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Case Report

CASE REPORT

IL-5 in the plasma-cell-dominant Castleman disease: a nosological entity

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Abstract

A 40-year-old male presented with a history of low-grade fever, weight loss, night sweats and breathlessness of 3 months duration. On examination, the patient had freely mobile lump in left lumbar region. The lump was surgically excised. Histological examination and immunohistochemistry of the specimen were consistent with the diagnosis of plasma cell variant of the Castleman disease. The patient had polyclonal hypergammaglobulinemia, anemia, eosinophilia and elevated interleukin (IL)-6 level. The level of IL-5 was not measured; however, the presence of eosinophilia indirectly suggests an increased IL-5 level. He obtained complete remission after resection of lump and 20 months of surgery had no signs and symptoms of diseases recurrence with normal hematological parameters. We discuss the role of IL-5 in the pathophysiology of the Castleman disease along with dysregulated overproduction of IL-6.

INTRODUCTION

The Castleman disease is a group of rare lymphoproliferative disorders of unknown etiology. It has three subtypes on the basis of histology: the hyaline vascular, the plasma cell dominant and the mixed type. The hyaline vascular variant is more common (>90%) and tends to be localized, whereas plasma cell type is a rare subtype (<10%) with more aggressive behavior and usually presents with multicentric disease. The pathophysiology of the Castleman disease is related to increased systemic inflammatory response [1]. The dysregulated overproduction of interleukin (IL)-6 is considered crucial in the pathophysiology and symptomatology of the disease. Earlier, a case report described the role of IL-5 along with IL-6 in a patient of the plasma-cell-dominant Castleman disease who had eosinophilia and increased levels of IL-5 and IL-6 [2]. Herein, we discuss a case of plasma cell variant of the Castleman disease with polyclonal hypergammaglobulinemia, anemia, eosinophilia and elevated IL-6 level. Following excision of the mass, patient achieved complete remission.

CASE REPORT

A 40-year-old man presented to us because of a small lump in left lumbar quadrant of abdomen for 1 year. He had dull aching pain, low-grade fever, fatigability, anorexia, weight loss and occasionally altered bowel habits. He had no history of chronic blood loss, chronic illness or addictions. He denied history of any parasite infections, asthma and other allergies, and diseases that might have caused eosinophilia. At presentation, his vital parameters were stable. The abdomen was soft and non-tender. There was a single, soft, rounded, mobile and slightly tender mass of one rupee coin size in left lumber quadrant. There was no peripheral lymphadenopathy. The spleen, liver and kidneys were not palpable. Other system examinations were unremarkable.

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Table 1

Parameters	Value
Hemoglobin (g/l)	103
TLC (cells/mm^3)	9.3 × 10^9/l (N—63%, L—22%, M—3% and E—12%)
Platelets (lakhs/mm^3)	228 × 10^9/l
MCV	75 fl
Serum LDH	842 IU/l
Total protein	8.6 g/dl
Serum albumin	2.97 g/dl
A/G ratio	0.53
CRP	15 (mg/l)
ESR	50 mm in the first hour
IL-6	41 pg/ml (0–4 pg/ml)
Serum iron	56 µg/dl
TIBC	350 µg/dl
Serum ferritin	08 ng/ml
Serum protein electrophoresis	Polyclonal hypergammaglobulinemia. Monoclonal band was not detected. Protein α-1 was 0.47 g/dl, α-2 was 0.64 g/dl, β was 0.86 g/dl, γ was 3.67 g/dl.
Urinalysis, CX-ray, NCV, gastroscopy	Normal
HIV, HBV and HCV	Negative
Bone marrow and myelogram	Normal cellularity, erythropoiesis—predominantly normoblastic Myelogram—promyelocytes—2%, myelocytes—20%, metamyelocytes—15%, Neutrophils—17%, eosinophils—6%, normoblasts—34%, Megaloblasts—4%, plasma cells—2%.
CECT abdomen	Multiple tiny enlarged mesenteric nodes in left lumber region with one of them measuring 4 × 4 × 2.2 cm with mild splenomegaly.
Tissue and histopathology	The cut surface of tissue was smooth pinkish white, measured 4.5 × 4.5 × 2.1 cm in size, partly capsulated with oval grayish brown soft tissue. Preserved lymphoid follicles with diffuse presence of plasma cells in the interfollicular zone (Fig. 1).
IHC	Positivity of CD30 in few immunoblast and scanty plasma cells, CD15 in few granulocytes, CD20 in follicles, CD3 in interfollicular lymphocytes and CD45 was positive.

TLC, total leukocyte counts; N, neutrophil; L, lymphocytes; E, eosinophil; M, monocyte; ESR, erythrocyte sedimentation rate; MCV, mean corpuscular volume; CRP, C-reactive protein; A/G ratio, albumin globulin ratio; IL, interleukin; TIBC, total iron binding capacity; LDH, lactate dehydrogenase; CECT, contrast-enhanced computed tomography; CX-ray, chest X-ray; NCV, nerve conduction study; HIV, human immunodeficiency virus; HCV, hepatitis c virus; HBV, hepatitis b virus.

Hematology revealed hemoglobin of 103 g/L with eosinophilia and mildly microcytic hypochromic red blood cells. The blood sugar, urea, creatinine, transaminases, bilirubin, electrolytes and thyroid profile was within normal limit. The A/G ratio was reversed. Stool examination was normal. Serum protein electrophoresis showed polyclonal hypergammaglobulinemia. The C-reactive protein, erythrocyte sedimentation rate and IL-6 were elevated. The bone marrow examination showed normal cellularity and predominantly normoblastic erythropoiesis. The mass was removed with exploratory laparotomy after confirming with contrast-enhanced computed tomography (CECT) (Table 1). Histopathology and immunohistochemistry (IHC) findings were consistent with the diagnosis of plasma cell variant of the Castleman disease (Fig. 1). The postoperative course of the patient was uneventful. One month after follow-up, he was apparently asymptomatic, while the anemia has totally been resolved. He was followed up 20 months after the operation and was completely free of signs and symptoms of recurrence, with normal hematology.

DISCUSSION

The plasma cell variant usually presents with multicentric disease and has a diffuse interfollicular plasma cell proliferation with minimal vascular component. On the other hand, hyaline vascular variant is characterized by large follicles, showing marked capillary proliferation and hyalinization in a mass of lymphoid tissue. The lymphocytes form a concentric layer at the periphery of these follicles that comprise the mantle zone [1, 3, 4].

These patients can have B-symptoms including low-grade fever, night sweat, poor appetite, fatigue and mild symptoms of anemia. The clinical presentation of localized/unicentric form is usually asymptomatic or with minimal symptoms. Multicentric form is usually aggressive and presents with disseminated diseases with diffuse lymphadenopathy, splenomegaly, anemia, hyperglobulinemia, polyneuropathy and systemic inflammatory symptoms. This form is commonly found in patients suffering from HIV, and few of them can develop Kaposi's sarcoma or B-cell lymphoma [3–6].

The etiology of the Castleman disease is still controversial; however, a viral etiology resulting in disordered immune regulation and dysplastic lymphoproliferative process has been postulated. The symptomatology of disease is considered because of the release of various cytokines, ILs and vascular endothelial growth factor (VEGF). Among them, IL-6 is a pivot factor in the pathophysiology of the disease. The pathogenic role of Kaposi's sarcoma-associated herpes virus (HHV-8) in association with cytokines is supported by demonstrating

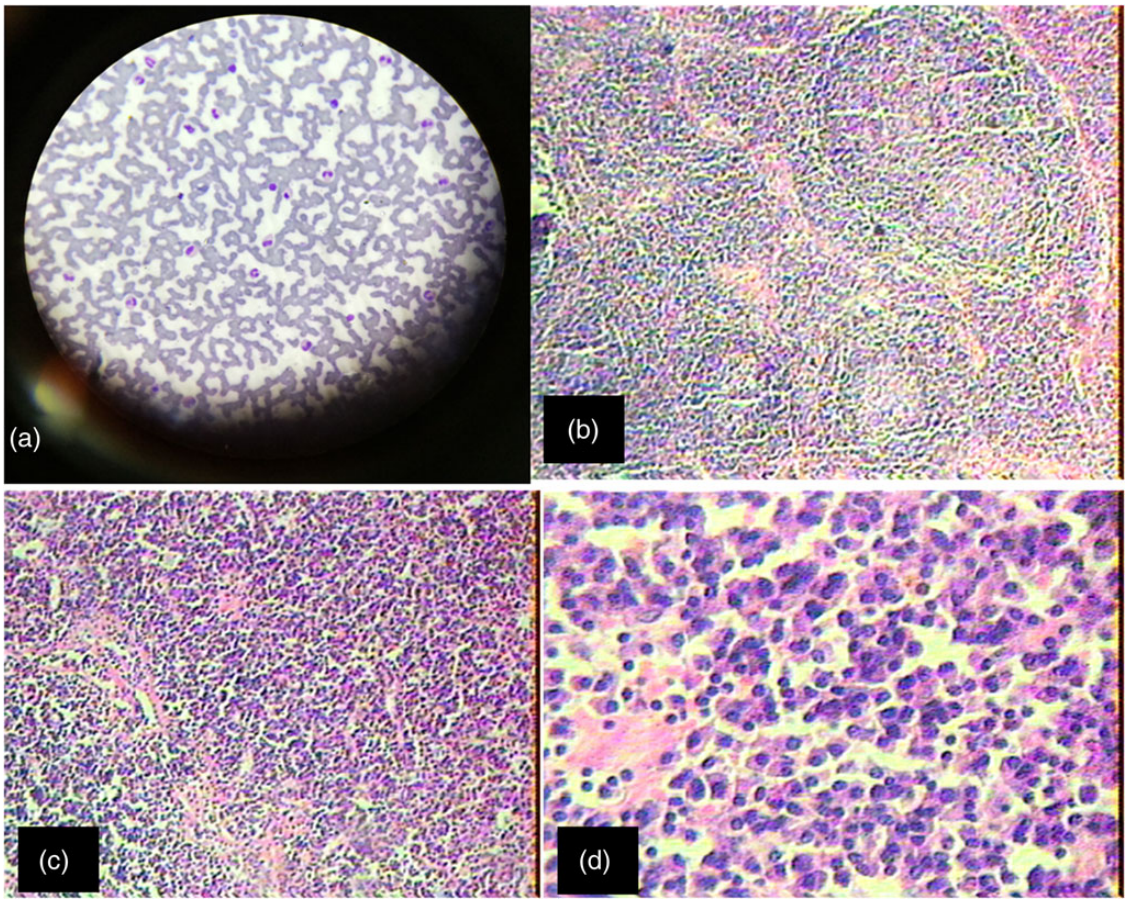

Figure 1: (a) Low magnification reveals follicular hyperplasia with focal central zone hyaline material. (b) Perivascular hyalinization presents with masked interfollicular zone due to proliferation of lymphoplasmacytoid cells. (c) Higher magnification shows a solitary blood vessel having perivascular hyaline. There is diffuse proliferation of plasma cells in the interfollicular zone.

that HHV-8 is able to produce an IL-6 homolog [5, 6]. IL-6 increases VEGF secretion that causes angiogenesis, proliferation of vascular muscle cells and capillary proliferation with endothelial hyperplasia [3]. It is also responsible for proliferation and differentiation of B cells into antibody-producing cells, resulting in hyperplastic follicles and lymph node enlargement [7, 8].

The role of IL-5 in the pathophysiology of the Castleman disease is not studied broad at present. Ishii *et al.* [2] described the role of IL-5 along with IL-6 in the pathophysiology of the Castleman disease. They found eosinophilia and remarkably elevated IL-5 and IL-6 levels from the serum and swollen lymph nodes of a patient having the multicentric plasma-cell-dominant Castleman diseases. IL-5 and eosinophilia normalized after treatment with corticosteroids with improvement in the clinical symptoms. IL-5 was considered to be related to the Castleman disease and responsible for eosinophilia.

IL-5 is a T-cell (Th2 cells)-derived cytokine. It has pleiotropic effects on various target cells, including eosinophils and B cells, and critically regulates expression of genes involved in proliferation, cell survival and maturation of eosinophils. Thus, IL-5 plays a pivotal role in innate and acquired immune responses and eosinophilia. Overexpression of IL-5 significantly increases eosinophils counts. IL-5 also stimulates B-cell growth and immunoglobulin secretion [9]. Disordered immune regulation in the Castleman disease may lead to increased production of IL-5 and eosinophilia. The constitutional symptoms may be related with elevated IL-5. The level of IL-5 was not done in our patient; however, the presence of eosinophilia indirectly suggests an increased IL-5 level.

The management of the Castleman diseases depends on the histological type, spread of the mass, associated infections and malignancies. The unicentric form has benign outcome and curable after the surgical resection of the mass. Radiation therapy is an alternative when disease cannot be completely excised, whereas multicentric form requires systemic therapies. The antiviral therapy, glucocorticoids, anti-CD20 (rituximab) and single agent (etoposide, vinblastine, liposomal doxorubicin) ± rituximab or high-dose zidovudine/valgancyclovir) and combination cytotoxic chemotherapy (R-CHOP, R-CVP or rituximab/IV etoposide) are established treatment modalities. The monoclonal antibody targeting IL-6 is a novel therapy and may be a better treatment option in near future [1, 3, 6].

To conclude, we report a rare case of unicentric plasma cell variant of the Castleman disease with eosinophilia. Usually, the plasma cell Castleman disease has aggressive course, but in our case the resection of the localized lesion brought about complete remission, which is lasting till date. Eosinophilia in our case might be due to elevated IL-5. However, the role of IL-5 in the pathogenesis of plasma cell variant of the localized Castleman disease remains a matter of discussion for further works. Further studies are required to define the mechanism underlying IL-5 and eosinophilia-mediated symptomatology or pathophysiology of the Castleman disease.

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CONFLICT OF INTEREST STATEMENT

None declared.

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ETHICAL APPROVAL

This is a single case report, so we did not obtain ethical approval.

CONSENT

Informed consent has taken from the patient's attendant.

GUARANTOR

All of the authors are guarantors of this article.

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