Diagnostic Issues in a Case of Hodgkin Lymphoma with Castleman Like Features

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Abstract Castleman disease (CD) is a benign heterogeneous lymphoproliferative disorder presenting with varied clinical manifestations. Histomorphologically, two distinct variants are known, hyaline vascular type and plasma cell type. CD is reported to be associated with lymphomas. Though Non Hodgkin lymphoma is more commonly associated with CD, its association with Hodgkin lymphoma (HL) is also well known and documented. Many a times, CD obscures or masks the underlying lymphomas thus delaying the diagnosis. There are also reports of HL showing Castleman like features. We report a case of HL with Castleman like features which posed diagnostic difficulty owing to the fragmented nature and tiny size of the initial lymph node biopsy. Striking peripheral blood rouleaux formation which was seen in our case along with bone marrow plasmacytosis has not been described in the previously diagnosed cases.

Keywords Castleman disease · Hodgkin lymphoma · Immunohistochemistry

Introduction

Castleman disease (CD) is a rare benign disorder first described by Benjamin Castleman in 1956. Clinically it can be unicentric/multicentric based on the extent of lymph node involvement. Histomorphologically it can be hyaline vascular

type, plasma cell type or mixed type. Development of Hodgkin lymphoma (HL) from CD has been described previously. Nearly 30 cases have been reported and most of them are reported concurrently and some being reported initially as CD and upon review turned out to be lymphoma [1]. There are also case reports of HL showing Castleman like features [2]. We report a case of HL showing co-existent Castleman like features with peripheral smear showing striking rouleaux formation, which posed a diagnostic difficulty.

Case Presentation

Our patient was a 24 year young man who presented with complaints of generalised malaise, loss of appetite and exertional breathlessness. On physical examination he had severe pallor and multiple bilateral cervical lymph nodes. There was no icterus or hepatosplenomegaly.

Complete haemogram showed a haemoglobin of 420 g/l on the day of admission which dropped to 260 g/l in a week. There was neutrophilic leucocytosis and thrombocytosis. Peripheral smear in addition showed rouleaux formation on several occasions (Fig. 1a). But there were no atypical cells or plasmacytoid lymphocytes. ESR was elevated (80 mm/h by Wintrobe's method). However, there were no bony lesions and his renal function tests were within normal limits. Liver function tests showed hypoalbuminemia with reversal of albumin globulin ratio. His total bilirubin was 2.4 mg/dl with direct bilirubin of 1.2 mg/dl. The haematological, biochemical parameters are shown in Table 1. As the peripheral smear showed rouleaux formation and albumin-globulin reversal was also present, serum protein electrophoresis was advised, however it showed a normal pattern. His HIV, HBsAg and HCV status was negative.

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Fig. 1 **a** Rouleaux in peripheral smear; *inset* showing the bluish colour of the smear (Leishman stain $\times 400$); **b** Bone marrow aspirate showing increase in plasma cells (Giemsa $\times 400$); **c** Initial Fragmented biopsy with few preserved lymphoid follicles (Hematoxylin

and eosin $\times 400$) *inset* showing fragmented biopsy; **d** CD23 highlighting follicular dendritic cells and expanded interfollicular area with increase in plasma cells highlighted by *Kappa* and *lambda* immunostaining (*inset*)

Table 1 Haematological and biochemical parameters

Hemoglobin	420 g/dl
Total WBC count	13,100/mm ³
Differential count	Neutrophils—79%, lymphocytes—20%, eosinophil—1%
Platelet count	5,82,000 /mm ³
ESR	80 mm/h
Total protein	8.2 gm/dl
Albumin	3.2gm/dl
Globulin	5.0gm/dl
Total bilirubin	2.4 mg/dl
Direct bilirubin	1.2 mg/dl

Chest X-ray done showed mediastinal widening owing to mediastinal lymphadenopathy. Ultrasonography of the abdomen revealed multiple peri-splenic lymph nodes with a small hemangioma in the liver.

Bone marrow aspirate done showed hypercellular marrow particles with increase in plasma cells, along with few

binucleate ones constituting 15 % (Fig. 1b). Immunocytochemistry using kappa and lambda revealed the polyclonal nature of these plasma cells.

Subsequently an excised cervical lymph node biopsy was sent for histopathologic examination. It was a fragmented tiny biopsy showing few preserved lymphoid follicles with expansion of interfollicular area showing sheets of plasma cells (Fig. 1c). Immunohistochemistry (IHC) done with CD23 highlighted few preserved lymphoid follicles with prominent germinal centres (Fig. 1d). Leucocyte Common Antigen (LCA) and CD 38 were positive in the plasma cells. CD 56 was negative. Immunostaining with kappa and lambda light chain showed polyclonality (Fig. 1d inset). Correlating with the clinical picture of multiple lymph node involvement, presence of anemia, sheets of plasma cells in the lymph node biopsy, a possibility of Castleman disease—plasma cell variant was suggested. But, in view of fragmented biopsy, a conclusive opinion was reserved and biopsy of an intact lymph node was advised.

Repeat lymph node biopsy done within a week showed effaced architecture with few preserved lymphoid follicles.

Fig. 2 **a** Repeat lymph node biopsy showing effaced architecture with similar few preserved lymphoid follicles and expanded interfollicular area (Hematoxylin and eosin $\times 100$) inset showing intact lymph node biopsy; **b** Few germinal centers showing hyaline vascular

areas with plasma cells in the interfollicular area (Hematoxylin and eosin $\times 400$); **c** Classical RS cells in the interfollicular area (Hematoxylin and eosin $\times 400$); **d** IHC with CD 15, CD30, CD20, PAX-5, EBV highlighting RS cells (DAB $\times 400$)

The interfollicular area was expanded and widely separated showing sheets of plasma cells (Fig. 2a). Few residual lymphoid follicles showed hyalinised centres (Fig. 2b). On further examination, the interfollicular area also showed numerous scattered large mononuclear cells, classic binucleate Reed-Sternberg (RS) cells in a background of lymphocytes and plasma cells (Fig. 2c). IHC showed membrane and golgi positivity for CD15 and CD30 in the large mononuclear cells as well as in binucleate RS cells (Fig. 2d). These large cells were also positive for CD20, weakly positive for PAX-5 and positive for EBV-LMP (Fig. 2d). CD 38 highlighted the plasma cells which showed polyclonal reactivity with Kappa and lambda light chains. Correlating with the clinical and imaging findings, a final diagnosis of Classical Hodgkin lymphoma—mixed cellularity (Ann Arbor Stage II) with co-existent Castleman like features was given. Patient received three cycles of Chemotherapy (ABVD regimen); he tolerated well and his lymphadenopathy regressed.

Discussion

CD is also known as angiofollicular lymph node hyperplasia, giant lymph node hyperplasia, lymph nodal hamartoma or follicular lympho-reticuloma. It is an unusual lymphoproliferative disorder of unknown etiology. Approximately 70 % of CD occur in the chest, 15 % in the neck, and 15 % in the abdomen and pelvis, involving primarily lymphatic tissues [3]. Two classification systems exist for CD. Depending on the extent of lymph node involvement it can be unicentric (localised) or multicentric CD. Histopathologically, CD is classified as Hyaline-vascular type, plasma cell type and a mixed type [3].

Hyaline vascular variant is more common representing 90 % of cases. It is unicentric in 90 % of cases and is usually asymptomatic, occurs in young adults, has a benign course which responds to local therapy. Plasma cell variant is rare representing approximately 10 % of cases. It occurs in elderly patients and is usually multicentric. Patients with

plasma cell type or a mixed hyaline-vascular and plasma cell type frequently have systemic manifestations related to production of cytokines such as fever, anemia, hypergammaglobulinemia, hypoalbuminemia, and an increase in acute phase proteins [4]. These manifestations of CD are non-specific and diagnosis is made based on histopathology.

Clinically HL and CD mimic each other [5]. These two entities have to be differentiated from each other histologically as the therapeutic approach varies. Castleman like features can occur in lymph node involved by both Non Hodgkin lymphoma (NHL) and HL, and certain conditions like acquired immunodeficiency syndrome, syphilis and autoimmune disorders which is attributed to secretion of interleukins [6]. Rare cases of HL can present initially with histological picture indistinguishable from CD which may cause delay in diagnosis particularly when the HL component is subtle and focal. Zarate-Orsorno et al. [2] reported three cases of HL with co-existent Castleman like features. HL can also show features like hyaline sclerosis, florid plasmacytosis which can be mistaken for CD. CD can also coexist with HL as reported by Abdel-Reheim et al [6].

To differentiate whether it's a case of HL showing Castleman like features or HL with coexistent CD one should look at the extent of histological changes suggestive of CD and whether the patient has symptoms attributable to CD. In case of lymphoma with Castleman like features the histological features of CD are often only focally present and the complete constellation of histologic findings that occur in CD is usually absent. Furthermore these patients do not have symptoms attributable to CD [2, 7].

A fragmented lymph node biopsy adds to the difficulty in identifying these cases as was in our patient, thus delaying the diagnosis. The prominent plasma cell proliferation in the initial fragmented biopsy made us consider the possibility of a CD. Our case also emphasizes that lymph nodes with hyaline-vascular changes and florid plasma cell proliferation should be evaluated cautiously to exclude an underlying lymphoma. HV-CD usually is not associated with systemic symptoms and generalised lymphadenopathy which should raise suspicion of a lymphoma when histological features suggesting CD are seen. IHC is helpful in such cases in identifying an occult lymphoma.

Our case, in addition to HL with Castleman like features, showed striking rouleaux formation on the peripheral smear. Hyperglobulinemia in our case was significant

enough to manifest as increased rouleaux formation in peripheral blood. We attribute the rouleaux formation in our case to polyclonal hyperglobulinemia and severe anaemia.

Castleman like histologic features may represent a non-specific immune response to a variety of immunologic stimuli including as in these cases, the presence of HL [2]. The presence of Castleman like features may delay the diagnosis of HL, so a possibility of HL needs to be considered and excluded before the diagnosis of CD is made. The clinical course and prognosis of patients with CD- HL is better than CD-NHL [8].

As CD can coexist with lymphoma, and lymphomas can show Castleman like features a high degree of suspicion, adequate histological material and IHC will help in identifying these lesions in an appropriate clinical setting, avoiding delay in diagnosis.

Conflict of interest None.

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