

Multiple Myeloma with Eosinophilia and Eosinophilic Pleural Effusion

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Abstract

The association of multiple myeloma (MM) with eosinophilia and eosinophilic pleural effusion is rare. We present a 69 year old female with MM, who presented with progressive shortness of breath for 6 months. She had anemia and leukocytosis, with predominant eosinophilia. She was found to have pleural effusion which on further work up was exudative with predominant eosinophilia. Bone marrow biopsy, serum, and urine protein electrophoresis were consistent with IgG MM. Bone marrow flow cytometry revealed plasma cells and eosinophil predominant cell lineage. Concomitant eosinophilic leukemia was ruled out. Pulmonary manifestations in MM have been reported, but pleural effusion is infrequently seen. Eosinophilic predominant pleural effusion is unusual in cases of MM.

INTRODUCTION

Eosinophils are derived from multipotent lineage-committed hematopoietic stem cells. (1) Major growth factors for eosinophils include interleukin (IL)-3, IL-5, and granulocyte monocyte-colony stimulating factor (GM-CSF). These cytokines are produced by activated T lymphocytes, mast cells, and tissue stroma cells. (2) Peripheral eosinophilia can be familial or acquired, and acquired eosinophilia can be primary or secondary. Primary acquired eosinophilia is a clonal proliferation, whereas acquired secondary eosinophilia is a cytokine-driven reactive phenomenon. The causes of acquired secondary eosinophilia include infections (mostly helminthic), drugs (Penicillin, NSAIDs, aspirin, ranitidine, and sulfasalazine), autoimmune diseases, inflammation, endocrinopathies, and malignancies. (3, 4) The association between MM and eosinophilia is rare and in a previous report that asserted the association of MM with eosinophilia, a patient's pre therapy serum revealed immunoreactive interleukin-3 (IL-3) but the post therapy serum sample was negative. (5) Pleural effusion is uncommon in MM, (6, 7, and 8) and eosinophilic pleural effusion with MM is rare. (9, 10, 11) We present a case of IgG MM associated with peripheral eosinophilia and eosinophilic pleural effusion.

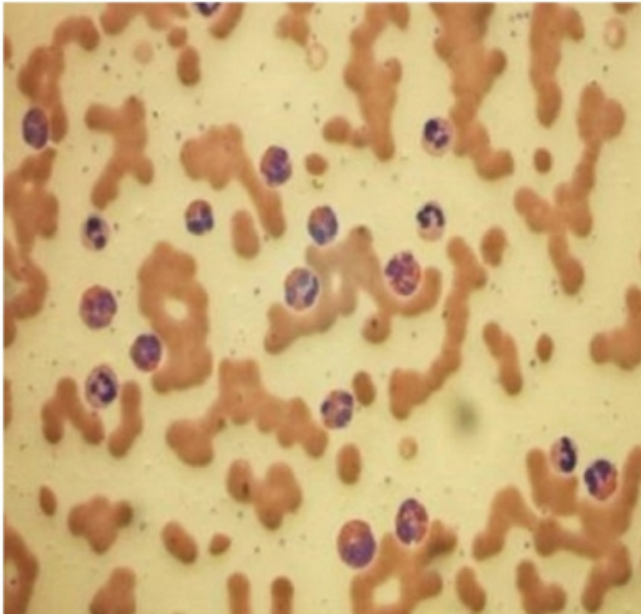
CASE REPORT

A 69 year old African American female presented to the emergency room with progressive shortness of breath for 6 months and constipation for 3 weeks. Her shortness of breath was initially only on exertion, gradually progressing over 6 months to orthopnea with paroxysmal nocturnal dyspnea. During this period she gained 22 kg and complained of generalized body swelling. She denied any fever, skin rash or allergic reactions. There was no recent travel history. She had a history of diabetes mellitus, hypertension and right hip fracture. Her home medications included enalapiril, losartan, insulin and simvastatin. There was no recent use of antibiotics, sulfa drugs, penicillins, NSAIDs, antihistamines, PPIs or gold salt. She had no known drug allergy. Family history was unremarkable, and she did not smoke or drink alcohol. She was a home maker and was independent for activities of daily living prior to the onset of symptoms. Physical examination revealed an obese, middle aged lady in no acute distress. She was afebrile and vitals were stable. There was anasarca and moderate pallor. Coarse breath sounds with diffuse rhonchi and decreased breath sounds at the lung bases were noted. Abdomen was soft and non-tender without organomegaly. Bilateral pitting edema up to the thighs was noted. No skin rashes were observed. Laboratory data revealed Hb 8.7g/dL (MCV 96.1), WBC 54.8 x103/uL, platelet count was 291 x103/uL. Differential WBC showed 69% eosinophil, (37.8 cells x103/uL), 26% neutrophils and 3.5% lymphocytes.

Peripheral blood smear revealed slight anisocytosis with predominant eosinophils (Fig.1).

Figure 1

Peripheral blood smear with predominant eosinophilia



No circulating myeloid precursors or left shifted neutrophils were seen on review of smear. Six months ago her Hb and WBC count were normal. Other laboratory data revealed creatinine of 0.67mg/dl and calcium of 8.0mg/dl. Chest X ray showed bibasilar infiltrates with bilateral pleural effusion. Beta Natriuretic Peptide (BNP) was 1824 pg/ml. She was treated with IV furosemide for congestive heart failure and acute coronary syndrome was ruled out. Echocardiogram showed normal left ventricular systolic function with right ventricular systolic pressures of 48 mm Hg (normal <15 mm Hg). Despite aggressive use of diuretics, shortness of breath did not improve and the WBC count remained high (40-50 x10³/uL). Additional tests showed ESR of 109 mm / hr and LDH 240 U/L. Our diagnostic evaluation of peripheral eosinophilia included a stool specimen negative for parasitic infection. Thick and thin blood smears were reviewed and no parasites were seen. Anti neutrophilic antibodies (ANA) and antidouble stranded DNA antibodies, HIV, Hepatitis B and C serology, all were negative. Solid tumor markers to rule out other neoplastic processes, Ca19-9, Carcinoembryonic Antigen (CEA), Ca-125 levels were all within normal limits. CT scan of chest, abdomen and pelvis showed bilateral pleural effusions and hepatic vascular congestion, with moderate splenomegaly (Fig. 2).

Figure 2

CT scan of chest showing bilateral pleural effusion



Abnormal lytic process was identified in the right iliac bone and sternum on CT scan of the chest, abdomen and pelvis. The possibility of MM with lytic lesions and anemia was considered. Serum electrophoresis showed total protein 9.2 g/dl, albumin 2.5g/dl, beta globulin 0.75g/dl, gamma globulin 5.1 g/dl with monoclonal spike 4.1 g/dl. Urine electrophoresis revealed total protein of 1091 mg/l with three monoclonal protein bands with concentrations of 156mg/L (14.3%), 96mg/L (8.8%) and 14.2 mg/L (1.3%). Serum quantitative immunofixation revealed high level of IgG 9099 mg/dL with normal IgM (28 mg/dL) and IgA (140 mg/dL) levels. Bone marrow aspiration and biopsy showed hypercellular marrow with high levels of plasma cells (15-25%) and eosinophils(18%). No myeloid precursors were identified. (Fig. 3) Immunohistochemical stains showed 25% CD138+ plasma cells with cytoplasmic kappa light chain restriction (Fig. 4).

Figure 3

Bone marrow aspirate with abundant eosinophils (400x)

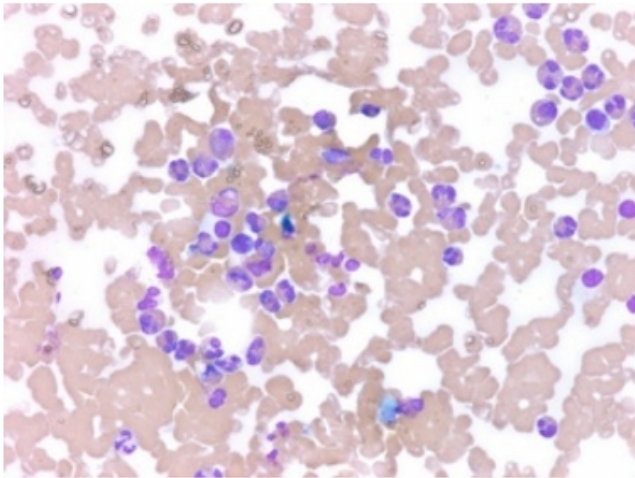
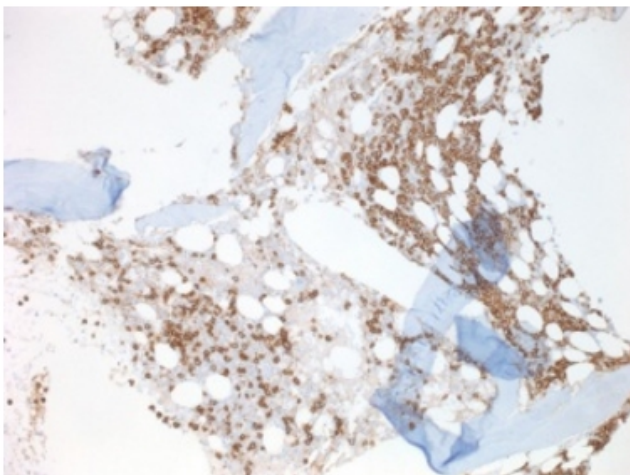


Figure 4

Bone marrow core biopsy, showing CD138+ plasma cell infiltrate (100x)



Bone marrow chromosomal study reported genotype of 46 XX with negative FISH analysis for platelet derived growth factor receptor (PDGFR) and BCR-ABL. Thus eosinophilic leukemia was ruled out. Flow cytometry results showed markedly increased CD10- and CD16 - eosinophils with CD138 + and CD38 + plasma cells. Pleural fluid analysis was consistent with an exudate (Pleural fluid LDH 880 and serum LDH 201), with WBC 820 cells/ μ L and 32% eosinophils (262cells/ μ L). No malignant or plasma cells were identified. She was diagnosed with MM, associated peripheral eosinophilia, and presumed pleural and pulmonary infiltration with eosinophils. She was offered induction therapy with lenalidomide plus dexamethasone, but she refused treatment and passed away after 4 months.

DISCUSSION

MM is a B cell lymphoid neoplasm, defined as a malignant proliferation of plasma cells. The median age of diagnosis of MM is 60-65 years. (12) According to International Myeloma Working Group the diagnosis of MM requires the fulfillment of the following criterion: (a) clonal bone marrow plasma cells \geq 10 percent or biopsy-proven bony or soft tissue plasmacytoma, (b) presence of related organ or tissue impairment– End organ damage is suggested by increased plasma calcium level, renal insufficiency, anemia, and bone lesions. (c) Presence of a biomarker associated with near inevitable progression to end-organ damage – \geq 60 percent clonal plasma cells in the bone marrow; involved/uninvolved free light chain (FLC) ratio of 100 or more, or MRI with more than one focal lesion (involving bone or bone marrow). (13) Our patient had bone marrow plasma cells around 25%, anemia and lytic lesion in right iliac and sternal areas thus diagnosis of MM was made. Although peripheral eosinophilia has been associated with a wide variety of solid (14, 15) and lymphoid tumors, (2, 3, 14, 15) association with MM is rare. (5) The exact etiology of peripheral eosinophilia in MM is unknown. It is identified that eosinophils and megakaryocytes are the functional components of the micro-environment of the bone marrow and are important sources of the cytokines responsible for plasma cell proliferation. In vitro studies on bone marrow micro environment have suggested that bone marrow stromal cells induce plasma cell proliferation via release of cytokines, predominantly IL-6 and A Proliferation-Inducing Ligand (APRIL). Neoplastic cells secrete IL-3 and IL-5, which may play a role in recruiting eosinophils. Eosinophils stimulate growth of plasma cells via a cytokine independent mechanism. Davind Wong and group conducted an experiment on murine bone marrow to identify the role of eosinophils and megakaryocytes to support the growth of tumor plasma cells. In the study they also identified that myeloma growth in early stages was retarded in eosinophil-deficient mice. Whether eosinophils represent the most important cells in the bone marrow supporting myeloma growth needs to be further explored. Bone marrow biopsies from normal donor and patients in different stages of monoclonal gammopathies demonstrated an increase in the percentage of eosinophils with disease progression.(16, 17) Pleural effusion is uncommon in multiple myeloma, and occurs in approximately 6% cases.(10) Most of these are not directly due to myelomatous infiltration of the lung or pleura, but related to pathologies such as pulmonary embolus, heart failure and nephrotic

syndrome. Several probable mechanisms have been postulated for myelomatous pleural effusion: invasion from adjacent skeletal lesions, extension from chest wall plasmacytomas, tumor infiltration of pleura and mediastinal lymph node involvement causing lymphatic obstruction. (10) Pleural fluid eosinophilia is defined as pleural fluid with a nucleated cell count of greater than 10 % eosinophils. The most common causes of eosinophilic pleural effusions are pneumothorax, hemothorax, malignancy, and infection. (18) Amongst malignancies, lung cancer is the most common. (19) Pleural effusion directly due to myeloma is said to occur in less than 1-2% of cases, with approximately 80% of cases reported in IgA MM. (20) Our patient had IgG MM, with eosinophilia and eosinophilic pleural effusion, and such a constellation has only been reported in a single case report. (9) The main therapy for plasma cell disorders are melphalan, lenalidomide, bortezomib, vincristine, adriamycin, cyclophosphamide and dexamethasone. (16) The most effective regimen for the treatment of MM patients with peripheral eosinophilia and pleural fluid eosinophilia is yet to be established.

CONCLUSION

Peripheral eosinophilia associated with solid organ and hematological malignancy has been rarely reported in association with MM. Eosinophilic infiltration in various organs in association with plasma cell myeloma has been described. Eosinophilic pleural effusion can be the first presenting sign of MM as occurred in our case and in previous cases. (9, 10, 11) Our patient had the rare combination of IgG MM with eosinophilia and eosinophilic pleural effusion. Newer treatment modalities could be offered if exact mechanisms of the disease process are known.

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