

## CASE REPORT

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## A case of pulmonary toxicity associated with G-CSF and doxorubicin administration

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**Abstract** The cytokine growth factor, G-CSF (granulocyte colony-stimulating factor), is commonly used in oncologic practice and is generally believed to be a safe agent to administer. We describe here a case of pulmonary toxicity associated with the concurrent administration of G-CSF and doxorubicin. We contend that G-CSF contributed to the life-threatening lung injury in our patient, and discuss additional reports in the literature of pulmonary toxicity associated with the use of this agent.

**Keywords** G-CSF · Doxorubicin · Toxicity · Pneumonitis

### Introduction

Recombinant human granulocyte colony-stimulating factor (G-CSF) has gained widespread popularity because of its use in diminishing the severity and duration of neutropenia associated with myelosuppressive chemotherapy and in mobilizing pluripotent bone marrow stem cells from healthy donors for harvesting for allogeneic stem cell transplants. In addition, it has been administered chronically without adverse effects as maintenance therapy for patients with severe congenital neutropenia and myelodysplastic syndrome. The overwhelming weight of evidence suggests that the administration of G-CSF is safe, with the most common side-

effects experienced being medullary bone pain, headache, fatigue, and nausea. Nevertheless, there are numerous case reports suggesting that G-CSF may, in rare cases, produce more severe adverse effects, including interstitial pneumonitis when given with cytotoxic chemotherapy and adult respiratory distress syndrome (ARDS). We report here a case of life-threatening respiratory dysfunction secondary to bronchocentric granulomatosis (BG) associated with the use of G-CSF administered together with doxorubicin.

### Case report

A 60-year-old woman with stage IIIA infiltrating ductal carcinoma of the right breast was treated by modified radical mastectomy. She subsequently received four cycles of adjuvant doxorubicin (60 mg/m<sup>2</sup>) administered every 2 weeks as per research protocol. Because of the dose intensity of this regimen, G-CSF support (filgrastim, Amgen, Thousand Oaks, Calif.; 300 mcg SC daily) was given on days 3–10 of each 14-day cycle according to the protocol. On day 12 of the third cycle, she developed low-grade fevers, which persisted without an obvious infectious source. On day 12 of the fourth cycle, her temperature reached 40°C, and she complained of mild dyspnea on exertion. A chest radiograph revealed a four-quadrant interstitial infiltrate in a reticulonodular pattern (Fig. 1). On admission to the hospital, her temperature was 38.6°C. She was breathing comfortably and had a room air oxygen saturation of 98%. Examination of the lungs revealed dry crackles in both lung bases. Serum chemistries and complete blood count were normal except for mild anemia. Blood and urine cultures were negative. Serological tests for *Chlamydia psittaci* and *C. trachomatis* were negative, as was a test for urine histoplasma antigen. Bronchoscopy revealed no evidence of infection by bacteria, acid-fast bacillus, fungus, *Pneumocystis carinii*, legionella, mycoplasma, herpes simplex virus, cytomegalovirus, Epstein-Barr virus, or parainfluenza. Transbronchial biopsy showed no evidence of acid-fast bacillus, *P. carinii* or fungus. It did, however, reveal a peribronchial granulomatous inflammation with bronchial destruction consistent with BG, having features consistent with hypersensitivity or drug reactions (Fig. 2). Following bronchoscopy, the patient developed a pneumothorax and was placed on high-flow oxygen therapy. Her pulmonary status rapidly worsened to respiratory failure, which ultimately necessitated mechanical ventilation. Despite initial therapy for bacterial, fungal, and tuberculous infections, the pulmonary lesion worsened. Once a diagnosis of BG was made, all antibiotics were dis-

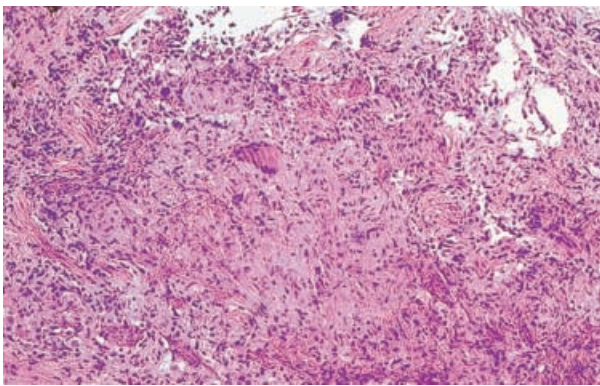
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**Fig. 1** Chest radiograph obtained at the time of hospital admission showing diffuse four-quadrant reticulonodular interstitial disease, most prominent laterally in the right upper lobe



**Fig. 2** Transbronchial biopsy showing peribronchial granulomatous inflammation with a poorly formed, noncaseating granuloma containing a small, multinucleated giant cell

continued and methylprednisolone (250 mg IV every 6-h) was started. The patient's respiratory function improved slowly, and she was successfully extubated after 8 days on the ventilator. Her slow improvement continued as her steroid dose was tapered, and she was discharged from the hospital after a 4-week stay. A chest radiograph obtained 8 weeks after the initiation of steroid therapy revealed complete resolution of the pulmonary abnormalities.

## Discussion

We have presented the case of a patient who developed bronchocentric granulomatosis while receiving doxorubicin concomitant with G-CSF. The uncommon diagnosis of BG is a descriptive, pathologic one, and is not associated with a single disease entity. Although it is seen as a manifestation of allergic bronchopulmonary aspergillosis (ABPA) in asthmatic patients [6], a clear etiologic factor cannot be identified in many instances.

An underlying hypersensitivity reaction to an unknown allergen residing within the bronchioles has been suggested as a possible pathogenetic mechanism. Another hypothesis is that the inflammatory granulomas are a relatively non-specific pathologic response to a variety of airway injuries [14].

In the present case, likely causes of pulmonary granulomatous disease were excluded. A carefully obtained history did not reveal environmental or occupational exposure. Extensive studies of the bronchial lavage and lung biopsy samples revealed no evidence for infection, including that by uncommon organisms associated with granulomatous inflammation. Lacking a clear explanation for the etiology of the lung injury in this case, we wondered whether it might have resulted from the administration of doxorubicin or G-CSF, the only medications she had been receiving at the time.

Although some chemotherapeutic agents are known to cause toxic injury to lung tissue, doxorubicin has not been considered one of them. In addition, the granulomas in the biopsy specimen were more consistent with a hypersensitivity reaction than with a toxic drug reaction of the type associated with chemotherapy. Although doxorubicin has been reported to cause a "flare" reaction of localized urticaria or erythema along the course of the vein into which it is being infused, generalized hypersensitivity and anaphylactoid reactions to this agent are rare [20], and delayed-type hypersensitivity has not been reported. Recently, pneumonitis and pulmonary fibrosis have been observed in dogs inhaling doxorubicin for the treatment of lung tumors [8]; however, the radiologic and histologic features in these cases were suggestive of a direct toxic effect of the drug on lung tissue when administered using this novel approach.

There is mounting evidence that G-CSF administration may be associated with lung injury. Initial attention to this issue was drawn by reports of a compelling increase in the pulmonary toxicity of combination chemotherapy regimens when G-CSF was added to attenuate myelosuppression [7, 9, 11–13, 15, 21]. Most patients were being treated for lymphoma, and a clear assessment of the contribution of G-CSF to the toxicity of the chemotherapeutic regimens was difficult as they all contained agents (i.e., bleomycin, methotrexate, or cyclophosphamide) with known pulmonary toxicity. In contradistinction to these reports, others have shown, both retrospectively [17] and in a randomized, placebo-controlled fashion [2], that the addition of G-CSF did not increase the incidence or severity of pulmonary toxicity of a bleomycin-containing regimen. We were unable to find a single report in the literature of a case of pulmonary toxicity associated with the use of G-CSF in combination with doxorubicin alone.

Evidence for a direct physiologic effect of G-CSF on lung mechanics can be found in a report of a liver transplant recipient with ARDS who was given G-CSF for antibiotic-induced neutropenia [18]. Administration of G-CSF subcutaneously was reproducibly associated

with oxygen arterial desaturation requiring 100% oxygen; the authors speculated that an increase in neutrophil activation secondary to G-CSF administration resulted in worsening gas exchange. In addition, recent reports describe a fatal case of ARDS developing after the unnecessary administration of G-CSF to a patient with anemia [16], and the development of ARDS in three patients being treated with G-CSF for drug-induced neutropenia [4]. It appears, therefore, that G-CSF can exert an untoward effect on the lung even in the absence of known pneumotoxic drugs, possibly through enhanced neutrophil migration and activation with subsequent local production of superoxide radicals in the lung interstitium. The worsening of our patient's condition after supplemental oxygen therapy supports the involvement of superoxide radicals in this disease process.

Hypersensitivity reactions have been reported with G-CSF administration [1, 3, 5, 10]. In addition, both acute urticarial and delayed-type hypersensitivity reactions have been associated with polysorbate 80 (Tween 80), a component of filgrastim [19]. It remains a possibility that our patient's febrile illness and the granulomatous inflammatory response evident in her lung biopsy were the result of a delayed-type hypersensitivity reaction to the G-CSF preparation. The time course of her fevers supports this hypothesis.

It is becoming evident that the administration of G-CSF is not without risk. Additional investigation into the mechanism of G-CSF-induced lung toxicity is needed, so that this negative effect can be minimized, thus allowing the continued safe use of this important therapeutic agent.

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