Elevated Granulocyte Colony-Stimulating Factor, Non-Infectious Leukocytosis and Fevers in a Patient with Multiple Myeloma

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Background: We report the case of a 56-year-old male with multiple myeloma in whom recurrent fevers and leukocytosis delayed potentially effective chemotherapy due to concern for active infection. Design and measurements: A thorough infectious workup, including CT and PET scans, was negative. The patient was eventually found to have an elevated serum granulocyte colony-stimulating factor (G-CSF) of 113 pg/ml (normal range 0.0 – 39.1 pg/ml), which was likely the cause of his persistent leukocytosis and fevers. Multiagent chemotherapy was initiated, and the fevers resolved in the next 4 days. Results: Leukocyte concentrations trended down after initiation of chemotherapy, but it is uncertain how much of the decline was attributable to immunosuppression. Conclusion: We report this well-documented case to demonstrate that G-CSF production should be considered as a cause of unexplained fever and leukocytosis in patients with multiple myeloma to prevent inappropriate and delayed definitive diagnosis and treatment.

KEY WORDS: multiple myeloma; granulocyte colony-stimulating factor; fever; leukocytosis.
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INTRODUCTION

We describe a case of a patient with multiple myeloma in whom persistent fevers and leukocytosis delayed potentially effective chemotherapy because of concerns for active infection. Eventually, an increased granulocyte colony-stimulating factor (G-CSF) concentration was discovered that was likely the cause of his fevers and leukocytosis. We present this case to illustrate an uncommon, but easily diagnosed complication of multiple myeloma with important clinical implications.

CASE REPORT

A 56-year-old male presented with acute renal failure in March 2007. He was diagnosed with stage IIIB IgG-kappa multiple myeloma and end-stage renal disease secondary to kappa light chain cast nephropathy. Bone marrow biopsy at diagnosis revealed 40% plasma cells, and there were no lytic lesions identified on bone survey. He was treated initially with dexamethasone, but had only a minimal response. His white blood cell count was elevated to 22,600/mcl in April 2007 and temperatures peaked at 37.3° C. Elevations in white blood cell count did not correlate with administration of oral dexamethasone. In May, he presented with clinical and radiographic evidence of bilateral upper lobe pneumonia and a cavitary lesion in the left upper lobe thought to be consistent with an infected emphysematous bleb. His leukocyte concentration was 33,400/mcl and temperatures peaked at 39.7° C. The patient underwent treatment with a prolonged course of moxifloxacin and clindamycin, and subsequent lung CT scans showed that the infiltrates resolved, but the bleb remained. However, leukocyte count and temperatures remained elevated despite successful treatment of pneumonia, and chemotherapy was delayed until August when bortezomib was given. Unfortunately, only two courses of bortezomib were completed before chemotherapy was again held due to persistent fevers and leukocytosis. Overall, the patient was admitted to the hospital seven times over 5 months for these concerns. Extensive investigations were performed during the 6 months from April to November, which included CT scans of the thorax, abdomen, and pelvis and multiple sets of blood, sputum, bone marrow, and urine cultures; none of these tests revealed an infectious source. Review of laboratory data during that time showed WBC count ranging from 9,000/mcl to 29,000/mcl with a left shift. The percentage of bands ranged from 10-38% with a mean value of 18.7% and a median value of 19%.

In November 2007 the patient was admitted to the hospital from the dialysis clinic for treatment of hypercalcemia. He again reported daily fevers of 38.9-39.4° C. Physical exam at the time of admission was unrevealing. Specifically, there was no lymphadenopathy, splenomegaly, or skin rashes or lesions. Peripheral blood smear was remarkable for toxic changes in neutrophils and monocytes and only occasional circulating malignant-appearing plasma cells. Bone marrow biopsy exhibited leukocytosis with left shift and prominent toxic changes, similar to previous specimens. Cytogenetics were normal (46 X,Y). The marrow had 35-50% involvement by atypical plasma cells, which was unchanged from the marrow involvement at diagnosis 7 months before. Serum protein electrophoresis was performed and showed stable monoclonal protein at 3.0 g/dl. Serum IgG was 3,570 g/dl; it had been 5,970 g/dl 8 weeks earlier. A transthoracic echocardiogram showed no vegetations. Serum B12 was 902.7 pg/ml (140-800 pg/ml). Hepatitis serologies as well as HIV, EBV, and CMV were negative. Antinuclear antibody (ANA) and anti-neutrophil cytoplasmic antibodies (cANCA and pANCA) were not detected. A repeat

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abdominal CT revealed a slight increase in retroperitoneal adenopathy. PET scan was obtained, which showed activity in only one node, which was felt to be most consistent with reactive changes or perhaps a plasmacytoma. There was no clear evidence of infection.

Serum specimens were tested for colony-stimulating factors to determine if one might be responsible for the persistent fevers and leukocytosis. Serum G-CSF was 113 pg/ml (normal range 0.0–39.1 pg/ml, measured by ELISA at University of Minnesota). Serum granulocyte macrophage colony-stimulating factor (GM-CSF) was normal (0.6 pg/ml with normal range of 0.0 – 7.8 pg/ml). Interleukin-6 (IL-6) level was elevated at 322.7 pg/ml (normal range <3 pg/ml), which was consistent with the known diagnosis of multiple myeloma. Based on these results and the lack of evidence for infection, the patient's leukocytosis and fevers were attributed to G-CSF-producing multiple myeloma. Multiagent chemotherapy was initiated with vincristine, adriamycin, and dexamethasone (VAD), and after 4 days body temperatures became normal. Leukocyte counts decreased after initiation of chemotherapy. The patient's quality of life due to multiple myeloma, end-stage renal disease, hemodialysis, and other medical problems had declined to the point that he decided to discontinue hemodialysis 3 weeks later and died within a few weeks.

DISCUSSION

Approximately 30 cases of plasma cell dyscrasias with persistent leukocytosis have been reported[1,2]. In 20 of these cases, neutrophilia has been attributed to chronic neutrophilic leukemia (CNL). The syndrome of CNL is characterized by persistent mature neutrophilia, toxic granulation and Döhle bodies, hepatosplenomegaly, elevated serum vitamin B12, hyperuricemia, and elevated neutrophil alkaline phosphatase. Basophilia, monocytosis, and the bcr-abl translocation are not present in chronic neutrophilic leukemia[1,2]. Fevers are usually not associated with CNL. Our patient had leukocytosis with toxic granulation and an increased serum B12 concentration. Bone marrow was examined, and the bcr-abl translocation was not detected. He did not have hepatosplenomegaly. Neutrophil alkaline phosphatase was not measured. Furthermore, there is evidence that G-CSF levels are decreased in some patients with CNL due to negative feedback[3]. Our patient's clinical presentation was therefore not consistent with a diagnosis of CNL.

In four of the reported cases of plasma cell dyscrasias, persistent leukocytosis has been attributed to increased serum concentrations of G-CSF[4–7]. In two cases, G-CSF protein was detected by immunohistochemical staining within atypical plasma cells[6,7]. In all cases, blood leukocyte levels declined after chemotherapy directed at plasma cell dyscrasias was given. In a fifth case, serum G-CSF was measured but not detected[8].

Non-infectious leukocytosis, fevers, and increased serum G-CSF concentrations in our patient appeared to be causally associated. Extensive observation and testing did not reveal another explanation. The fact that the G-CSF level was elevated while the GM-CSF level remained within normal range also supports our conclusion that the persistent leukocytosis was non-infectious in origin. The patient's fevers and leukocytosis remained unexplained for 5 months and delayed the administration of potentially effective chemotherapy. We believe that high-dose dexamethasone and bortezomib were not successful in controlling fevers and leukocytosis because neither agent definitively treated the underlying multiple myeloma as evidenced by a persistent degree of marrow involvement and the absence of a sustained response of the M-protein level. Body temperatures and leukocyte counts rapidly became normal after VAD chemotherapy for multiple myeloma. We attributed the resolution of fevers to the effect of chemotherapy on the underlying myeloma. The decrease in leukocyte counts might have been from the effect of chemotherapy on the myeloma, the myelosuppressive effects of chemotherapy on the bone marrow, or both.

We report this well-documented case to bring awareness to the fact that patients who present with non-infectious leukocytosis and fevers may receive inappropriate and delayed definitive diagnosis and treatment, such as the delay of potentially effective chemotherapy for multiple myeloma. The possibility that G-CSF can be produced by malignant plasma cells should be considered as a cause of unexplained fever and leukocytosis in patients with multiple myeloma.

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