LETTER

Mitomycin-Induced Interstitial Pneumonitis in a Patient with *BRCA2* Associated Metastatic Pancreatic Carcinoma

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Dear Sir:

Interstitial lung diseases are diffuse parenchymal lung diseases, and represent a heterogeneous group of disorders including lymphocytic interstitial pneumonitis, interstitial lung diseases of unknown etiology, including sarcoidosis, idiopathic pulmonary fibrosis, and pulmonary fibrosis associated with connective tissue diseases [1]. Most of the interstitial disorders have a restrictive pattern with reductions in total lung capacity, functional residual capacity, and residual volume [2]. The lung has significant susceptibility to injury from a variety of chemotherapeutic agents (Table 1). The clinician must be familiar with classic chemotherapeutic agents with well-described pulmonary toxicities and must also be vigilant about a host of new agents that may exert adverse effects on lung function [3].

BRCA2 mutations have been known to be associated with higher incidence of breast, ovarian and pancreatic adenocarcinoma [4, 5, 6]. Although present in only a minority of pancreatic cancers, mutations in the *BRCA2* gene could provide a rational target for treatment with chemotherapeutic agents. Van der Heijden *et al*. have demonstrated that pancreatic cancer cells having defects in Fanconi anemia and *BRCA2* pathway are remarkably sensitive to mitomycin-C both in culture and mice [7, 8]. Isacoff *et al*. reported good results with mitomycin-C plus fluorouracil regimen in first-line therapy of locally advanced pancreatic cancer, with two out of 50 patients achieving complete remission [9]. Another study using the same regimen in patients with metastatic pancreatic carcinoma also showed some activity including one complete remission [10].

We present here a case of a mitomycin-induced interstitial lung disease in a patient with *BRCA2* associated metastatic pancreatic carcinoma.

Our patient presented at the age of 71 years with a dual diagnosis of locally advanced prostate carcinoma and metastatic pancreatic carcinoma on the background of a significant family history of cancer. On genetic testing, he was found to have the common Ashkenazi Jewish *BRCA2* mutation, 6174delT. He initially received 22 cycles of docetaxel, capecitabine, and gemcitabine followed by single agent irinotecan every 3 weeks for 27 cycles, and then weekly cetuximab was added to the regimen at cycle 28. His disease then remained stable for an additional 13 months. He did not have mutated *K-ras*. Upon progression on irinotecan/cetuximab, he was switched to mitomycin-C and oxaliplatin. He immediately developed hypersensitivity reaction to oxaliplatin, and single agent mitomycin-C was continued at 7 mg/m^2 every 21 days. After three cycles of mitomycin-C, he presented to the oncology clinic with dry cough, progressive dyspnea, and hypoxemia. Pulse oximetry showed 96% at room air. A CT angiogram of chest showed right middle lobe ground glass changes without pulmonary embolism. Subsequent CT scan showed persistent nodules and ground glass opacity. Patient underwent bronchoscopy, and right middle lobe appeared to be generally unremarkable. Transbronchial biopsy of right middle

Table 1. List of few chemotherapeutic agents associated with interstitial lung disease.

Vinca alkaloid (mitomycin-vinca alkaloid combination therapy) causing acute respiratory distress syndrome (ARDS)	3-6%
Vinorelbine (vinca alkaloid) causing bronchospasm	5%
Bleomycin causing pleuropulmonary reactions	6-10%
Methotrexate-induced pleuropulmonary disease	3-4%
Nitrofurantoin causing acute pleuropulmonary effects	5-25%
Interleukin 2 causing pleuropulmonary abnormalities	75%
Anti-epidermal growth factor receptor (EGFR) drugs	Less than 1%

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and lower lobes showed mild mixed lympho-plasmacytic infiltrate and were negative for malignancy and granluloma. Bronchoalveolar lavage was negative for *Pneumocystis carinii* but showed *Serratia marcescens* and coagulase-negative staphylococcus. Infection due to *Serratia* was not likely. Four hours after bronchoscopy, he developed acute hypoxemic respiratory failure and required intubation. It was thought that his underlying chronic obstructive pulmonary disease and bronchoscopy-induced bronchospasm contributed to respiratory failure. He responded to steroids and oxygen therapy and was subsequently extubated and discharged from intensive care unit. Echocardiogram showed normal left ventricle ejection fraction and mild pulmonary hypertension. Since *Serratia* is not commonly pathogenic, it was thought that his ground glass opacities in lungs represent mitomycin-induced interstitial pneumonitis. Therefore, based on the pulmonologist's recommendation we did not rechallenge the patient with further mitomycin. A repeat one chest CT demonstrated disappearance of most ground glass opacity except mild glass opacity at bilateral bases. Irinotecan was resumed as a single agent every 3 weeks after patient which he has been tolerating well.

Mitomycin-C has been known to cause interstitial pneumonitis, and its related lung toxicity is a dose-dependent side effect, occurring at cumulative dose levels of 20 mg/m^2 or more. The incidence is likely to be less than 10% according to a perspective study [11]. A case series reported incidence of mitomycin-C-induced pulmonary toxicity ranging from 2% to 38% and average total dosage of drug implicated is 78 mg [12]. Since pulmonary hypertension may complicate interstitial lung diseases and is associated with increased disease severity and decreased survival [13], it is reasonable to perform transthoracic echocardio-graphy and measure DLCO in cancer patients with underlying COPD who are treated with mitomycin-C. However, further studies are required to determine whether mitomycin-C should be excluded from the chemotherapy regimen to avoid interstitial pneumonitis if moderate to severe pulmonary hypertension and reduction in diffusion lung capacity for carbon monoxide is detected in asymptomatic patients.

Serratia species are opportunistic gram-negative bacteria classified in the tribe *Klebsielleae* and the large family *Enterobacteriaceae*. *Serratia marcescens* is the primary pathogenic species of *Serratia*. Rare reports have described disease resulting from infection with *Serratia plymuthica*, *Serratia liquefaciens*, *Serratia rubidaea*, *Serratia odorifera*, and *Serratia fonticola* [14, 15, 16, 17]. Some strains of *Serratia marcescens* are capable of producing a pigment called prodigiosin, which ranges in color from dark red to pale pink, depending on the age of the colonies. *Serratia marcescens* has a predilection for growth on starchy foodstuffs, where the pigmented colonies are easily mistaken for drops of blood. Over a century, physicians have used *Serratia marcescens* as a biological marker for studying the transmission of microorganisms because, until the 1950s, this bacterium was generally considered a harmless saprophyte. Only since the 1960s has *Serratia marcescens* been recognized as an opportunistic pathogen in humans. In the hospital, *Serratia* species tend to colonize the respiratory and urinary tracts, rather than the gastrointestinal tract, in adults. *Serratia* infection is responsible for about 2% of nosocomial infections of the bloodstream, lower respiratory tract, urinary tract, surgical wounds, and skin and soft tissues in adult patients. Outbreaks of *Serratia marcescens* meningitis, wound infections, and arthritis have occurred in pediatric wards. *Serratia* infection has caused endocarditis and osteomyelitis in people addicted to heroin. Cases of *Serratia* arthritis have been reported in outpatients receiving intra-articular injections but pulmonary infection is unlikely as in our case.

The diagnosis of chemotherapy-associated lung disease remains an exclusionary process, particularly with respect to considering usual and atypical infections, as well as recurrence of the underlying neoplastic process in these immune compromised patients (Table 2). Such diagnosis relies on typical radiologic features and exclusion of other potential causes, such as congestive heart failure, infections, or lymphangitic carcinomatosis [18]. It is important to revise other neoplastic drugs that can lead to interstitial pneumonitis, acute hypersensitivity pneumonitis, acute permeability edema with or without acute respiratory distress syndrome, such as gemcitabine, vinorelbine, docetaxel, or ifosfamide. In many instances, chemotherapy-associated lung disease may respond to withdrawal of the offending agent and to the judicious application of corticosteroid therapy.

Table 2. Differential diagnoses.

Acute pulmonary embolism (helical CT)
Acute respiratory distress syndrome
Alveolar proteinosis
Asbestos-related disease
Asbestosis
Aspergillosis, thoracic
Aspiration pneumonia
Bronchiolitis obliterans organizing pneumonia
Lung, metastases
Lung, nontuberculous mycobacterial infections
Pulmonary edema, noncardiogenic
Pulmonary hypertension
Pulmonary interstitial emphysema
Radiation pneumonitis

Conflict of interest The authors declare no conflicts of interest

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