast majority of cells in the nodules are positive for CD10 (e, ×200) and Bcl-2 (f, ×200)

Three years later, the patient was admitted to the emergency department after experiencing dizziness and bruising of his extremities for 2 days. Physical examination showed pale conjunctiva and multiple ecchymoses along the extremities. The laboratory studies showed a white blood cell count of 55,260/μl (normal, 4500-11,000/μl; neutrophil = 5.1%, lymphocyte = 84.7%), hemoglobin 6.1 g/dl (normal, 12-16 g/dl), platelet count 5000/μl (normal, 150-400 × 103/μl), and a leukoerythroblastic picture. Normal liver, renal, and coagulation function was observed. Contrast-enhanced CT of the abdomen revealed multiple lymphadenopathies in the para-aortic region, mesentery, retroperitoneal space, and bilateral inguinal region. An excisional biopsy of the inguinal lymph nodes was performed again. Bone marrow examination showed hypercellularity with a marked increase in atypical B-cell lymphocytes characterized by small- to medium-sized nuclei with irregular nuclear borders. Immunohistochemistry revealed positivity for CD 10, CD20, and negativity for Bcl-6. Flow cytometry of the bone marrow revealed positivity for CD5, CD10, CD19, CD20, CD22, and FMC-7, and negativity for CD23 and CD25. 18 F-positron emission tomography scan showed multiple fluorodeoxyglucose-avid lesions in the neck, axillary, and intra-abdominal lymph nodes and throughout the entire skeleton [Figure 1b]. FL, Ann-Arbor

stage IVA with bone marrow involvement was diagnosed. After reviewing this case in a multidisciplinary team meeting, focal areas with homogeneous nodules lacking tangible-body macrophages and mantle zones were identified [Figure 2d]. The vast majority of the cells in the nodules were positive for CD10 and Bcl-2 [Figure 2e and f]. Therefore, FL with hyaline vascular CD features was diagnosed. Leukocytosis, severe anemia, and thrombocytopenia improved after one cycle of chemotherapy with an rituximab, vincristine, cyclophosphamide, and prednisolone regimen (R-COP). The patient achieved good metabolic remission after six cycles of R-COP treatment [Figure 1c] and remained under tri-monthly rituximab maintenance for 2 years.

DISCUSSION

CD is a benign lymphoproliferative disease characterized by follicular hyperplasia with germinal center involution and marked follicular and interfollicular capillary proliferation. Three histopathological subtypes of CD have been identified: hyaline vascular (HV), plasma cell (PC), and mixed subtypes.[8] HVCD, which comprises 80%90% of CD cases, is characterized by increased follicular hyperplasia with atrophic germinal centers, penetrating hyalinized blood vessels (lollipop-like follicles), surrounding concentric layers of mantle zone lymphocytes (sometimes described as the onionskin mantle zone), and interfollicular vascular proliferation. In contrast, PC CD (10%-20% of CD cases) features hyperplastic follicles and a marked proliferation of interfollicular area PCs.[2] CD can be divided into unicentric CD (UCD) involving a single enlarged lymph node, often with HV histopathology, and multicentric CD (MCD) involving multiple lymph nodes, often with PC histopathology.[9] CD is currently categorized into several disorders that share a spectrum of characteristic histopathological features but have different etiologies, presentations, treatments, and outcomes.[9]

Few cases of FL-HVCD have been reported in the literature. Pina-Oviedo *et al*.[5] comprehensively reviewed the clinicopathologic features of 11 cases with FL-HVCD. The median age of the patients was 68 years, and multifocal lymphadenopathy was the most common presentation. These cases showed typical FL with centrocytes and centroblasts that were positive for CD10 or Bcl-6 and all were positive for Bcl-2. Furthermore, all these cases had some characteristic features of HVCD, such as lollipop-like follicles, onionskin-like mantle zone, and interfollicular increased vascularity. Our case had multifocal lymphadenopathy as the initial presentation and HVCD-like features on histopathological examination, which was similar to previous case reports. FL was diagnosed after disease progression with bone marrow involvement. Dominant HVCD-like histopathology may mask underlying lymphoma, leading to misdiagnosis.

On the other hand, many cases in the study by Pina-Oviedo *et al*.[5] presented with multifocal or systemic lymphadenopathy, which is uncommon in HVCD. HV histopathology usually has been discovered in UCD and manifests as an asymptomatic localized lymphadenopathy. CD may coexist with or develop subsequent lymphoma, including non-Hodgkin or Hodgkin types.[10] This occurs most often with MCD/PC but is rare with HV histopathology. Therefore, caution should be exercised in patients with HVCD who present with systemic symptoms and generalized lymphadenopathy. Additional studies should exclude the possibility of occult lymphoid neoplasms. Distinguishing FL variants with HVCD features from HVCD is essential because the treatment and prognosis are different. The under-recognition of FL-HCVD may delay FL therapy.

CONCLUSION

In conclusion, we report a case of FL-HVCD. Physicians should consider the possibility of occult lymphoma before confirming the diagnosis of HVCD and initiating treatment strategies, especially if the clinical presentation is uncommon for the histopathologic features.

Declaration of patient consent

The authors certify that they have obtained appropriate patient consent forms. In the form the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that his name and initials will not be published and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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