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A case of multicentric HHV-8 positive Castleman's disease presenting with marked lymphocytosis

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ABSTRACT

Castleman's disease is a rare lymphoproliferative disease which is morphologically and clinically heterogeneous. Histopathologically it is classified into hyaline vascular, plasma cell and mixed variants and clinically into unicentric and multicentric types. Although it presents with diverse clinical and laboratory findings, as far as we know, there is no case in the literature that presents with such a marked lymphocytosis which can simulate chronic lymphocytic leukemia. In this report, a case of Castleman's disease, that is HHV-8 positive multicentric hyaline vascular type and displaying marked lymphocytosis is presented. [Turk J Cancer 2009;39(3):110-114]

KEY WORDS: Castleman's disease, hyaline vascular type, HHV-8, lymphocytosis

INTRODUCTION

Castleman's disease (CD) is an uncommon disease that was first described as a pathologic entity in 1954 and defined by Castleman et al. in 1956 (1,2). Histopathologically three variants (hyaline vascular, plasmacytic and mixed) and clinically two types (unicentric and multicentric) have been described (3-5). Localized disease usually presents with a single enlarged lymph node. Histologically, hyaline vascular type accounts for 90% of cases of Castleman's disease and patients are generally asymptomatic. Multicentric variant is a systemic disease that presents with multiple lymphadenopathy, hepatosplenomegaly and B-type symptomatology. Multicentric CD is generally plasmacytic and mixed type and rarely hyaline vascular type (6). It may be associated with anemia, thrombocytopenia, leukopenia, hypergammaglobulinemia, elevated erythrocyte sedimentation rate (ESR), proteinurea, abnormal rise in liver function tests, and nonspecific neurological findings of rheumatoid disease (3,7,8). However, marked lymphocytosis is not a usual finding in these patients. In this report, a disease of Human Herpes Virus-8 (HHV-8) positive multicentric hyaline vascular type CD case that presented with marked lymphocytosis is described.

CASE REPORT

A 57 year-old male patient referred to the hematology department with the complaints of fatigue, weakness and swelling at both sides of the neck and in inguinal region. Previously, he had undergone lymph node biopsy and bone marrow biopsy in other centers, but definitive diagnosis was not obtained.

In physical examination, there were multiple lymphadenopathies in the cervical, inguinal and axillary regions. They varied in size, reaching maximally about 2.5 cm in diameter. Hepatosplenomegaly was not observed. Laboratory findings are summarised in table 1.

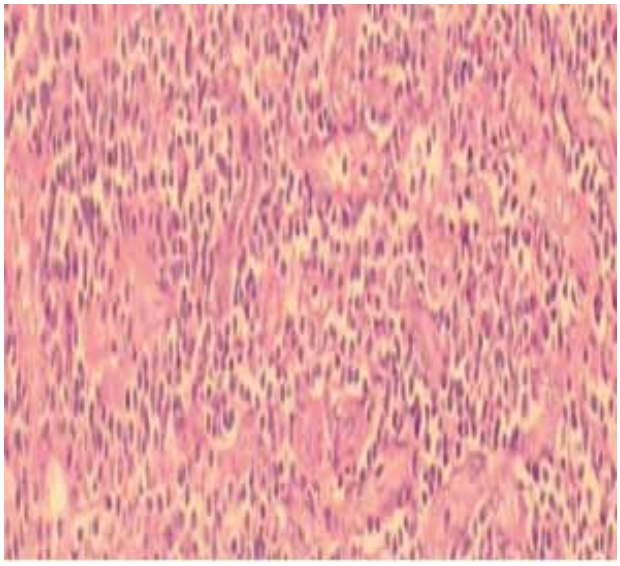

Fig 1. Small burnt out follicles are present. Thickened, hyalinized vessels transecting the follicles and onion skin appearance of the mantle zone lymphocytes are prominent. Post capillary venules are increased in number and thickened (H&E, X100)

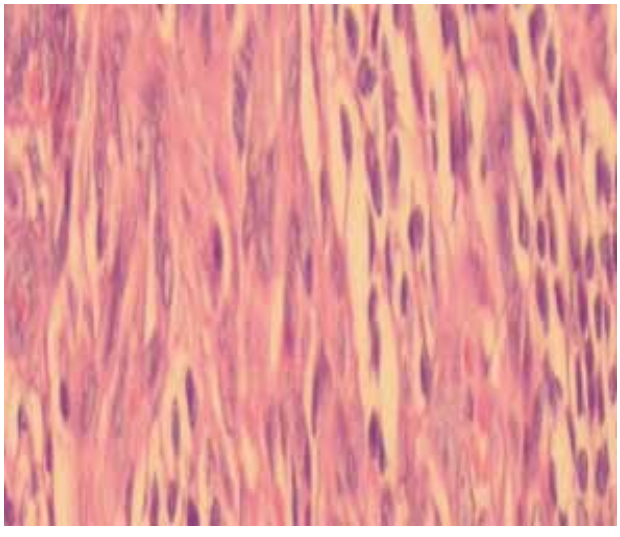

Fig 2. Hypocellular follicle center and vessels are seen better in higher magnification (H&E, X200)

In the thorax computerized tomography (CT), multiple enlarged lymph nodes at the pathological dimension were detected with pretracheal, anterior mediastinal, preaortic, precarinal, subcarinal and aorticopulmonary localisations. In abdominal CT, millimetric lymph nodes were elongated in peripancreatic, mesenteric regions and bilateral inguinal fossa.

In the ultrasonography (US) of the neck, multiple enlarged lymph nodes, the largest of which was the size of 30x15 mm, were detected. In axillary US, multiple enlarged lymph nodes, which showed occasional conglomeration were detected. The largest was at size of 24x33 mm at right axillary region and 24x17 mm at left axillary region.

The results of the flow cytometry analysis are as shown below:

CD3: 22%, CD7: 21%, CD10: (-), CD11c: 56%, CD14: 24%, CD5: 23%, CD19: 69%, CD5+CD19: 1%, CD38: 13%, CD22: 77%, CD23: 47%, CD25: 3%, FMC7:71%, Anti HLA DR: 76%, Anti Lambda: 12%, Anti Kappa: 76%, CD 20: 72%.

The histopathological examination result of the axillary lymph node biopsy showed reactive changes. It was diagnosed as hyaline vascular type angiofollicular lymph node hyperplasia (Castleman's disease) consequent to axillary and cervical lymph node biopsy (Figures 1,2). Bone marrow aspiration and biopsy evaluation showed normal histopathological findings. HHV-8 Ig G (Immunoglobulin G) results were positive at high titration. Oral methyl prednisolone at the dose of 1 mg/kg/day was commenced. Complaints and lymph node enlargement improved completely after one month.

DISCUSSION

Castleman's disease is a heterogeneous lymphoproliferative disease group, the cause of which remains unknown. Hypothesis for the causes of CD have included autoimmunity, disorder cytokine production and infection with the HHV-8. HHV-8 has been associated with the multicentric form of CD in 25% of cases. As it occurs rarely, our information on this disease is mostly based upon retrospective studies with a limited number of patients and case presentations.

Table 1
Laboratory findings

	Laboratory findings	Normal Range
WBC (x10^9/l)	28.8	4.4-11.3
Lymphocyte (x10^9/l)	20.2	0.9-3.2
Neutrofil (x10^9/l)	6.0	1.3-6.7
Platelet (x10^9/l)	435	150-450
Hb (g/dl)	11.1	14.0-17.5
Ig G (g/l)	28.3	7-16
Ig M (g/l)	1.06	0.4-2.3
Ig A (g/l)	4.37	0.7-4
RF (IU/ml)	8.75	0-15
CRP (mg/l)	161	0-5
ASO (IU/ml)	142	0-200
LDH (U/l)	152	125-243
HBsAg, Anti-HIV, Anti-HCV	(-)	
Anti Toxoplasma Ig M (IU/ml)	0.06	0.6-0.7
Anti-Rubella Ig M (IU/ml)	0.11	0.8-1.2
Anti-CMV Ig M (AU/ml)	0.06	0.7-0.9
Anti-HSV Tip 1 Ig M	(-)	
Anti-HHV-8 Ig G	(+)	(-)
Wright ag. test	(-)	
Rose Bengal ag. test	(-)	
Sedimentation rate (mm/h)	88	0-10

CD is usually of unicentric hyaline vascular type. Keller et al. (2) described 81 cases. Of these, 91% was of hyaline vascular variant and the disease was localized. Localized CD is a self-limited process, curable with local therapy.

Eighty to ninety percent of the cases of multicentric CD belong to plasma cell variant (6). Of 21 cases reported by Chronowski et al. (9) 9 were multicentric and among them only one was histologically hyaline vascular type. Herreda et al. (5) reported 15 patients and among them 8 cases were with multicentric development and only one of them was of hyaline vascular type. In our case, the most striking laboratory finding was that he had pronounced lymphocytosis (absolute lymphocyte number 20x10^9/l). Incorporation of immunophenotypic features into the diagnostic criteria is helpful in differentiating CLL from other lymphoproliferative disorders. Lymphocytes in B-CLL coexpress CD19, CD20, CD23, CD5, and a single immunoglobulin light chain, kappa or lambda. CD10 (CALLA) expression is usually absent. Mantle cell lymphoma is distinguished from CLL by absent or very dim expression of CD23 (10). In our case lymphocytes coexpress CD11c, CD19, CD22, CD23, FMC7, HLA DR, kappa, and CD 20. Flow cytometric study did not support CLL and other lymphoproliferative disorders.

In literature review, slight lymphocytosis was reported (2). Nevertheless, a CD case presenting with marked lymphocytosis was not encountered.

Leukopenia and thrombocytopenia may be observed in multicentric CD (3,7). In bone marrow examination, slight increase in plasma cells may be observed (3,4,11). In our case, increase in plasma cells and lymphocytes were not seen in bone marrow aspiration and biopsy evaluation.

Interleukin 6 (IL-6) has been implicated in the pathophysiology of CD. The multicentric variant of CD is as-

sociated with HHV-8 in many cases (12-14). This virus encodes a functional analogue of IL-6, providing further evidence that this cytokine has a pivotal role in the disease (15). It causes B-cell proliferation resulting in hyperplastic follicles and hence the enlarged lymph nodes. IL-6 also increases secretion of vascular endothelial growth factor (VEGF), causing angiogenesis and capillary proliferation with endothelial hyperplasia. IL-6 is also responsible for polarization of T lymphocytes to a Type 2 cytokine profile leading to autoimmune phenomena including autoimmune hemolytic anemia**,** antinuclear antibody (ANA) positivity and elevation of IgE. IL-6 induces an acute phase reaction comprising increases in ESR, C-reactive protein (CRP), IgGs, serum fibrinogen, and serum Amyloid A Protein (SAA). Increased SAA levels may result in AA Amyloidosis, whilst hyperfibrinogenemia may play a role in venous thrombosis and thrombotic. Finally, B-type symptomatology is virtually always associated with increased IL-6 levels (16,17). It is suggested that high IL-6 levels may account for some pathological characteristics of the disease and clinical and laboratory findings (3,6,18,19). Administration of recombinant IL-6 at pharmacological doses may lead to slight lymphocytosis (20,21). However, it is difficult to describe the marked lymphocytosis seen in our case by the effect of IL-6 since the lymphocytosis associated with IL-6 is mild. Lymphocyte infiltration not having been detected in bone marrow may be explained by focal involvement.

In the study of Bacon et al. (11) bone marrow was evaluated in 12 HHV-8 positive CD cases. In three cases, lymphoid follicles similar to the lymph nodes in multicentric CD were detected. They suggested that this is characteristic for HHV-8 associated multicentric CD. Our case was also HHV-8 positive. However, in the study of Bacon et al. (11) all cases were also HIV-positive and none of the cases was lymphocytosis unlike our case. The cause of marked lymphocytosis seen in our case could not be explained.

In conclusion, Castleman's disease is a heterogeneous disease in terms of histological, clinical and laboratory findings. It should be borne in mind that patients may have marked lymphocytosis as well as anemia, neutropenia and thrombocytopenia. These cases can simulate chronic lymphocytic leukemia. However, these cases may be distinguished from CLL or other B cell lymphoproliferative diseases.

References

1. Castleman B, Iverson L, Menendez VP. Localized mediastinal lymph node hyperplasia. Cancer 1956:9:822-30.
2. Keller AR, Hochholzer L, Castleman B. Hyaline-vascular and plasma cell types of giant lymph node hyperplasia of the mediastinum and other locations. Cancer 1972;29:6832.
3. Peterson BA, Frizzera G. Multicentric Castleman's Disease. Semin Oncol 1993;20:636-47.
4. Maslovsky I, Uriev L, Lugassy G. The heterogeneity of Castleman disease: Report of five cases and review of the literature. Am Med Sci 2000;320:292-5.
5. Herrada J, Cabanillas F, Rice L, et al. The clinical behavior of localized and multicentric Castleman disease. Ann Intern Med 1998;128:657-62.
6. Waterston A and Bower M. Fifty years of multicentric Castleman's disease. Acta Oncol 2004;43:698-704.
7. Frizzera G, Peterson BA, Bayrd ED, et al. A systemic lymphoproliferative disorder with morphologic features of Castleman's disease: Clinical findings and clinicopathologic correlations in 15 patients. J Clin Oncol 1985;3:1202-16.
8. Hanson CA, Frizzera G, Patton DF, et al. Clonal rearrangement for immunoglobulin and T Cell receptor genes in systemic Castleman's disease. Association with Epstein-Barr virus. Am J Pathol 1988;131:84-91.
9. Chronowski GM, Ha CS, Wilder RB, et al. Treatment of unicentric and multicentric Castleman disease and the role of radiotherapy. Cancer 2001;92:670-6.
10. Jaffe ES, Pittaluga S. The Pathologic Basis for The Classification of Non-Hodgkin's Lymphomas. In: Hoffman R, Benz EJ, Shattil SJ, et al., editors. Hematology Basic Principles and Practice, 4th Ed. Philadelphia: Elsevier Churchill Livingstone, 2005;1381-2.
11. Bacon CM, Miller RF, Noursadeghi, M, et al. Pathology of bone marrow in human herpes virüs-8HHV8. associated multicentric Castleman disease. Br J Haematol 2004;127:585-91.

12. Nishimoto N, Sasai M, Shima Y, et al. Improvement in Castleman's disease by humanized anti-interleukin-6 receptor antibody therapy. Blood 2000;95:56-61.
13. Parez N, Bader-Meunier B, Roy CC, et al. Paediatric Castleman disease: report of seven cases and review of the literature. Eur J Pediatr 1999;158:631-7.
14. Soulier J, Grollet L, Oksenhendler E, et al. Kaposi's sarcoma-associated herpesvirus-like DNA sequences in multicentric Castleman's disease. Blood 1995;86:1276-80.
15. Wilkinson S, Forrester-Wood CP. Surgical resection of a solitary plasmacytoma originating in a rib of a patient with Castleman's disease. Ann Thorac Surg 2003;75:1018-9.
16. Parravicini C, Corbellino M, Paulli M, et al. Expression of a virus-derived cytokine, KSHV vIL-6 in HIV-seronegative Castleman's disease. Am J Pathol 1997;151:1517-22.
17. Staskus KA, Sun R, Miller G, et al. Cellular tropism and viral interleukin-6 expression distinguish human herpesvirus 8 involvement in Kaposi's sarcoma, primary effusion lymphoma, and multicentric Castleman's disease. J Virol 1999;73:4181-7.
18. Casper C. The etiology and management of Castleman disease at 50 years: translating pathophysiology to patient care. Br J Haematol 2005;129:3-17.
19. Bowne WB, Lewis JJ, Filippa DA, et al. The management of unicentric and multicentric Castleman's disease: a report of 16 cases and a review of the literature. Cancer 1999;85:706-17.
20. Ulich TR, Del Castillo J, Guo KZ. In vivo hematologic effects of recombinant interleukin-6 on hematopoiesis and circulating numbers of RBCs and WBCs. Blood 1989;73:108-10.
21. Dedera DA, Urashima M, Chauhan D, et al. Interleukin-6 is required for pristane-induced plasma cell hyperplasia in mice. Br J Haematol 1996;94:53-61.