Bone Marrow Involvement in Multicentric Castleman Disease in a HIV Negative Patient

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Abstract There are few reports on the bone marrow involvement in multicentric Castleman disease in human immunodeficiency virus (HIV) negative patients, mostly the characteristic morphologic findings within the bone marrow are reported in HIV-positive patients. Here we describe bone marrow involvement in a HIV-negative patient with multicentric Castleman disease.

Introduction

Castleman's disease, first described in 1956, is a rare lymphoproliferative disorder, which is commonly found in mediastinum and lung hila. Clinically it is divided in two types: a localized form, which is usually asymptomatic and presents as a mass or swelling, and a multicentric type characterized by fever with chills, anemia, generalized lymphadenopathy, hepatosplenomegaly and with a more aggressive behavior [1]. Histologically, the disease is also classified into two separate subtypes: the hyaline vascular and plasma cell variants, the earlier being more common and showing greater vascularity [2]. Bone marrow histology in multicentric Castleman disease in human immunodeficiency virus (HIV) negative patients is not well

reported [3]. Mostly the characteristic morphologic findings within the bone marrow is reported in the group of HHV-8 and HIV-positive patients [4]. Here we describe bone marrow involvement in a HIV-negative patient with multicentric Castleman disease.

Case Report

A 42-year old male presented to neurology outpatient clinic with complains of pain followed by progressive weakness in bilateral lower limb since 9 months. He also complained of progressive weakness in bilateral upper limbs for one and a half months. On examination he had hepatomegaly 3 cm below the right costal margin and generalized lymphadenopathy. His central nervous examination revealed bilateral fundal papilloedema with no obvious cranial nerve palsies, thickened peripheral nerves and decreased reflexes in all the limbs. Based on this a clinical possibility of lower motor neuron sensorymotor syndrome was kept with the possible etiology being either non-Hodgkin's lymphoma, Waldstrom's macroglobulinemia, plasma cell dyscrasia or HIV immunocompromised state. The patient was worked up on these lines and planned for a lymph node biopsy. His hemogram was normal with hemoglobin of 11.8 g/dL, platelet count of $167 \times 10^9/L$ and total leucocyte count of $13.1 \times 10^9/L$. The myeloma work up was negative with no M-band on serum and urine protein electrophoresis. Abdominal fat pad was negative for amyloid. Contrast enhanced computed tomography of abdomen revealed hepatomegaly, retroperitoneal lymph nodes, pleural and pericardial effusion. Serology for HIV and Epstein Bar virus were negative. Histopathological examination of the cervical lymph node showed maintained nodal architecture with small sized follicles and presence of vessels in the

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germinal center, along with marked paracortical expansion with plasma cell infiltration in the interfollicular area; overall features being consistent with Castleman disease, plasma cell type. The skin biopsy was also performed from hyperpigmented areas; it showed mild lymphoplasmacytic infiltrate in dermis. POEMS (Polyneuropathy, Organomegaly, Endocrinopathy, M-protein, Skin abnormalities) syndrome was ruled out as patient had no monoclonal M-band on electrophoresis. This was followed by bone marrow examination and trephine biopsy revealed interstitial increase in mature looking plasma cells, present at perivascular locations, along with clustering with large syncytial-appearing forms and palisading. The clustered plasma cells were large with moderate to abundant cytoplasm and only minimal nuclear atypia. At places, these plasma cell aggregates were associated with lymphoid nodules comprised of small, mature appearing lymphocytes. The bone marrow surrounding these lympho-plasmacytic aggregates displayed increased vascularity, the findings being compatible with the marrow involvement by Castleman disease (Fig. 1). The patient was referred to clinical hematology unit for further treatment. Patient was planned for CHOP (Cyclophosphamide, Hydroxydaunorubicin, Oncovin, Prednisolone) chemotherapy, however due to patients' financial constraints; he has been started on CVP (cyclophosphamide, vincristine, prednisolone) chemotherapy.

Discussion

Castleman disease is characterized by enlargement of hilar and mediastinal lymph nodes. Although the most common site of the disease is within the thorax, rare extrathoracic presentations have been described within the abdomen, including the left lobe of the liver [2, 5]. Castleman disease in HIV-negative individuals is more often unicentric with higher proportions of the hyaline vascular and mixed cellularity histological sub-types than patients with HIV infection. HIV-positive patients show higher incidences of the plasmacytic pattern with interfollicular sheets of plasma cells, marked paracortical plasmacytosis, hyalinized germinal follicles and less vascular stroma. There can be mantle zone expansion with abnormal proliferations of polyclonal plasmablasts and these individuals show HHV-8 co-infection and have poorer outcomes compared to HIV-negative patients. Marrow involvement in Castleman disease is almost exclusive to the multicentric plasmacytic type (hence is rare in HIV-negative persons) and a spectrum of morphological findings has been described [1–4].

Kreft et al. [3] in their study described various patterns of bone marrow involvement in three HIV negative patients. In one patient they found lymphoid follicle with

regressed hyalinized germinal centers surrounded by a small mantle zone, and polyclonal, bland plasma cells peripherally. In second they found the plasma cells were increased up to 30 % of the nucleated cells of the bone marrow; these plasma cells being condensed to large, grapelike clusters with more than 100 cells in histologic section. These clusters were centered on small vessels, arterioles, and sinusoids. Some binuclear plasma cells and Mott-cells were also noted, but all plasma cells revealed a bland cytomorphology. Small number of hemosiderin laden macrophages, granulopoietic cells and small lymphocytes were intermingled. Those areas were not sharply demarcated from the surrounding normal hematopoiesis. In the immunohistochemical analysis the plasma cells revealed a polyclonal pattern with predominantly kappa light chain positive plasma cells. This accumulation of plasma cells was possibly provoked by interleukin-6 (IL6), which is the central mediator in the perpetuation of Castleman disease [6], known to stimulate plasma cell proliferation and maturation [7]. These large clusters differ from multiple myeloma by the bland morphology and perivascular localization of the plasma cells. Similar picture showing increased plasma cells interstitially, in perivascular locations and at places being associated with lymphoid nodules was seen in our patient. They also differ from immunocytoma by the lack of a significant lymphoid cell population. They could be further separated from those monoclonal lymphoproliferative disorders by the polyclonal pattern of plasma cells [8]. The third pattern of bone marrow histology is the presence of human herpes virus-8 (HHV-8) positive cells within the bone marrow. These cells have the size of plasma cells, revealing a mature nucleus and resemble the plasmacytoid cells reported in the majority of HHV-8 positive, and mostly HIV-positive, patients with multicentric Castleman disease [4]. Literature reviewed mentions that HHV8-positive cells are found in the patients with the most compromised immune system [4] and not in immunocompetent patient [9]. HHV-8 not specific for multicentric Castleman disease but also seen in HIV-positive patients with Kaposi sarcoma and other lymphoproliferative disorders [10–12]. Within the bone marrow HHV-8 positive cells were accompanied by a slight increase of plasma cells of up to 5 % of the nucleated cells, not significantly exceeding the normal range, as found in previous reports for most patients with multicentric Castleman disease [13]. The presence of HHV8 positive cells within the bone marrow, implies the dissemination of the virus, which is associated with multicentric Castleman disease, but also seen in other HHV8-related disorders and compromised immune status.

The pathogenesis of Castleman disease is unknown, although most believe that a defect in immunoregulation resulting in excessive proliferation of B-lymphocytes and

Fig. 1 Trephine biopsy section showing infiltration by Castleman disease, **a** Plasma cell aggregates surrounding the lymphoid nodules, (Hematoxylin and Eosin, $\times 200$); **b** Higher magnification of same, Hematoxylin and Eosin, $\times 400$; **c** Plasma cells, present at perivascular

locations, along with clustering with large syncytial-appearing forms and palisading (Hematoxylin and Eosin, $\times 200$); **d** Higher magnification of same, Hematoxylin and Eosin, $\times 400$

plasma cells in lymphoid organs is responsible for its origin [14]. It has been suggested that expression of Castleman disease is partly due to IL-6 activity; HHV-8 is known to encode a viral IL-6. One hypothesis for the origin is that HHV-8 expresses viral IL-6, which induces vascular endothelial growth factor, which then induces human IL-6 production by endothelial cells [15]. Further supported by the fact that use of neutralizing antibodies against IL-6 and monoclonal antibody blocking the IL-6 receptor, have demonstrated clinical efficacy, resulting in symptom resolution in these patients.

There are two major pathologic variations. Hyaline-vascular type, the most frequent, characterized by small hyaline-vascular follicles and capillary proliferation; and the plasma-cell type, in which large lymphoid follicles are separated by sheets of plasma cells. The hyaline-vascular cases usually are largely asymptomatic, whereas the less common plasma-cell variant may present with fever, anemia, weight loss, and night sweats, along with polyclonal hypergammaglobulinemia. The plasma cell variant of Castleman disease is less common and clinically more aggressive, with involvement of multiple enlarged lymph

nodes [2]. Patients with the localized plasma-cell variant can have systemic manifestations including fever, excessive sweating, fatigue, arthralgia, anemia, elevated erythrocyte sedimentation rate, polyclonal hypergammaglobulinemia, and bone marrow plasmacytosis. These systemic manifestations usually resolve after surgical excision of the mass. Radiologically, these lesions are less vascular and thus demonstrate only mild-to moderate contrast enhancement on computed tomography.

Although the best treatment for Castleman disease is still unknown, surgical removal of the localized type of the mass has long been considered standard therapy for the disease. However, patients with multicentric Castleman disease of either histological subtype have a poor prognosis. They are usually treated with a combination of radiation therapy, corticosteroids and chemotherapy.

It is important to consider Castleman disease in the differential diagnosis for patients presenting with extensive lymphadenopathy, especially those with acquired immunodeficiency. The clinical index of suspicion for Castleman disease is heightened by the presence of other factors such as HIV infection, hypoalbuminemia, POEMS syndrome,

hypergammaglobunemia, fever of unknown origin, and night sweats. Given the guarded prognosis for multicentric Castleman disease, it is prudent to pursue appropriate diagnostic work up for this condition along with other differential diagnoses in order to arrive at an accurate diagnosis and prescribe appropriate therapy.

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