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Acute Pulmonary Toxicity from Thalidomide in a Patient with Multiple Myeloma

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We report a case of acute pulmonary toxicity causing severe shortness of breath and hypoxemia from the use of thalidomide for treatment of multiple myeloma. It is known that thalidomide can increase the risk of thromboembolic events, such as deep venous thrombosis and pulmonary embolism, but there have only been two reported cases of thalidomide alone causing pulmonary toxicity. Our case is unusual in that our patient was on the thalidomide/dexamethasone protocol for multiple myeloma and demonstrated worsening and improvement of pulmonary opacities on computed tomography (CT) in relation to prolongation and withdrawal of thalidomide. Thalidomide induced pulmonary toxicity should be considered in multiple myeloma patients who present with acute shortness of breath.

Introduction

There are many factors which determine the drug combination a patient is prescribed when diagnosed with multiple myeloma. Some of these factors include the patient's age, level of abnormal serum proteins, abnormal metaphase cytogenetics, and whether or not a patient is a candidate for autologous stem cell transplant (1). Thalidomide is a chemotherapeutic drug that acts by inhibiting angiogenesis. It is used alone or in combination with dexamethasone to treat recurrent or resistant multiple myeloma. Thalidomide is an immunomodulator as well as anti-angiogenic, is a known teratogen, and can increase the risk of thromboembolic events, such as deep venous thrombosis (DVT) and pulmonary embolus (PE) (2). Although many other classes of chemotherapeutic drugs have been known to cause pulmonary disease, thalidomide as the inciting agent has been reported only once in the English literature (3) and twice in the world literature (4-5).

Case Report

A 63-year-old male presented to the emergency department with a two week history of fever and shortness of breath. He had a history of multiple myeloma, which was diagnosed two months prior to presentation. This diagnosis was confirmed by biopsy, showing a plasma cell clone with trisomy 11, tetrasomy 14, and IgH (Immunoglobulin Heavy) deletion. The patient had been on the thalidomide/dexamethasone protocol for three weeks before presenting to the emergency department. He took thalidomide, 200 mg per os (PO) daily. Dexamethasone 40 mg PO was taken for four days on, then four days off. A CT scan of the chest was performed demonstrating nonspecific scattered ground glass opacities (Figure 1). All CT imaging on this patient was performed on a Siemens Somatom Sensation 64 (Siemens Medical Solutions USA, Malvern, PA) using standard 2 mm slice thickness, without intravenous (IV) contrast.

Broad spectrum antibiotic therapy was initiated. A bronchoalveolar lavage showed no evidence of infection or neoplasm. There was no preponderance of lymphocytes or

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Abbreviations: CT, computed tomography, DVT, deep venous thrombosis, PE, pulmonary embolus, PO, per os, IV, intravenous, IgH, immunoglobulin heavy

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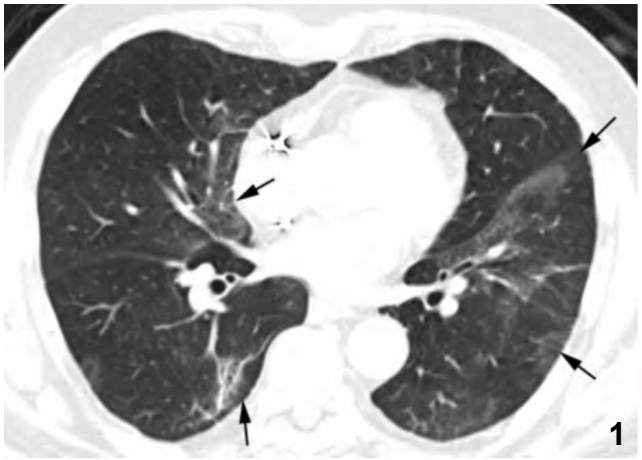
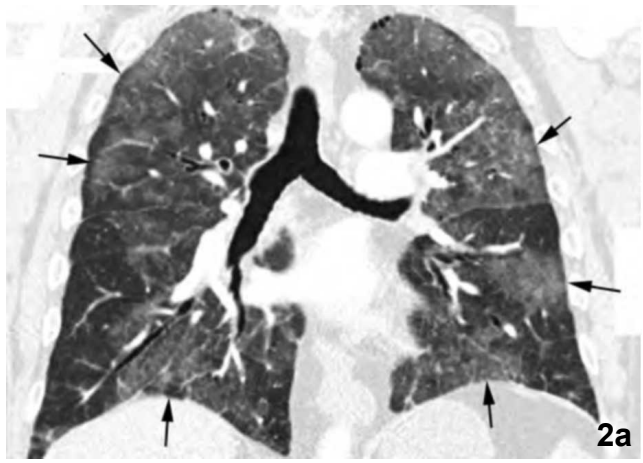


Figure 1. Axial CT demonstrating patchy, nonspecific ground glass opacities (arrows) in a patient who had started thalidomide therapy for multiple myeloma three weeks prior.



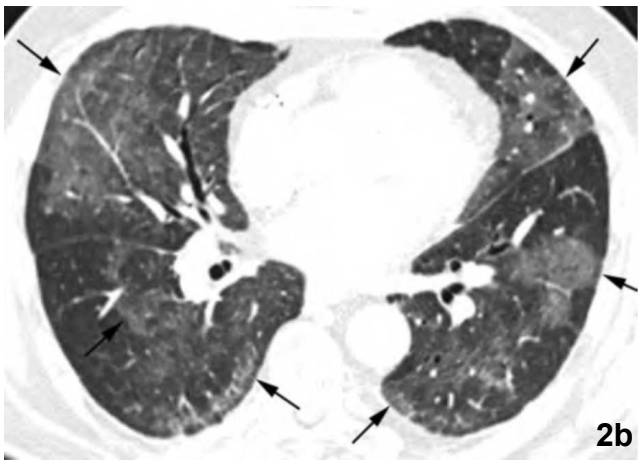


Figure 2. Coronal reformat (**a**) and axial (**b**) CT, performed three weeks after the CT shown in Figure 1, shows interval worsening of ground glass opacities (arrows). Thalidomide therapy was discontinued at this time.

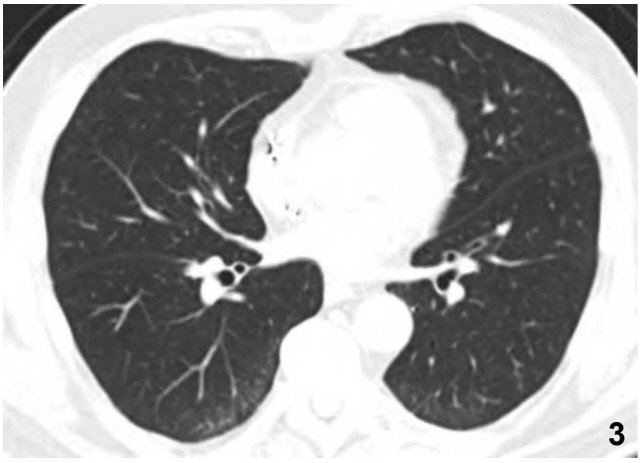


Figure 3. Axial CT obtained one month after discontinuation of thalidomide therapy demonstrates near complete resolution of pulmonary opacities.

eosinophils to suggest a hypersensitivity reaction. Blood cultures were also negative and antibiotics were discontinued at that time. The patient remained on the thalidomide/dexamethasone protocol when discharged home.

Three weeks later, the patient presented to the hospital with acute shortness of breath. The patient had not been taking dexamethasone for the two weeks prior to admission. On presentation, the patient denied associated chest pain, however the shortness of breath was worse with exertion and was associated with weakness, anorexia and constipation. He denied having any hemoptysis, epistaxis or hematochezia. He had a cardiovascular history, significant for paroxysmal atrial fibrillation, requiring ablation and subsequent pacemaker placement. He had no history of thromboembolic disease. Family history was non-contributory. He had an oxygen saturation of 86% at rest, with improvement to 95% on 4 liters/min oxygen. He was afebrile and had a respiratory rate of 18 breaths/min. His blood pressure and heart rate were normal. He was pale, but in no distress. His lung exam was normal. He had no peripheral edema. Laboratory work up was negative for infection, congestive heart failure or acute myocardial infarction.

A CT scan of the chest (Figure 2) demonstrated extensive ground-glass attenuation throughout both lungs, which had significantly worsened since the previous CT scan. The differential diagnosis at that time included pulmonary edema, drug reaction, infection and hemorrhage. There was no evidence of pulmonary embolism.

The patient was admitted to the hospital and his thalidomide/dexamethasone protocol was discontinued. Solu-Medrol 100 mg IV was administered. The patient responded well, with improvement in his symptoms, and tolerated a decrease in supplemental oxygen to 2 liters/min. A repeat CT scan obtained 48 hours after discontinuing the thalidomide showed improvement in the ground-glass opacities. After 72 hours, the patient was discharged home with supplemental oxygen and a two week steroid

taper. One month after discharge a repeat CT scan was performed, revealing near resolution of the pulmonary opacities (Figure 3).

Discussion

Thalidomide, originally used as a sedative and hypnotic in the 1950's, is a medication which inhibits angiogenesis and acts as an immunomodulator (3). More recently, thalidomide has been added to a growing list of new medications being used in the treatment of multiple myeloma (6). This medication increases angiogenesis in the bone marrow of patients with newly diagnosed, refractory or relapsed multiple myeloma.

The therapeutic combination of thalidomide with dexamethasone has been studied comparing its effectiveness against dexamethasone alone (7). Although the combination showed higher reduction in paraproteins, it also caused more toxic side effects, including deep venous thrombosis and pulmonary embolism (7). Acute drug-induced pulmonary toxicity was not identified as a potential side effect.

Interstitial lung disease is the most common pattern of drug-induced pulmonary injury and has been reported with over 350 drugs (8). Drugs can cause a variety of pathological changes within the lung, including alveolar changes, due to edema or hemorrhage. They can also cause non-specific or eosinophilic pneumonia and even vasculitis (8).

Pulmonary ground glass opacity on CT is defined as a region of increased attenuation that does not obscure the underlying vasculature (9). Ground glass opacity represents thickening of the interstitium, incomplete filling of the alveoli or a combination of the two. The ground-glass opacity demonstrated in our patient was nonspecific and could be seen with pulmonary edema, hemorrhage, drug toxicity, organizing pneumonia, mild pulmonary fibrosis, alveolar proteinosis, idiopathic interstitial pneumonia or infection. The clinical presentation of the patient is critical in helping to determine the nature of the underlying pathology (10).

Treatment of drug-induced interstitial lung disease is cessation of the inciting drug. Corticosteroid use can be considered depending on the clinical situation and the response to withdrawal of the offending drug.

Conclusion

Multiple myeloma is a complex disease process. New chemotherapy regimens have been extensively studied, but not all potential side effects have been clearly defined. Patients taking thalidomide who present with acute shortness of breath should be evaluated for pulmonary embolism and pulmonary toxicity. Our patient responded well to supplemental oxygen and high dose steroids. Serial CT imaging should be considered to guide management and monitor resolution of the transient toxic pulmonary effects.

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