Multiple Myeloma and HIV Infection: An Association or a Coincidence

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ABSTRACT

Background: Multiple myeloma has been infrequently observed in human immune deficiency virus (HIV)-infected individuals and a marginally higher post-acquired immune deficiency syndrome (AIDS) incidence has been reported. The average age at presentation among HIV-infected individuals with plasma cell dyscrasias is 33 years, and the route of transmission of majority of these cases is through anal sex.

Patients and Materials: We describe a 65-year old African American male with AIDS who developed multiple myeloma with an aggressive course and review the literature.

Results: Our patient developed on aggressive course of multiple myeloma, which paralleled the progression of AIDS (decreased CD4 cell count and increased viral load). He developed anemia, high grade fevers, severe epistaxis, marked thrombocytopenia, prolonged bleeding time (28 minutes) with a serum LDH level of 869 U/L. Serum protein electrophoresis later revealed his monoclonal band to have increased to 4.05 g/L. Repeat bone marrow examination was remarkable for nearly complete replacement of normal elements with essentially 100% plasma cells, some with blastic appearance, some monstrously large with 6 to 8 nuclei, looking like megakaryocytes. Unusual for myeloma, several mitotic figures were seen, indicative of the aggressive nature of the patient's accelerating disease. The patient finally expired.

Discussion: Multiple myeloma should be considered in the differential diagnosis of B-cell neoplasms complicating HIV infection. Multiple myeloma generally runs an aggressive course in such patients and follows the decline in CD4 cell counts. A prospective study to gather incidence date and explore the association between multiple myeloma and HIV infection is warranted.

INTRODUCTION

The disciplines of infectious diseases, hematology, immunology, and oncology are seen to often intersect in human immune deficiency virus (HIV) illness. For example, several neoplasms are seen with much greater frequency in HIV disease, such as Kaposi's sarcoma, non-Hodgkin's lymphoma and invasive cervical cancer, that they are considered acquired immune deficiency syndrome (AIDS)-defining.[1] Many other tumors are reported more often in patients with

HIV, although are not AIDS-defining.[1] Multiple myeloma is an example, which is shown in some series to occur with greater frequency in HIV-infected patients.[1,2]

Various series of reports of bone marrow examinations in patients with HIV or AIDS reveal a common finding of increased cellularity with increased plasma cells.[3,4] Hypergammaglobulinemia and paraproteinemias have also been observed.[2] However, even in the setting of B-cell stimulation and activation, as occurs in HIV, development of frank multiple myeloma is a relatively rare event.[1,2] To the best of our knowledge, more than 49 cases of AIDS complicated by multiple myeloma have been reported in the medical literature.[5-42] We report another case of highly aggressive myeloma in an HIV-positive patient and briefly review the related literature.

CASE PRESENTATION

The patient was a 65-year-old heterosexual African American man with known prostate cancer, stage T1c (managed with combined androgen blockade), presented with neck pain and spinal cord impingement due to T1 vertebral body compression and retropulsion with resultant mild to moderate cord compression. A bone scan was negative for bony prostate metastasis (PSA < 0.1). The patient, who was generally recalcitrant to medical treatment, declined neurosurgical intervention to stabilize the cervical spine. Thus, he was treated with local radiation and decadron and given a neck collar for support.

During this hospitalization, he underwent further evaluation of his mild anemia and thrombocytopenia. He was found to be HIV positive with a viral load of > 500,000/cmm. Skeletal survey revealed no lytic lesions, but did show generalized osteopenia. Serum protein electrophoresis (obtained *after* high-dose decadron was given for spinal cord impingement) was notable for a 3.16 g/L IgG lambda paraprotein. Bone marrow examination ensued which was hypercellular with a plasmacytosis (plasma cells representing 24% of nucleated cells) (Figure 1). His hospital stay was complicated by the development of a deep venous thrombosis (DVT) and (pulmonary embolus (PE), which was treated with heparin and coumadin. Therapy for his HIV disease was begun with Combivir and Viramune. Melphalan and prednisone were given for the myeloma; additionally, he received a dose of pamidronate.

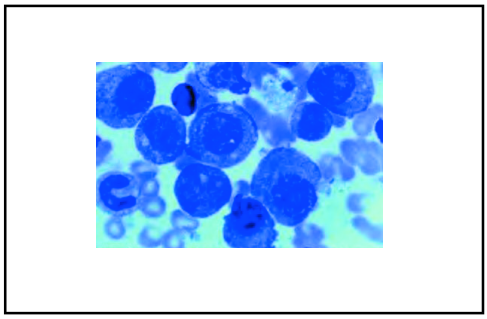

Figure 1. Bone marrow examination demonstrated sheets of malignant plasma cells.

After this single cycle of chemotherapy, a repeat serum electrophoresis one month later signaled an excellent response, with the monoclonal spike declining to 1.21 g/L. Unfortunately, the patient, who was reluctant to accept medical care failed to maintain follow-up for approximately 7 months. When he did return to hematology clinic, his monoclonal spike was found to be 1.6 g/L. Because of the relative stability of the monoclonal spike and his poor compliance, he was followed expectantly for evidence of progressive myeloma, and was restarted on pamidronate.

Two months later, he was called to present for admission after it was noted that his hematocrit had dropped from 30% to 23%, without overt bleeding symptoms. His CD4 cell count was > 50/cmm. During this final month-long

hospitalization, he had a precipitous decline. Shortly after admission, he began to have fevers to 102˚F and severe epistaxis. Broad-spectrum antibiotics were begun. There was also a marked decline in platelet count to < 20,000/cmm, later attributed to consumption and poor production related to underlying multiple myeloma. Extensive fever evaluation, including numerous blood and urine cultures, CSF examination for bacteria or fungus, sputum analysis, chest x-ray, purified protein derivative (PPD) all remained negative. There was also no serologic evidence of disseminated intravascular coagulopathy (DIC) to explain his rapid decline in platelets. PSA was again < 0.1. The epistaxis was initially treated with nasal packing. His bleeding time (which was performed when the platelet count was 114,000/cmm) was markedly prolonged at 28 minutes, which corrected to 8 minutes with desmopressin (DDAVP). The serum LDH level was 869 U/L.

Serum protein electrophoresis later revealed his monoclonal band to have increased to 4.05 g/L. Repeat bone marrow examination was remarkable for nearly complete replacement of normal elements with essentially 100% plasma cells, some with blastic appearance, some monstrously large with 6 to 8 nuclei, looking almost like megakaryocytes. Unusual for myeloma, several mitotic figures were seen, indicative of the aggressive nature of the patient's accelerating disease.

His fevers, anemia, prolonged bleeding time (even in the setting of near-normal platelet number) and general decline were attributed to the progressive myeloma, which was treated again with a cycle of melphalan and prednisone.

The epistaxis proved difficult to treat. During his last four weeks, he received 20 units of packed red blood cells, 18 units of random-donor and 9 units of single-donor platelets, and 6 units of fresh frozen plasma. DDAVP was administered on three occasions; high-dose estrogen was given for 5 days and he was also placed on Amicar. At times his bleeding stopped. Ear, nose and throat examination and sinus CT scan revealed no discreet lesion.

In his last days, he became more tachypneic and produced frothy pink sputum. Pulmonary hemorrhage was suspected by chest x-ray, but unproven. His mental status declined and he died. Per his request, no cardiopulmonary resuscitative efforts were initiated. No autopsy was performed.

DISCUSSION

Although multiple myeloma is of rare occurrence in HIV-infected individuals, bone marrow plasmacytosis is a relatively common finding in such patients, especially who manifest polyclonal hypergammaglobulinemia.[1,2] In asymptomatic HIV-infected individuals, monoclonal gammopathy is also noticed at a higher incidence 2.5% as compared to 0.15% in the general population.[43] The relative significance of monoclonal gammopathy in the natural history of HIV infection is not clear at present.

Almost fifty cases of patients with HIV infection complicated by plasma cell dyscrasias have been reported in the literature.[5-42] Our patient is another case who developed an aggressive course which paralleled the progression of AIDS as manifested by increase in plasma cells and CD4 cell counts. Immunosuppression (evidenced by decreased CD4 cell counts) appears to be related to a poorer outcome in AIDS patients complicated by multiple myeloma. The diagnosis of multiple myeloma can be difficult to ascertain in an AIDS patient secondary to renal failure (HIV-related nephropathy, drugs, infections), anemia (HIV-related, infections or drugs), thrombocytopenia (HIV-related), and bone marrow plasmacytosis are

often encountered in these patients. Therefore, it has been suggested to consider a strict criteria of considering the presence of lytic bone lesions, hypercalcemia, or documented monoclonal plasma cell expansion to support the diagnosis of multiple myeloma in this population.[2] The average age of presentation among HIV-infected patients with plasma cell disorders is 33 years, far younger than the average age of presentation in the general population.[2] It has also been observed that there is a marginally higher post-AIDS incidence (RR 4.5 [95% CI 0.9 – 13.2]).[1] The risk ratio of multiple myeloma increases significantly from zero in early pre-AIDS to 1.3 fold in post-AIDS, as described by Goedert et al.[1] He also reported that majority of these cases (10/16) contacted HIV infection through anal sex.[1]

The pathogenesis of multiple myeloma in HIV-infected patients is probably similar to that described in other B-cell neoplasms such as B-cell lymphomas. Such pathobiological mechanisms may include: altered immuno-regulation, nonspecific antigenic stimulation, and disregulation of cytokines which could lead to the development of B-cell neoplasms in patients, such as AIDS with predominant helper-T cell defect.[2] Konrad et al[18] reported a case of an HIV-infected patient with multiple myeloma and found that the paraprotein was specifically directed against HIV-1 p24 antigen. This finding suggests the existence of "a casual relationship between antigenic stimulation and myeloma" in HIV-infected patients. Furthermore, Voelkerding et al[41] revealed the presence of Epstein-Barr virus genomes in tumor tissue but not in non-tumor tissue of one of such patients with multiple myeloma leading to the hypothesis that HIV-mediated immunity may result in emergence of EBV-infected B clones. In particular, a second oncogenic event, possibly a c-myc oncogene expression, may contribute to malignant transformation.[2]

It has been long ago known that IL-6 is a growth factor for plasma cells including those in multiple myeloma.[44] IL-6 is generally secreted by stroma cells of the bone marrow and act in a paracrine fashion to stimulate growth of neoplastic plasma cells and prevent apoptosis of these cells. It reveals that these stroma cells play an important role in mediating the paracrine stimulation of myeloid cell growth. The discovery of human herpesvirus-8 (HHV-8) and its ability to produce large amounts of potent vIL-6 prompted several investigators to investigate the potential role in bone marrow plasma cell dyscrasias. To date, several studies have been conducted to address the potential role of HHV-8 in the etiology and pathogenesis of multiple myeloma and produced somewhat controversial results. Burger R et al[45] found that vIL-6 support the growth of multiple myeloma cells that undergo apoptosis in the absence of IL-6 in tissue culture. The reason for this controversy may be multifactorial: lack of epidemiological link between Kaposi's sarcoma to multiple myeloma; similar prevalence of antibodies to HHV-8 latent nuclear antigen in patients with multiple myeloma and in general population as opposed to Kaposi's sarcoma where patients have higher titers;[46] failure of PCR to detect HHV-8 in bone marrow aspirates from patients with multiple myeloma; and finally functional dendritic cells obtained with apheresis from patients with multiple myeloma failed to harbor PCR-detectable HHV-8 DNA.[47-49]

In 1996, Rettig et al[50] reported that HHV-8 could be detected in bone marrow dendritic cells, but not in malignant cells, of patients with multiple myeloma and HIV infection. In order to rule out the possibility of a cell culturing artefact, the study was reproduced on fresh bone marrow core biopsies in which dendritic

cells in 17 of 20 multiple myeloma patients confirmed to be HHV-8 positive.[51] Based on the available positive data, it has been postulated that infection of bone marrow dendritic (stroma) cells by HHV-8 may stimulate the runaway growth of malignant plasma cells "by remote control".[52,53] In other words, the HHV-8 infection of these dendritic cells probably eliminates the last existing physiological checkpoint on the control of the growth of the malignant plasma cells. Unfortunately, currently available molecular and serological methods to detect HHV-8 infection are not very reliable.[54,55] Another reason for conflicting data may arise from the variability of the virus itself (mutations). In a nut shell, though the available data is insufficient to establish an unequivocally valid model of multiple myeloma pathogenesis linked with HHV-8, the role of HHV-8 as a causative agent in multiple myeloma needs to be further explored and it may pose a bigger challenge in HIV-infected individuals.

Review of the medical literature and the case reports also revealed that elevated serum LDH in AIDS patients with multiple myeloma is related to severe clinical course and a poorer outcome.[56] Immunosuppression as evidenced by decreased CD4 cell counts also appear to be related to a poorer outcome in AIDS patients complicated by multiple myeloma. A prospective study aiming at the HIV specificity of paraprotein in AIDS patients, incidence of monoclonal gammopathy of unknown significance (MGUS) leading to multiple myeloma, incidence of multiple myeloma itself in such patients with a long term clinical follow-up and plasma cell malignancy screening may help to address this issue.

CONCLUSION

Multiple myeloma is a very uncommon neoplasm complicating HIV infection but when it occurs, it is associated with an aggressive course and a worse prognosis. Multiple myeloma can accelerate progression of HIV infection. Elevated serum LDH level is related to a poorer outcome in AIDS patients. The occurrence of multiple myeloma in these patients probably underlines the possible role of EBV, HHV-8, and HIV in the pathogenesis. One could postulate that it may present another manifestation of aggressive B-cell neoplasms in HIV-infected patients that should be considered in the differential diagnosis of B-cell neoplasms complicating HIV infection. Specific stains should be employed to aid the diagnosis. If more cases of multiple myeloma continue to be reported in AIDS patients, then multiple myeloma may be added to the spectrum of B-cell neoplasia associated with HIV infection. A prospective study to better evaluated the incidence and association between these two diseases is necessary.

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