

# Multiple Myeloma in a Patient with Castleman's Disease

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## Abstract

Multiple myeloma is characterized by malignant plasma cells in the bone marrow, overproduction of a monoclonal protein, and lytic bony destruction. It is an incurable disease accounting for approximately 20 percent of deaths from hematologic malignancy and 2 percent of deaths from all cancers.<sup>1</sup> It has no established relationships with secondary malignancies; and, the exact cause of the disease is unknown. We will report the first case of multiple myeloma in a patient with multicentric Castleman's disease and explore etiologies of both diseases.

## INTRODUCTION

Multiple myeloma (MM) is characterized by malignant plasma cells in the bone marrow, overproduction of a monoclonal protein, and lytic bony destruction. It is an incurable disease accounting for approximately 20 percent of deaths from hematologic malignancy and 2 percent of deaths from all cancers.<sup>1</sup> It has no established relationships with secondary malignancies; and, the exact cause of the disease is unknown. We will report the first case of multiple myeloma in a patient with multicentric Castleman's disease and explore etiologies of both diseases.<sup>2</sup>

## CASE REPORT

A previously healthy 37 year old male presented to clinic in April 2001 complaining of a painless lump in his left inguinal region of 6 months' duration. Physical exam revealed a soft, nonmatted 3 cm mass in the left inguinal canal. History was unremarkable. Laboratory examination revealed a normal CBC and chemistry panel. Plain films and CT scan of the chest, abdomen and pelvis showed a lytic lesion of the left pubic ramus, measuring 2.6 cm by 2.7 cm. The surrounding bone appeared to be slightly irregular with an increased radiographic density, as shown below.

Figure 1



The patient promptly underwent a left inguinal lymph node biopsy which showed angiofollicular lymphoid hyperplasia, which was consistent with Castleman's disease, hyaline-vascular type. Flow cytometry failed to identify monoclonal lymphoid cells, ruling out the possibility of malignant lymphoma. Further laboratory investigation by serum protein electrophoresis showed a small monoclonal IgG gammopathy with normal uninvolved immunoglobulins. Bone biopsy of the lytic lesion in the pelvis revealed a monoclonal plasmacytoma for which radiation therapy was initiated. After radiation was complete, the monoclonal gammopathy resolved. A bone marrow aspirate was unremarkable. Skeletal survey in September 2001 showed regular lytic bony destruction of the left pubic bone consistent with monoclonal plasmacytoma. The frontal

projection of the left knee showed small vague lucencies suspicious for additional bony lesions. The patient was followed every six months by his hematologist. Repeat bone marrow aspiration in October 2001 remained unremarkable. He was doing well until December 2005 when repeat CT scan showed enlargement of the left iliac lesion. Laboratory examination showed recurrence of monoclonal gammopathy. Bone marrow aspirate in January 2006 remained unremarkable.

He was referred to University of Mississippi Medical Center in February 2006 to begin evaluation for bone marrow transplant. After receiving cyclophosphamide for conditioning, the patient had his peripheral stem cells harvested. He began treatment with dexamethasone and thalidomide for multiple myeloma with plans for future transplant.

In July 2007, he underwent autologous peripheral stem cell transplant. He tolerated the procedure well and has remained disease-free.

### DISCUSSION

Castleman's disease (CD) has been associated with malignancies such as Kaposi's sarcoma, lymphoma, and POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome. Etiology of immunological dysfunction associated with CD has remained a mystery, but theories include interleukin-6 (IL-6) overexpression and human herpesvirus-8 (HHV-8) activity. In animal models, overexpression of IL-6 by hematopoietic stem cells results in a syndrome comparable to multicentric CD, with peripheral lymphadenopathy, plasma cell infiltration of lymphoid tissues, splenomegaly, anemia, and hypergammaglobulinemia.<sup>3,4</sup> Early studies demonstrated reduction of both symptoms and IL-6 levels in patients with CD who underwent lymph node excision.<sup>5,6</sup> It has been suggested that blastic B-cells of the germinal centers, follicular dendritic cells, or cells present in the interfollicular regions are responsible for IL-6 production.

<sup>5,6,7</sup>

One hypothesis for the origin of multicentric CD, shown in animal and human models, is that HHV-8 expresses viral IL-6, which induces vascular endothelial growth factor (VEGF).<sup>4</sup> This compound encourages human IL-6 production by endothelial cells.<sup>8</sup> High levels of IL-6 are frequently seen in patients with CD. While HHV-8 replicates, a viral IL-6 gene (vIL-6) that activates the human IL-6 receptor is expressed. This can cause proliferation of

human myeloma cell lines.<sup>9,10</sup> Further investigation has shown that antibodies to human IL-6 block its function, leading to resolution of the systemic symptoms and hypergammaglobulinemia of multicentric CD.<sup>11,12</sup> Although not fully understood at present, it is believed that either viral or human IL-6 is partially responsible for the pathogenesis of HHV-8 positive multicentric CD.<sup>13</sup> Although these data may address the role of HHV-8 in the pathogenesis of multicentric CD, they do not advance our understanding of the pathogenesis of HHV-8 negative multicentric form. It is likely that these subtypes have a different, unidentified source of immune stimulation.

Although controversial, there is evidence that infection with HHV-8 plays a role in multiple myeloma.<sup>14</sup> Several small studies have detected HHV-8 in the stromal dendritic cells from bone marrow biopsies of patients with multiple myeloma. HHV-8 was demonstrated in the nonmalignant cell population of long-term bone marrow cultures from patients with MM, as well as in fresh bone marrow biopsy specimens.<sup>15,16</sup> Other studies have confirmed the presence of HHV-8 in bone marrow dendritic cells, but many researchers have not been able to identify HHV-8 in either bone marrow or peripheral blood samples from patients with MM.

<sup>17,18,19,20,21,22,23,24</sup>

Less controversial is the relationship between MM and IL-6. IL-6 is made in bone marrow stromal cells and malignant cells. Production is upregulated by cytokines and CD40.<sup>25</sup> Most MM cell lines and fresh bone marrow MM cells express IL-6 receptors. Binding of IL-6 yields a cascade of effects which activates signal transduction pathways which mediate MM cell growth, survival, and drug resistance.

<sup>25,26,27</sup> Preliminary studies reveal that IL-6 blockade is possible in vivo in patients with MM.<sup>28</sup>

These studies form the basis for our theorized relationship between MM and multicentric CD. We propose that the two conditions are linked through mechanisms involving HHV-8 and/or IL-6 which could lead to future treatment options.<sup>28</sup> Already ongoing is an investigational study using chimeric anti IL-6 in patients with MM or CD. Development of a human IL-6 antibody could also prove to be helpful in these two diseases.

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