

CASTLEMAN'S DISEASE: A CLINICOPATHOLOGICAL STUDY IN A TERTIARY CARE HOSPITAL, LAHORE

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ABSTRACT

Castleman's Disease is a rare, localized or generalized lymphoproliferative disorder of unknown etiology and varying clinical manifestations with a frequent mediastinal location but can be found in any other nodal or extranodal site. We report 4 patients with Castleman's Disease diagnosed over a 2 year period (June 2011 to July 2013) at KEMU / Mayo Hospital, Lahore. The age, history, clinical presentation, laboratory investigations, radiological findings, gross and microscopic features of the lesions are presented indicating the heterogenous nature of this unique form of lymphoid hyperplasia.

Key Words: Hyaline Vascular (HV) type, Plasma Cell (PC) type, Lymphoid hyperplasia, lymphadenopathy, Interleukin – 6 (IL₆).

INTRODUCTION

Castleman's Disease (CD) is an uncommon heterogeneous group of usually benign lymphoproliferative disorders of unknown pathogenesis characterized by massive lymphoid hyperplasia.¹ The disease was first described and defined as a distinct pathologic entity by Dr. Benjamin Castleman in 1956² in a group of patients with large thymoma like masses in the anterior mediastinum but closer study proved that these masses were neither neoplastic nor thymic. Microscopy showed a peculiar form of benign lymph node hyperplasia with or without germinal centre formation and marked capillary proliferation with endothelial hyperplasia. Later a variant rich in plasma cells was described by Keller et al in 1972,³ who distinguished and classified the historically described and far more common localized "Hyaline Vascular" (HV) type from the less common multicentric "Plasma Cell" (PC) type associated with systemic signs and symptoms. However, both these types showed overlapping histological features and were considered manifestations of the same disease process.¹

CD can be found throughout the body at many nodal and extranodal sites with 60 – 70% cases located in the mediastinum but it can also be seen in the neck, axilla, abdomen, pelvis, mesentery, retroperitoneum, skin and skeletal muscle.⁴⁻⁹ There are 3 major histological subtypes of CD namely a unicentric "Hyaline Vascular" (HV) type, a multicentric "Plasma Cell" (PC) type and a multicentric Plasmablastic variant associated with HHV – 8 and HIV.¹⁰ Most cases are of the localized unicentric HV type seen in young adults characterized microscopically by the formation of small hyalinized lymphoid follicles with prominent interfollicular capillary proliferation. This type is usually asymptomatic and may

present as an isolated lesion.¹¹ The multicentric PC type shows large follicles with abundant interspersed sheets of plasma cells. This type is always symptomatic associated with fever, weight loss, anemia, elevated ESR, hypergammaglobulinemia, lymphadenopathy and often hepatosplenomegaly.^{11,12}

The pathophysiology of CD remains an enigma but it is considered a systemic B cell lymphoproliferation probably arising in immunodeficient states and associated with immune dysregulation.^{1,13-15} A key event is the abnormal production of a B – cell growth factor like IL₆ leading to lymphoproliferation and plasma cell differentiation.^{13,14} In this event HHV₈ has been found to play a crucial role in the multicentric PC type⁽¹²⁾. Co-existence of Hodgkin lymphoma and CD is well documented due to the secretion of IL₆ by the Reed Sternberg (RS) cells and the immune dysregulation associated with Hodgkin Disease.^{16,17}

CASE REPORTS

Case No. 1

A 30 year old female presented at the Surgical Department of Mayo Hospital, Lahore with fever, pain and tenderness in the right hypochondrium for the last one and a half year. Ultrasound and CT scans revealed a mass measuring about 6 × 6 cm in the right sub-hepatic area with hepatosplenomegaly of moderate severity. Investigations showed Hb = 8.2 gm/dl, ESR = 62 mm/hr, LFT's = Normal, X-Ray Chest = Normal. An exploratory laparotomy revealed a mass 5 × 5 cm in the mesocolon / mesentery which was excised and sent for histopathology. The gut appeared to be normal looking with no adhesions or mass formation anywhere else in the abdomen. On gross examination the mass was rounded, well circumscri-

bed, solid, uniform and tan white (Fig. 1). There was no cyst formation, haemorrhage or necrosis. Low power microscopic examination gave the impression of a large reactive lymph node showing numerous lymphoid follicles with germinal centres (Fig. 2). High power resolution demonstrated expanded interfollicular zones with sheets of plasma cells and many rounded Russell bodies with exuberant small blood vessel proliferation and hyalinized vessel walls (Fig. 3 and Fig. 4). The case was signed out as Castleman's Disease (Giant Lymph Node Hyperplasia): Plasma Cell type.



Fig. 1: Gross appearance of Case No. 1 (Mesenteric CD) showing a part of the well circumscribed and rounded mass (left). Cut section showing the solid, tan white homogenous nature of the lesion (centre and right).

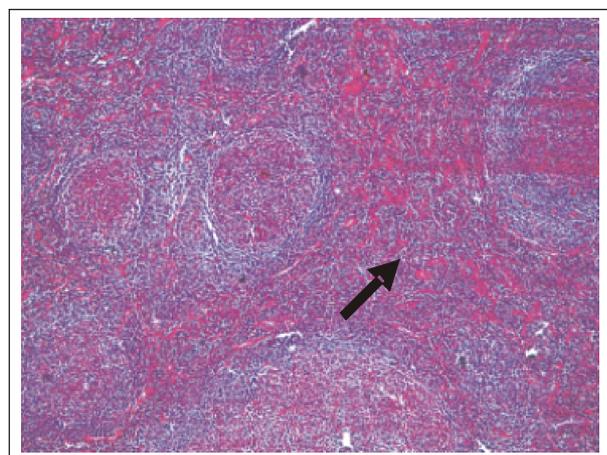


Fig. 2: Low power light microscopic image of the same case of CD showing the variable sized hyperplastic lymphoid follicles with enlarged germinal centres. Note the interfollicular area (arrow) with vascular proliferation, hyalinization and sheets of plasma cells.

Case No. 2

A 43 year old male resident of Faisalabad had a 5 year history of right neck mass which was enlarging slowly and now on presentation measured about 10

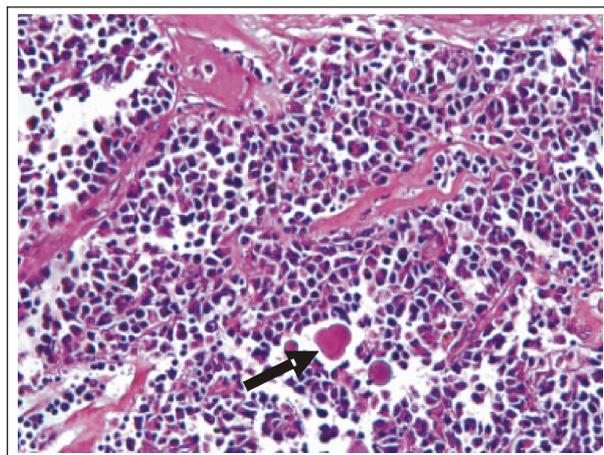


Fig. 3: High power microscopy of the interfollicular area of the same case of CD showing hyalinized vessel walls, sheets of plasma cells and rounded, eosinophilic Russell bodies (arrow).

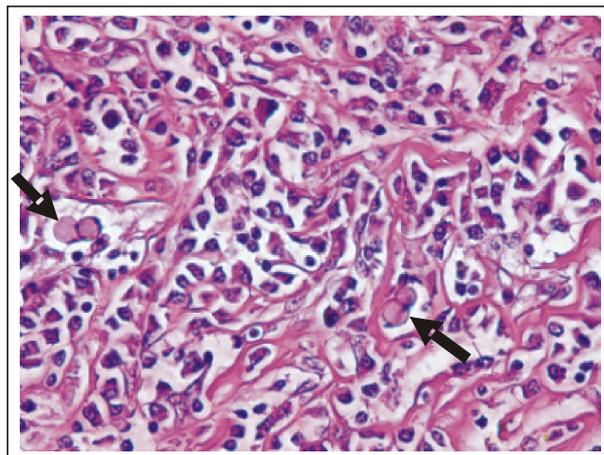


Fig. 4: Another high power microscopic image of CD showing prominent hyalinization, plasma cells and Russell bodies (arrows) in the interfollicular zones of lymph nodes.

cm in diameter. He had no history of fever, weight loss or any other complaint. Initial investigations showed Hb = 13.9 gm/dl, TLC = 8,200 cells / mm³, ESR = 90 mm/hr, LFT's = Normal. FNAC of this mass done 5 years back at Faisalabad had been reported as Chronic Granulomatous Inflammation (most likely Tuberculosis). The patient took ATT for 14 months but did not respond and the mass increased in size. Surgical biopsy was advised and his preoperative investigations were normal except ESR = 110 mm/hr, and Hb = 10.7 gm/dl. He was Anti HCV = Negative, HBsAg = Negative and Anti HIV = Non-reactive. Histopathology was reported as "Chronic Granulomatous Inflammation highly suggestive of Toxoplasmosis." The patient took Septran DS for 40 days but did not respond and the mass kept on in-

creasing reaching the present huge dimensions of 10 cm. He was advised 2nd opinion regarding histopathology. We received 3 prepared paraffin wax blocks and 3 stained slides at Pathology Department, KEMU, Lahore, Additional levels were cut and more slides were prepared. Microscopy showed lymph nodes with partially effaced architecture and a mixed inflammatory infiltrate of lymphocytes, plasma cells, eosinophils, some large cells with prominent nucleoli and abundant blood vessels. The case was reported as being suspicious of Hodgkin's Lymphoma and IHC was advised for confirmation. However, Castleman's Disease and Rosai Dorfman Disease was also given in the differential diagnosis. Results of immunohistochemistry (IHC) performed from a private centre showed CD 15- and CD 30- (both negative) in the large cells. CD 20 was focally + and the diagnosis of CD was favoured.

Case No. 3

Gross surgical specimen of matted left cervical lymph nodes of a 50 year old male were received at the Pathology laboratory of KEMU, Lahore. His previous FNAC had been reported as Granulomatous Inflammation and the patient had been on Antituberculous therapy (ATT) for the last 4 months. The specimen comprised of 3 matted lymph nodes measuring 3x2 cm. Cut section showed a uniform, homogenous, soft white tan tissue and 3 blocks were prepared. Histopathology showed the morphology of a lymphoid lesion with small hyalinized germinal centres and expanded mantle zones. A significant number of proliferating blood vessels, plasma cells and Russell bodies were also identified. The case was signed out as Castleman's Disease (Mixed type).

Case No. 4

An 8 year old boy presented to the Surgical Unit of Mayo Hospital with enlarged left cervical lymph nodes. He had a history of fever, cough and weight loss for the last 8 months, His Hb = 8.4 gm/dl, ESR = 136 mm/hr. Abdominal USG revealed hepatosplenomegaly and multiple enlarged para-aortic lymph nodes. Surgical excision of the cervical mass showed matted lymph nodes measuring 3x2.5x2cm, with a strong suspicion of Lymphoma on a previously performed FNAC. Histopathology showed enlarged, encapsulated lymph nodes with partial architectural effacement and nodule formation due to bands of fibrous tissue. Many reactive enlarged lymphoid follicles with germinal centres were identified and the interfollicular areas showed numerous plasma cells, Russell bodies and vascular proliferation. No Reed Sternberg cells or eosinophils were identified. The case was reported as CD of the Plasma Cell type.

DISCUSSION

CD is a poorly understood, highly controversial and

rare lymphoproliferative disease that creates a diagnostic and therapeutic problems for clinicians. In recent years, it has become evident that CD is a morphologic syndrome uniting a group of diseases with related and occasionally overlapping pathogenesis.¹⁰ A review of literature reveals that since its original discovery by Castleman et al in 1956,² the disease has been given a variety of names like giant lymph node hyperplasia, lymph node hamartoma, angiofollicular lymph node hyperplasia, angiomatous lymphoid hyperplasia and benign giant lymphoma.¹⁸⁻²⁰ Perhaps the most appealing, appropriate and precise is that chosen by Denenberg⁽²¹⁾, who called it "*the lymphoma imposter*". This unusual clinicopathological entity is distinctive from reactive lymph node proliferations and malignant lymphomas.²²

On clinical and radiological grounds CD can be classified as unicentric vs. multicentric type and on histopathological basis it is classified as Hyaline – Vascular (80 – 90%) vs. Plasma Cell type (10 – 20%) vs. Mixed cellularity.^{6,7} Recently, authors favour the histological classification over the traditional unicentric vs. multicentric model and have added another category called Plasmablastic variant associated with HHV – 8 and HIV.^{10,12,13,23}

Histologically the classic "Hyaline – Vascular type" (HV-type) is characterized by distinctive lymphoid follicles having expanded mantle zones composed of small lymphocytes forming concentric rings surrounding one or more atretic germinal centres having a single prominent penetrating blood vessel.² This "onion skinning" of the mantle zone lymphocytes and the prominent central vessel has the appearance of a "lollipop".¹⁰ Another important feature is the prominent interfollicular vascular proliferation with hyalinized vessel walls.^{2,10} The HV type presents as a localized mass most commonly located in the mediastinum or pulmonary hilum.^{2,7,11,13} It is usually asymptomatic in 50% cases and discovered incidentally.^{11,12,23} Complete surgical excision is curative for this type.¹² VEGF may contribute to the prominent vascular proliferation in the interfollicular areas.¹⁰

The "Plasma Cell type" (PC type) is predominantly multicentric showing polyadenopathy and multi-system involvement.^{6,11,12} It is often associated with hepatosplenomegaly and symptoms like fever, weight loss, skin rash, anemia and hypergammaglobulinemia due to excessive IL – 6 production.^{6,10,12} A POEMS (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein and Skin changes) syndrome is observed in 24% of these patients.¹² HIV seropositive individuals appear to be at an increased risk for multicentric CD (MCD) due to the increased incidence of HHV – 8 infection.¹⁰ The multicentric PC type is considered a systemic B cell lymphoproliferation arising in immunodeficient states resulting in an outgrowth of a clonal B cell population.^{1,13} Lo-

calized unicentric types of PC variants have also been described associated with systemic symptoms and abnormal laboratory investigations. The PC variant exhibits hyperplastic germinal centres, sheets of plasma cells in the interfollicular regions, proliferation of blood vessels with hyalinization and a scattered population of plasmacytoid immunoblasts.¹⁰ The frequent combination of the HV and PC types (Mixed type CD) along-with the morphological transition from one type to the other and from the localized to the multicentric form during the course of the disease and the development of autoantibodies has suggested that CD is a single disorder related to immune dysregulation.¹³

Many cases of abdominal involvement by CD have been reported in literature. Our Case No. 1 of a 30 year old female with a mesenteric mass had associated hepatosplenomegaly, fever, weight loss, elevated ESR and gross anemia classifying it as the multicentric plasma cell type of CD. Rodefeld⁸ reported a case of PC variant in the abdomen of a 12 year old boy with an associated 5 year history of microcytic anemia, hypergammaglobulinemia, ESR = 80 – 90 mm/hr, arthralgia and an abdominal mass measuring 5x3cm adjacent to the superior mesenteric artery. Shah and Darji⁶ also reported a unicentric abdominal CD of the HV type measuring 5 × 5 × 3 cm in a 40 year old man. There were no systemic manifestations and no evidence of any other mass lesion elsewhere in the body. Ergul²⁴ reported a rare case of CD in the duodenum of a 49 year old woman measuring 5.5 × 4.2 × 4 cm with no associated intra-abdominal lymphadenopathy or any other visceral or systemic manifestations. Zakiullah and Khan²² reported a case of HV type in the abdominal lymph nodes of a 16 year old boy associated with systemic symptoms of chronic fatigue, fever, microcytic hypochromic anemia and hypergammaglobulinemia. The boy also had gross splenomegaly and a mass in the right hepatic lobe alongwith cervical lymphadenopathy. Although the boy had systemic manifestations and multisystem involvement but the histopathological variety was HV type of CD rather than the PC type or Mixed type.

Our Case No. 2 of a 43 year old male with a huge cervical mass and no systemic manifestations created considerable diagnostic difficulty having being reported as tuberculosis, toxoplasmosis, and Hodgkin lymphoma on different occasions from different diagnostic centres. Finally, it was diagnosed and reported as CD of the PC type when immunohistochemical stains (CD 15- and CD 30-) ruled out the possibility of Hodgkin lymphoma. Similarly our Case No. 3 of a 50 year old man with matted left cervical lymph nodes was also suspected of being tuberculosis (on FNAC) or lymphoma clinically but histopathology confirmed the diagnosis of mixed variant of

CD. These case reports highlight the importance of obtaining a definite histological diagnosis in patients with lymphadenopathy and systemic symptoms because differentiation from malignant lymphomas and other reactive infective diseases cannot be made reliably on radiological grounds or FNAC. Associated clinical findings and laboratory investigations like multifocal lymphadenopathy, hepatosplenomegaly, anemia, hypergammaglobulinemia, elevated ESR and constitutional symptoms like fever, weight loss, malaise, night sweats also point towards diagnosis.

Although CD usually affects the young adult population it can rarely also occur in childhood. There are only about 100 pediatric cases reported in literature so far.²³ The youngest patient reported to have this disease was 6 months old.²⁵ According to Spencer⁵ a syndrome of anemia, growth retardation and hypergammaglobulinemia is seen in the plasma cell type in children. Our 4th case and the most recently reported at our centre was an 8 year old boy with left cervical and paraaortic lymphadenopathy, hepatosplenomegaly, fever, anemia and a markedly elevated ESR. He was suspected of having a lymphoma but histopathology of the excised cervical lymph nodes was reported as PC variant of CD. Farruggia²³ reported 3 childhood cases from Italy, all were of the HV type having ages of 3.3 years, 3.8 years and 13 years. One child had axillary swelling, one had subcutaneous and intramuscular nodules and the 3rd child had an anterior neck mass. Bhandary⁹ reported a case of HV type from Nepal in a 13 year old boy with a left sided neck swelling. Baruch et al²⁶ reported 3 childhood cases of CD out of a total of 8 cases in their study. Two cases were of the mixed type and 1 was of the HV type.

Cases of spontaneous remission of CD have been described but the course of multicentric PC type is poor due to complications like infections, severe autoimmune anemia, sarcoidosis, POEMS syndrome and evolution into malignant tumours like lymphomas, follicular dendritic cell sarcomas and especially in HIV+ patients the development of Kaposi's sarcoma.²⁷⁻³⁰ Surgical excision is the treatment of choice for the localized HV subtype with a 100% control rate. However, no therapeutic consensus exists for the Multicentric PC type of CD.¹²

CD must be borne in mind in the differential diagnosis of localized or generalized lymphadenopathy with or without systemic manifestations. The differential must include B cell lymphomas, Hodgkin lymphoma, thymomas, plasmacytomas, angioimmunoblastic lymphadenopathy, reactive lymphadenopathies associated with infections (tuberculosis, sarcoidosis, toxoplasmosis) and immunodeficiencies, autoimmune diseases and various HIV related lymphadenopathies.^{10,12}

It is **concluded** that the discussion of these cas-

es and review of literature emphasizes the fact that it is of utmost importance to obtain a definite and accurate histological diagnosis in patients with lymphadenopathy and systemic symptoms because CD is an entity which is distinct from malignant lymphoproliferative disorders histologically, prognostically and regarding treatment options. The diagnosis must be based on clinical assessment which includes patients' history, radiological findings, laboratory studies like IL₆ and CRP levels, gammaglobulin levels, ESR, CBC, HIV serology, FNAC, HHV₈ serology, and HHV₈ DNA PCR but the ultimate gold standard for the accurate diagnosis of CD is histological examination of the excised lymph nodes or tumour masses.

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