Multicentric Plasma-Cell Type Castleman Disease Masquerading As Hodgkin Lymphoma: A Case Report

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Abstract

Castleman disease (CD), or angiofollicular hyperplasia, or giant lymph node hyperplasia, is a heterogeneous benign lymphoproliferative disorder of unknown etiology. It has three distinct histologic subtypes (hyaline vascular, plasma cell, and mixed hyaline vascular plasma cell types) as well as unicentric Castleman disease (UCD) and multicentric Castleman disease (MCD) variants. In the unicentric form, the disease is confined to one anatomical lymph node and usually with no systemic symptoms. However, in the multicentric form (further subdivided into idiopathic MCD, human herpes virus-8-associated MCD, and POEMS-associated MCD), lymphadenopathy is more generalized with more aggressive systemic symptoms mimicking a malignant lymphoma. Therefore, this case report aims to underscore the importance of immunohistochemical evaluation as an indispensable ancillary technique to routine histopathological examination of a lymph node biopsy specimen, as a gold standard for definitive diagnosis of proliferative lymph node lesions.

Keywords
- Castleman disease
- immunohistochemistry
- lymphoproliferative disorders

Introduction

Castleman disease (CD), or angiofollicular hyperplasia or giant lymph node hyperplasia, is a rare non-neoplastic lymphoproliferative disorder with variable clinicopathologic subtypes.[1,2] It was first described by Castleman et al in 1954 in a group of patients with localized lymph node hyperplasia.[2,3] The etiology of CD remains largely unknown; the pathogenesis show inflammatory response to a mysterious antigenic stimulus with chemical mediators (cytokines) of inflammation particularly interleukin-6 (IL6) playing a prominent role.[1,2] CD can be categorized histomorphologically into three distinct subtypes, namely: hyaline vascular, plasma cell, and mixed hyaline vascular plasma cell types.[1,2,4-8] CD also has two clinicopathological presentations, namely: unicentric Castleman disease (UCD) and multicentric Castleman disease (MCD) forms, wherein the unicentric forms are more common.[1,2,5,6,8] The UCD form presents as a solitary (unifocal) lymph node lesion especially in the mediastinum and less commonly in extrathoracic sites and may not be accompanied by systemic symptoms such as fever, night sweats, fatigue, weight loss, splenomegaly, anemia, and hypergammaglobulinaemia.[1,2,5,6,8] The MCD form, on the other hand, presents as a multifocal lymph node lesion with generalized lymphadenopathy, especially in the neck region, associated with more aggressive systemic symptoms such as fever, night sweats, fatigue, cachexia, splenomegaly, cytopenia, and hypoglobulinemia/hyperglobulinemia, hence resembling a malignant (Hodgkin's) lymphoma.[1,2,5,6,8] Furthermore, this MCD form can be subcategorized into three subtypes, namely: human herpes virus-8 associated MCD (HHV8-MCD), polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, skin changes-associated MCD (POEMS-MCD), and idiopathic MCD (iMCD).[2,6,8,9] Additionally, iMCD is further subdivided into two types, namely: iMCD associated with thrombocytopenia, anasarca, fever, reticulin

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myelofibrosis and renal dysfunction and organomegaly (iMCD-TAFRO) and iMCD not associated with TAFRO hence not otherwise specified (iMCD-NOS).[2,8] It is also noted that nonidiopathic MCDs occur in the background of human immunodeficiency virus (HIV) infection especially in association with Kaposi sarcoma herpesvirus (KSHV) or HHV8 as well as in association with secondary amyloidosis.[1,2,6,8,10]

Histomorphologically CD is distinct from malignant lymphoma; however, these two lesions can coexist or even, indeed, mimic each other like in this case report.[1,6,11-18] In such scenarios, immunohistochemical (IHC) evaluation of the lymph node specimen in addition to routine H&E histopathological evaluation becomes the gold standard in arriving at a definitive diagnosis.[1,5,11,13-15,19]

This case is reported because of its rarity and thus should be considered in the differential diagnosis of generalized lymphadenopathy, and also to show how important IHC is in resolving diagnostic dilemmas in lymph node pathology.

Case Report

The patient is a 68-year-old woman who presented with a 1-year history of abdominal swelling and pain. These symptoms were of gradual onset and progressive over time. There was history of constitutional symptoms including low grade fever, night sweat, and weight loss. There was also a history of easy fatigue and mild unproductive cough. Clinical examination revealed moderate to severe pallor, bilateral axillary lymphadenopathy. Abdomen was mildly distended and tender with splenomegaly of approximately 14 cm and liver was tipped. Other systems examined were unremarkable.

Routine laboratory investigations such as full blood count showed normocytic normochromic anemia with hemoglobin level of 7.0 g/dL; renal and liver function test and other biochemical tests were normal. HIV serology was nonreactive.

Abdominal ultrasound scan showed massive splenomegaly. Computerized tomography of the abdomen revealed minimally enhancing solid presacral soft tissue mass with solitary metastasis to the spleen and lumber vertebrae suggestive of lymphoma. Bone marrow aspiration showed feature of nutritional anemia and small lymphoid follicular aggregates. Excision biopsy of both axillary lymph nodes was performed and subjected to routine histopathological and IHC evaluations.

Routine histopathological evaluation revealed complete effacement of normal lymph node architecture by polymorphous population of cells comprising mainly lymphocytes, plasma cells, and macrophages which were intimately admixed with cells having vague "Hodgkin-Reed-Sternberg" lacuna cell appearance. The background of this lesion was largely collagenized to sclerotic as well as edematous in few areas. These morphologic features were suggestive of Hodgkin Lymphoma (►**Fig. 1A**,**B**).

Subsequent IHC evaluation showed: negative expression of CD15, CD30, EBER, and PAX5 (effectively ruling out Hodgkin-Reed-Sternberg cells); positive expression of CD5 and CD3 (showing the T-cell rich areas in the paracortical/interfollicular zones), CD23 (showing follicular dendritic cells of the germinal centers), leucocyte common antigen (showing the polymorphous [T and B cells] nature of this lesion), CD20 (showing the B cell rich areas in the follicular zones of the cortex), CD138 (showing presence of plasma cells), Kappa+Lambda (showing polyclonal immunoglobulin expression); Ki67 expression was variable (showing the variably low mitotic index); negative expression of BCL2 (ruling out follicular lymphoma). Based on these patterns of IHC expression a diagnosis of CD, plasma cell type was made (►**Fig. 2**).

Based on the above diagnosis, anemia was corrected with three unit of packed red cells and CHOP-21 (cyclophosphamide, adriamycin, oncovin, and prednisolone) chemotherapy was initiated. Three cycles were given, and patient responded remarkably well.

There was complete regression of the enlarged spleen and liver including the axillary lymph nodes. Patient is currently asymptomatic and on routine clinic follow-up.

Discussion

CD is a rare clinicopathological disease entity with various subtypes.[1,2,5] The etiology of CD remains largely unknown; however, it is of note that some association with

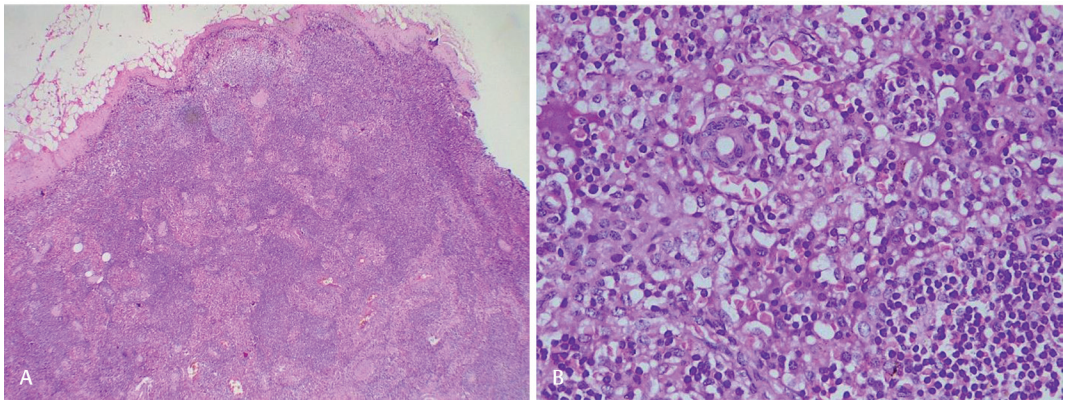

Fig. 1 (**A**,**B**) Photomicrograph of lymph node showing partial effacement of normal lymph node architecture by sheets of discohesive lymphocytes, plasma cells, histiocytes as well as thick-walled blood vessels (H&E stain ×4 and 40, respectively).

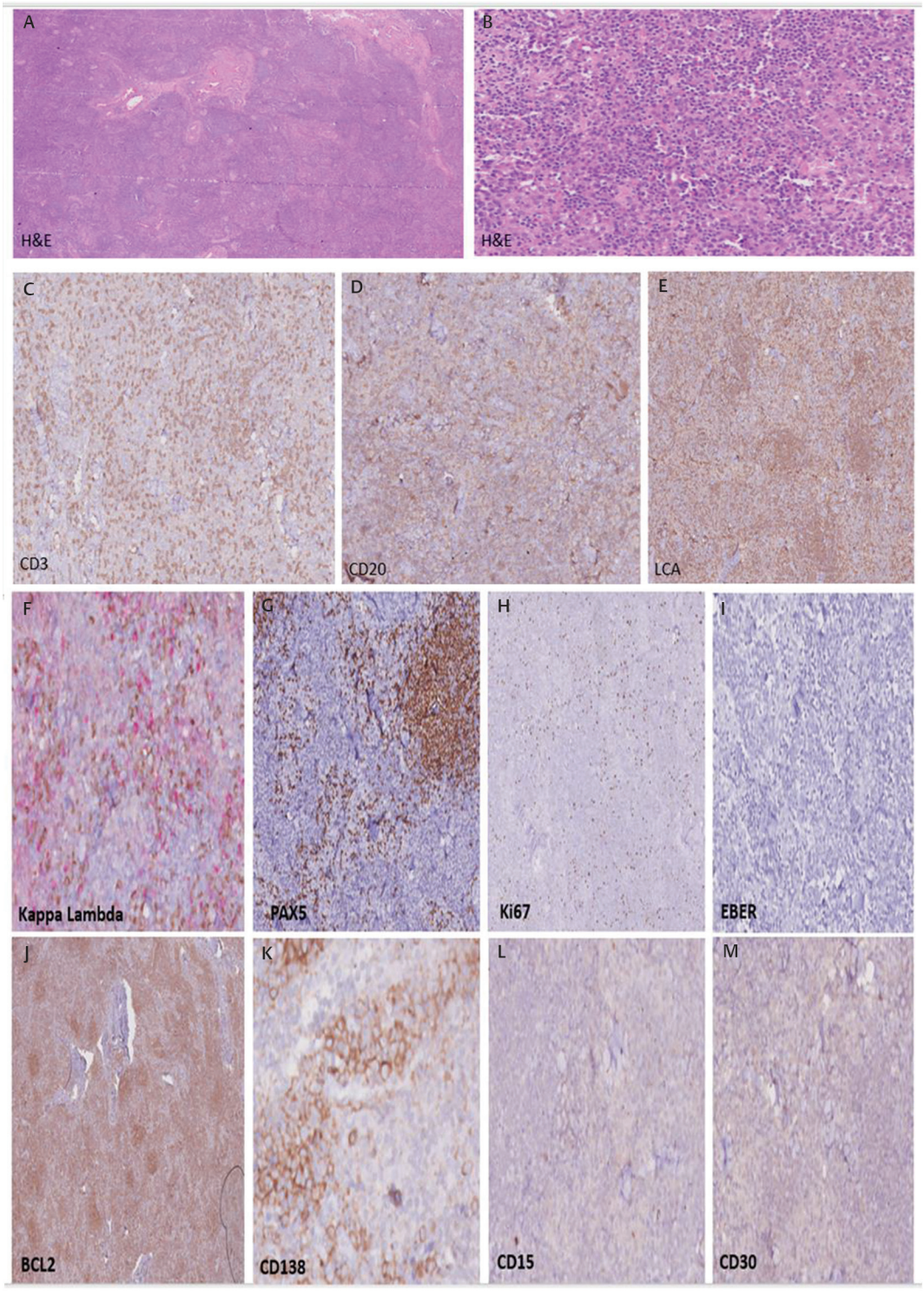

Fig. 2 (**A**) Histologic section, low power view, of lymph node biopsy showing complete effacement of normal lymph node by monomorphic population of lymphocytes. (**B**) Histologic section, intermediate power view, of lymph node biopsy showing complete effacement of normal lymph node by monomorphic population of lymphocytes. (**C**) Positive CD3 immunostain; this is a T-cell marker and shows expression in the paracortex; this verifies that we were dealing with a lymph node. (**D**) Positive CD20 immunostain; this is a B cell marker in the germinal center of the cortex, this verifies that we were dealing with a lymph node. (**E**) Weakly patchy positive leucocyte common antigen (LCA) or CD45 immunostain showing polymorphous nature; this rules out lymphoma (Immunohistochemical stains). (**F**) Kappa Lambda immunostain shows presence of polymorphous immunoglobulins. (**G**) PAX5 immunostain is negative for Hodgkin-Reed-Sternberg cells as well as HHV8-infected cells. (**H**) Ki67 immunostain shows the "Mitotic index," which is < 5% in this case, thus is not mitotically active. (**I**) Negative EBER immunostain, which is Epstein Barr virus (EBV) marker rules out EBV association like in Hodgkin lymphoma. (**J**) Negative BCL2 immunostain is a follicular lymphoma marker; thus, the negative staining rules out follicular lymphoma in this lesion. (**K**) Positive CD138 immunostain, which is a plasma cell marker. (**L**) Negative CD15 immunostain is a marker for Hodgkin-Reed-Sternberg cells (HRS), hence rules out Hodgkin lymphoma marker in this lesion. (**M**) Negative CD30 immunostain is a marker for Hodgkin-Reed-Sternberg (HRS) cells, hence rules out Hodgkin lymphoma marker in this lesion (immunohistochemical stains). EBV, Epstein Barr virus; EBER, EBV-encoded RNA; HHV8, human herpes virus type 8.

immunosuppressive conditions mediated by HIV, Epstein Barr virus, KSHV (Kaposi's sarcoma-associated herpes virus) or HHV-8 (human herpes virus-8) as well as secondary amyloidosis have been found in some cases.[2,6,8-10,20] The incidence of CD also remains largely unknown; however, it is of note that the prevalence of CD is approximately < 1 per 100,000 worldwide.[1,18] The majority of CD cases are adults, particularly females, with less than 100 cases reported in children (especially amongst teenage girls).[1,18,20,21] These adults affected are found within the third to fourth decade for UCD and fourth to fifth decade for MCD, with UCD accounting for approximately 87% of CD cases.[1,18]

The hyaline vascular (HV) subtype of CD is characterized histomorphologically by prominent vascular proliferation and hyalinization of vessel walls admixed with variable follicular patterns such as lollipop follicles, onion skin mantle zone, and mantle zones fusion with twinning of germinal centers.[1,22,23] This subtype accounts for approximately 90% of cases and commonly seen in the localized or unicentric form (UCD) of the disease.[1,4,5,23] It is asymptomatic in over 50% of cases, commoner among young adults and most cases are often discovered incidentally on imaging studies as a soft-tissue mass located in the neck or mediastinum and rarely in the retroperitoneum.[4]

The plasma cell subtype of CD is characterized histomorphologically by sheets of mature plasma cells within the interfollicular zones of the lymph node interspersed by surrounding larger/hyperplastic germinal center with less vascularity.[1,11] The MCD form of CD is associated with this plasma cell variant.[1] It usually affects older patients and clinically it is characterized by generalized lymphadenopathy, constitutional symptoms, multisystem organ involvement, and deranged laboratory findings.[6,9,18,24] These constitutional symptoms are considered a consequence of elevated chemical mediators of inflammation, namely: IL6, interleukin-2 (IL2), and vascular endothelial growth factor (VEGF).[1,6,8,9,18,20,25] These constitutional symptoms include: pallor, chronic diarrhea, asthenia, fever, weight loss, generalized lymphadenopathy, edema (sometimes ascites and/or anasarca), and hepatosplenomegaly.[1,6,8,9,18] The deranged laboratory findings include: anemia, thrombocytosis or thrombocytopenia, hypoalbuminemia, hypocholesterolemia, hypergammaglobulinemia, proteinuria, increased acute phase reactants (such as serum C-reactive protein), and increased chemical mediators of inflammation levels (such as IL6, IL2, and VEGF).[6-9] It is of note that unlike UCD, MCD is strongly associated with secondary amyloidosis as well as immunosuppression and HHV-8 infection usually in the background of HIV infection.[1,6,10] The clinical progression is often fatal due to high risk of opportunistic infections and likelihood of malignant neoplastic transformation often to Kaposi sarcoma and lymphoma.[2,6,18]

Interestingly, our patient in this case report was diagnosed with this less common multicentric plasma cell subtype of CD. She also presented with anemia, fever, and generalized lymphadenopathy consistent with MCD in addition to other symptoms associated with this subtype of CD in agreement with CD literature reviewed above. Interestingly, it is of note that though MCD is associated with HIV and HHV-8 infection, with some studies even demonstrating the presence of the HHV-8 sequence in approximately 60 to 100% of patients infected with HIV and 20 to 41% in those who were not, our index patient was HIV negative and her IHC evaluation was also negative for HHV-8 expression antibodies through the PAX-5 surrogate marker (even though direct serum HHV-8 antibodies could not be done for her).[1,14,15,25] The gold standard for our diagnosis in this case was a combination of routine histopathological and IHC evaluations of her cervical lymph node biopsy. The application of IHC as an ancillary technique in this case was especially critical in deciphering this case given the diagnostic dilemma initially presented by her overlapping clinical features and the initial Hodgkin's lymphoma pathologic diagnosis; thus IHC evaluation in combination with routine histopathological evaluations has been recommended as a standard method for lymph node examination especially where routine histopathological evaluation is nonspecific.[1,5,11-15,19]

Surgical resection of the affected lymph node is the treatment of choice for UCD, usually with no risk of recurrence; however, the MCD variant requires multimodal therapies with cytotoxic chemotherapy or CVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone, or prednisolone)/CHOP (cyclophosphamide, vincristine, doxorubicin, dexamethasone, or prednisolone), corticosteroids (dexamethasone/prednisolone), immunomodulators (lenalidomide or thalidomide, bortezomib, interferon α), intravenous immunoglobulins, plasmapheresis, radiotherapy, monoclonal antibodies (tocilizumab, siltuximab, and rituximab) and autologous hematopoietic stem cell transplantation.[2,6,9,18,20] In accordance with these literature our patient was successfully treated with CHOP. It is of note that a combinations of these treatment options give a better prognosis in MCD.[9,18,20] The IL-6 monoclonal antibodies (tocilizumab and siltuximab) are particularly useful in the alleviation of systemic manifestation.[6,18,20] Fortunately, a 5-year survival rate of 82% have been reported in MCD, a much better prognosis when compared with lymphoma.[26]

Conclusion

Multicentric plasma cell subtype of CD is a relatively uncommon disease entity that can present as a diagnostic dilemma because of its overlapping clinicopathological presenting features similar to malignant (Hodgkin's) lymphoma. Hence, this case report brings to the fore the importance of carrying out IHC evaluation of lymph node biopsy specimens with lymphoproliferative picture in addition to its routine histopathological examination for definitive diagnosis in view of expert management.

Conflict of Interest

None declared.

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