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Pomalidomide-Induced Pulmonary Toxicity in Multiple Myeloma

Pomalidomide is a 3rd generation immunomodulatory agent (Imid) used for the management of multiple myeloma refractory to both lenalidomide and bortezomib.[1] Pomalidomide-induced pulmonary toxicity is extremely rare. Patients usually present with nonspecific symptoms mimicking pneumonia and respiratory failure. There have been only 2 previous reports of acute lung toxicity related to pomalidomide.[2] Because this drug is being increasingly used in multiple myeloma, it is very important to recognize this yet unknown severe adverse reaction in timely manner to avoid significant morbidity in patients. In this article, the authors report an additional case of pomalidomide-induced pulmonary toxicity based on temporal relationship between drug administration and onset of symptoms as well as characteristic imaging findings. This side effect is new and undiscovered, and additional studies are needed to recognize this entity earlier in disease course.

A 69-year-old man with a 9-year history of IgG kappa Multiple Myeloma (MM) presented with progressive dyspnea and productive cough for 5 days. The patient had been initiated on pomalidomide 8 months before presentation. He had received multiple lines of therapy since the time of diagnosis. Initially, he received bortezomib, liposomal doxorubicin, and dexamethasone with good response. Then, he developed disease relapse 10 months later and was started on lenalidomide and dexamethasone. This treatment was complicated by multiple infections. The therapy was placed on hold before resuming it again 6 months later with rise in serum M protein. Three months later, with further rise in M protein, cyclophosphamide was added to the regimen, He achieved partial response and subsequently underwent autologous stem cell transplant with high-dose melphalan conditioning. He remained off therapy for about a year when he was initiated on bortezomib, bendamustine, and dexamethasone with disease relapse; however, he had to be switched to lenalidomide, bortezomib, and dexamethasone after a brief duration because of minimal response to prior regimen. He responded partially to the latter regimen. Subsequently, dexamethasone was stopped, and lenalidomide and bortezomib maintenance was continued until 8 months before current presentation when he again developed relapse. Lenalidomide and bortezomib were discontinued, and he was initiated on pomalidomide 4 mg/d, days 1 through 21 with dexamethasone 20 mg once weekly.

Approximately 8 months after starting treatment with pomalidomide, the patient developed fever, progressive dyspnea, productive cough, and generalized weakness for 5 days duration before presenting to the hospital. On physical examination, temperature was 102.8°F, heart rate 100/min, and respiration 48/min saturating 77% on room temperature. The patient was in severe respiratory distress with lung examination showing poor chest expansion and diminished breath sounds in bilateral lung bases. A chest film showed right upper lobe and left parahilar infiltrates. Ventilation perfusion (V/Q) scan was low probability for pulmonary embolism. Laboratory studies were within normal limits including white blood cell count of 4.5 K/CUMM (reference range, 3.9–10.7 K/CUMM) with eosinophil count of 0.1K/CUMM. Sputum and blood cultures were unrevealing. The patient was empirically treated with broad spectrum antibiotics for community-acquired pneumonia and initially required noninvasive positive pressure ventilation to maintain appropriate oxygenation. Pomalidomide was held during this time to minimize immunosuppression during a severe infectious process. The patient had gradual improvement of his symptoms and was discharged after 7 days of hospitalization.

Within 4 weeks, the patient reinitiated pomalidomide, and 2 weeks after restarting the medication, he developed recurrent symptoms. On physical examination, the patient was again febrile, tachycardic, tachypneic, and hypoxic requiring supplemental oxygen. Lung examination revealed coarse breath sounds bilaterally. Laboratory abnormalities included a white blood cell count of 0.9 K/CUMM with an absolute neutrophil count of 0.3 K/CUMM (reference range, >1.5 K/CUMM), absolute eosinophil count of 9/CUMM, hemoglobin 8.5 g/dL (reference range, 14–17 g/dL), platelet count of 97 K/CUMM (reference range, 150–350 K/CUMM), and creatinine 1.8 mg/dL (reference range, 0.7–1.3 mg/dL). Additional studies showed (normal range in parenthesis) serum IgG 3180(700–1500 mg/dL), IgA 22(60–400 mg/dL), and IgM 25(60–300 mg/dL), free kappa light chain 10.36(3.3–19.4 mg/L), and free lambda light chain of 1.42(5.7–26.3 mg/L) with ratio of abnormal kappa to lambda light chains 7.30(0.26–1.65).

A high-resolution computerized tomography of the chest showed interstitial changes and bilateral upper lobe ground glass opacities (Figure 1). Given the concern for infectious etiology, multiple other studies were performed including urine pneumococcal and legionella antigens, influenza A and B PCR, respiratory syncytial virus (RSV) PCR, serum aspergillus antigen, serum cytomegalovirus (CMV) PCR, parvovirus B19 PCR, and serum beta D glucan, all of which were negative. Transthoracic echocardiography showed normal cardiac function. V/Q scan showed very low probability of pulmonary embolism. The patient was empirically started on broad spectrum antibiotics. Pomalidomide was again discontinued to minimize immunosuppression during a presumed active infectious process.

Fiberoptic bronchoscopy was performed, and bronchoalveolar lavage (BAL) was negative for CMV DFA, pneumocystis cariini stain, herpes simplex virus I and II, adenovirus, coronavirus, RSV, influenza, human metapneumovirus, rhinovirus, parainfluenza virus, chlamydia, mycoplasma, acid fast bacilli,

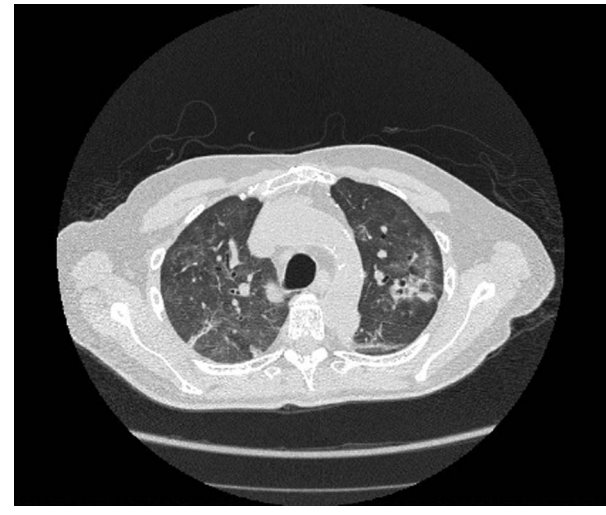

FIGURE 1. High-resolution computerized tomography of the chest showing ground glass opacities in bilateral lungs.

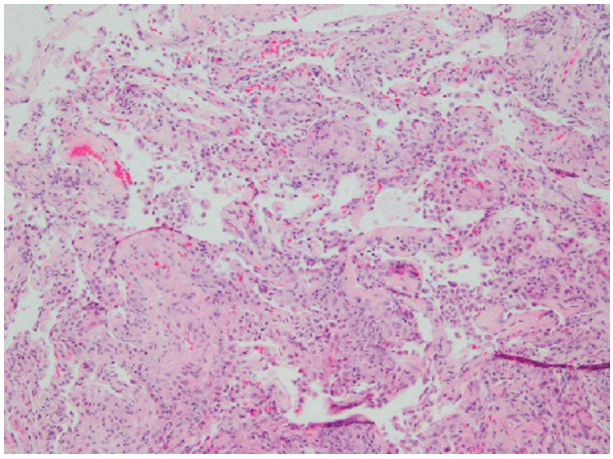

FIGURE 2. Lung biopsy (H&E stain) showing chronic interstitial inflammation with focal organizing pneumonia.

aspergillus fumigates, and legionella. The BAL cell count and differential were not performed. The lung tissue biopsy showed chronic interstitial pneumonia with a focal feature of organizing pneumonia (Figure 2). The patient again improved over 7 days and was discharged home with oral antibiotics. Pomalidomide, which was held during the acute illness, was resumed again in the outpatient setting.

One month later, the patient was admitted 3rd time for similar symptoms. Repeat CT scan of the chest again demonstrated bilateral ground glass opacities. The patient's recurrence and resolution of symptoms in a temporal relationship to therapy with pomalidomide, along with ground glass opacities on CT, led to a strong suspicion of pomalidomide-induced pulmonary toxicity. The patient was started on prednisone (1 mg/kg) resulting in a significant clinical improvement. Pomalidomide was discontinued permanently.

Pomalidomide is a 3rd generation immunomodulatory agent. Mechanism of action includes angiogenesis inhibition, immunomodulation, impeding cytokine production, and interaction with bone marrow and tumor microenvironment. Both pomalidomide and lenalidomide interfere with cell cycle and apoptosis. Pomalidomide is 100 times more potent than thalidomide and 10 times more potent than lenalidomide. Neutropenia (26%–66%), anemia(~17%), thrombocytopenia(~13%), and fatigue(~62%) are the most common side effects/complications of pomalidomide. Venous thromboembolism is also seen in up to 12% to 26% patients treated with IMiD/dexamethasone.[3,4]

Pulmonary toxicity is an uncommon but increasingly reported clinical complication of IMiD agents, particularly thalidomide and lenalidomide.[4–7] Pomalidomide-induced pulmonary toxicity is thus far extremely rare. In literature, only 2 such cases have been reported so far.[2] The mechanism of pulmonary toxicity is not clearly understood. Usual time interval between initiation of treatment to onset of symptoms is 8 to 120 days, but toxicity from pomalidomide may be delayed. The most common presenting symptoms of IMiD pulmonary toxicity are dyspnea, cough, fever, and hypoxia simulating pneumonia. Ground glass opacities are the most common radiologic findings. Reported BAL results have been variable, spanning lymphocytosis with elevated CD4:CD8 ratio to lymphocyte depletion with reverse CD4:CD8 ratio with or without eosinophilia.[2]

Diagnosis is often confused with infectious etiology, and the majority of patients receive empiric antibiotics without any apparent benefit. Temporal relationship of initiation of the drug and symptom onset is often the diagnostic clue. Pomalidomide-induced pulmonary toxicity is frequently a diagnosis of exclusion. Most patients improve with discontinuation of the drug. Methylprednisolone 1g/d for 3 days is the treatment of choice when symptoms are severe or do not resolve after discontinuation of the drug.[5]

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