Pneumocystis carinii Pneumonia Complicating Multiple Myeloma*

R. Scott McKenzie, M.D.;† Luther D. Glenn, M.D.; and Jonathan C. Goldsmith, M.D.

Pneumocystis carinii pneumonia complicated the course of two patients with multiple myeloma. The diagnosis was established in both cases by bronchoalveolar lavage, which demonstrated the typical pneumocysts. Clinical and roentgenographic improvement in both patients was observed following a course of trimethoprim-sulfamethoxazole. One patient had lymphocyte subsets performed with a CD4/CD8 ratio of 0.8; both patients were HIV antibody-negative by ELISA. Both patients tolerated prophylactic TMP-SMX given concurrently with the subsequent chemotherapy for myeloma. We suggest that the immune defect seen in multiple myeloma may have placed these patients at risk for opportunistic infections such as P carinii pneumonia; however, as opposed to patients with AIDS, our patients tolerated therapy with TMP-SMX quite well. (Chest 1991; 99:656-59)

Multiple myeloma is frequently complicated by infection which causes significant morbidity and mortality. Postmortem examinations reveal 85 percent of myeloma patients have some evidence of infection, and nearly 70 percent die as a result of infection. The majority of infections arise from the respiratory and urinary tracts, frequently resulting in bacteremia or sepsis. Impaired (nonparaprotein) immunoglobulin synthesis predisposes myeloma patients to infection with polysaccharide-encapsulated organisms, particularly Streptococcus pneumoniae. Over the past two decades, Gram-negative bacilli and Staphylococcus aureus have emerged as important pathogens due to increased hospitalization, instrumentation, and cytotoxic therapy during the course of myeloma. Viral and protozoal infections are rarely included in reports of organisms causing disease in myeloma patients.

In normal hosts, P carinii does not cause clinically apparent infection; however, exposure is common. Serologic observations in healthy adults demonstrate 100 percent seroconversion. Clinically active infection appears in patients who are congenitally immunodeficient or become immunosuppressed. The former group includes severe combined immunodeficiency, x-linked agammaglobulinemia, and common variable immunodeficiency. More frequently, acquired alterations of the immunologic system due to neoplasia, cytotoxic therapy, or viral infections predispose to P carinii pneumonia. Acute and chronic lymphocytic leukemia, Hodgkin's disease, and non-Hodgkin's lymphoma are the most frequently associated neoplasms. Immunosuppressive therapy (cytotoxic agents and corticosteroids), particularly following organ transplantation, has been complicated by PCP. Human immunodeficiency virus (HIV-1; HTLV-III/LAV) infection has led to a significant increase in incidence of PCP, stimulating new insights into pathogenesis and therapeutic intervention.

The diagnosis and successful management of PCP complicating multiple myeloma has been previously undocumented. This report details two cases of PCP diagnosed by bronchoalveolar lavage and successfully treated with trimethoprim-sulfamethoxazole.

Case Report

Case 1
A 45-year-old white man presented with back pain in March 1985 and was subsequently diagnosed with IgA-lambda multiple myeloma, stage III. Therapy was initiated with melphalan and prednisone. In May 1985, his chemotherapeutic regimen was changed to vincristine, cyclophosphamide, melphalan, and prednisone. In June 1986, he presented with nonproductive cough, chills, and renal insufficiency prompting hospitalization. Medications included propranolol for hypertension and ibuprofen for back pain. He reported a 30-year smoking history, but no history of symptomatic long-term obstructive lung disease.

He was afebrile. Inspiratory rhonchi were heard over the left posterior base.

White blood cell count was 7,600/cu mm with a normal differential; hemoglobin value was 9.3 g/dl; and platelet count was 113,000/cu mm. Creatinine level was 3.4 mg/dl (n = 0.6-1.1). Arterial blood gas values on room air were pH of 7.46; PCO2, 33 mm Hg; and PO2, 67 mm Hg. Quantitative immunoglobulins were as follows: IgG, 196 mg/dl; IgA, 5,470 mg/dl; and IgM, 15 mg/dl. Serum viscosity was 2.5 centipoise. The HIV antibody was negative by ELISA method on two occasions. Chest x-ray film showed lingular consolidation and diffuse interstitial thickening (Fig 1).

Bronchoscopy with bronchoalveolar lavage demonstrated mild tracheobronchitis and thin purulent sputum in the lingula and left lower lobe. Alveolar fluid revealed 80 percent of nucleated cells to be polymorphonuclear leukocytes and numerous cysts of P carinii.
were seen on Gomori stain. Silver stain was negative for fungus, and cultures were negative for cytomegalovirus, fungus, and Mycobacterium species. TMP-SMX was administered intravenously (5 mg/kg trimethoprim component every 6 h). Because of hyperviscosity, apheresis was performed with 60 percent exchange accomplished on two consecutive days. After three days of intravenous administration of antibiotics, oral TMP-SMX (2 mg/kg trimethoprim component bid) was administered to complete a 21-day course, with roentgenographic improvement during this period.

The patient was placed on a regimen of prophylactic TMP-SMX (2 mg/kg trimethoprim component every day) which was tolerated without adverse effects until he died of refractory myeloma and renal failure 13 months after the episode of PCP.

CASE 2

A 63-year-old white man presented with fevers and cough in October 1987, and a right lower lobe pneumonia was noted on chest x-ray film. Fiberoptic bronchoscopy revealed no endobronchial lesions, and bronchial washings were negative for neoplasia or infection. He responded to intravenous cefalosporins. He was noted to have an anemia and was referred for evaluation. Subsequent work-up revealed IgG-kappa multiple myeloma, stage III. The patient received a transfusion and was started on a regimen of melphalan and prednisone. After two cycles of chemotherapy, a painful lytic lesion developed in the lumbosacral spine, and a course of radiotherapy was given to this region. After completion of radiotherapy, the patient was started on a regimen of cyclophosphamide, vincristine, melphalan, and prednisone. He had been transfusion-dependent since the time of diagnosis.

Three weeks after receiving chemotherapy, he presented with increasing lethargy, nausea, vomiting, and shortness of breath with scant clear sputum production. Physical examination revealed coarse rales in the right lung base. Complete blood count revealed a white blood cell count of 1,600/cu mm with 74 percent neutrophils, 13 percent band forms and 13 percent lymphocytes. Hemoglobin value was 10.5 g/dl, and a platelet count was 39,000/cu mm. Serum creatinine value was 1.9 mg/dl. Quantitative immunoglobulins were as follow: IgG, 8.480 mg/dl; IgA, 8 mg/dl; and IgM, 3 mg/dl. Arterial blood gas values on room air revealed a pH of 7.49; PO2, 29 mm Hg; and PO2, 43 mm Hg, and a chest x-ray film showed a diffuse interstitial pneumonitis (Fig 2).

The patient underwent bronchoscopy which revealed hemorrhagic mucosa, and cytospins performed on the bronchoalveolar lavage specimens stained with Gomori-methenamine silver revealed cysts of P carinii. The patient received a 14-day course of TMP-SMX (5 mg/kg trimethoprim component IV every 6 h), during which time there was a dramatic improvement in his symptoms, chest x-ray film, and arterial blood gas values. Lymphocyte surface markers revealed a CD4/CD8 of 0.8, while HIV antibody by ELISA was negative. The patient is currently receiving chemotherapy and TMP-SMX prophylaxis (2 mg/kg trimethoprim component orally daily) three months following this episode with no further signs of opportunistic infections.

**DISCUSSION**

These cases illustrate antemortem diagnosis and successful therapy of PCP complicating multiple myeloma. Roentgenographic findings and identification of alveolitis with cysts of P carinii at bronchoalveolar lavage provided rapid diagnosis. Both patients achieved clinical and roentgenographic improvement using TMP-SMX. No adverse reactions, including rash, fever, leukopenia, or thrombocytopenia, were detected. Prophylactic use of TMP-SMX prevented recurrence of PCP during subsequent cytotoxic chemotherapy.

The occurrence of PCP complicating multiple myeloma is extremely rare. Four case reports have described fulminating pneumonia in myeloma patients in which autopsy examination revealed P carinii. In all cases, the diagnosis was made as an unsuspected postmortem finding. 15-17 Multiple reviews describing the patterns of infection with myeloma have stressed the importance of bacterial pathogens. 18,19 Viral and protozoal infections are essentially absent from these series.

The diagnosis of PCP depends on a high index of

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**FIGURE 1.** Chest x-ray film of patient 1 on admission revealing lingular consolidation and diffuse interstitial thickening.

**FIGURE 2.** Chest x-ray film of patient 2 on admission showing diffuse interstitial infiltrates.
clinical suspicion and identification of cysts and trophozoites by Comori methenamine-silver and Giemsa stain, respectively. In the past, diagnostic lung sampling involved open lung biopsy, endobronchial biopsy, or percutaneous needle aspirations biopsy. The morbidity and variable yield of these procedures prompted investigation of bronchoalveolar lavage in the diagnosis of PCP. This method allows evaluation of alveolar contents without the risks of invasive surgical procedures. The histopathologic features of PCP are alveoli filled by proteinaceous exudates surrounding cysts and trophozoites of Pneumocystis. Recently, bronchoalveolar lavage has been shown to be 90 percent sensitive in AIDS-related PCP and 85 percent sensitive in the diagnosis of PCP in immunocompromised hosts (bone marrow transplant or immunosuppressive drug therapy).

The occurrence of PCP in the patients in this report was unexpected. Predisposition to PCP has been associated with abnormal cell-mediated immunity; however, multiple myeloma is characterized by impairment of humoral immunity. Both patients received prednisone. Corticosteroid-induced changes may have attenuated their cell-mediated immunity; however, this is somewhat unlikely as prednisone had not been administered for over two weeks prior to presentation of symptoms and had never been given on a continuous basis. Exogenous immunosuppression due to human immunodeficiency virus was excluded by serologic testing on both patients. Neither patient had received blood transfusions prior to May 1985 and had no other known risk factors for contracting the virus.

The nature of the immune defect in multiple myeloma has not been completely elucidated. Plasmacytoma-bearing mice and patients with multiple myeloma demonstrate decreased antibody response to immunization with both T-independent and T-dependent antigens, suggesting that the immune suppression is not primarily T-cell mediated. Nevertheless, several groups have shown that patients with myeloma have increased numbers of T-cells with membrane-bound Fc receptors which are specific for the myeloma paraprotein isotope; these cells suppress pokeweed mitogen-induced immunoglobulin secretion and may contribute to the immune deficiency seen in myeloma patients. Oken and Kay have demonstrated depletion of Tu cells in myeloma patients. In untreated patients, T4+ (CD4) cells, representing T helper cells, have been shown to be reduced in three studies and within normal limits in a fourth, while T8+ (CD8) cells, representing T suppressor cells, were shown to be normal in three studies and increased in only one study. Only one of these studies demonstrated a significantly decreased CD4/CD8 (helper to suppressor) ratio in previously untreated patients.

The recognition of PCP in myeloma patients relies primarily on a high index of suspicion as no classical presentation exists. It is unclear which patients with myeloma might be at risk for the development of PCP; however, other patients who develop PCP have profound abnormalities of cell-mediated immunity, as was demonstrated in one of our patients. In addition, both of our patients developed PCP shortly after vincristine and cyclophosphamide were added to their therapeutic regimens.

The progression or failure of clinical improvement of a pneumonia in a patient with multiple myeloma who is on adequate antibiotic coverage should alert the physician to the possibility of PCP. The diagnosis is easily made by sputum examination or bronchoalveolar lavage, and treatment of our patients with TMP-SMX was effective and well tolerated. Consideration should also be given to prophylaxis with TMP-SMX in patients with myeloma as they undergo increasingly vigorous induction regimens and bone marrow transplant-supported ablative therapies.

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