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Exacerbation of pre-existing interstitial lung disease after oxaliplatin therapy: A report of three cases

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In fond memory of Dr. William W. Douglas, respected teacher and mentor, valued colleague, and dear friend
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FOLFOX;
Pulmonary fibrosis

Summary
Background: To describe the possible role of oxaliplatin in worsening pre-existing interstitial lung disease.
Methods: After we encountered a patient with an interstitial lung disease who experienced a fatal progression of his pulmonary disease associated with oxaliplatin therapy, a computer-aided search was conducted to identify other similar patients. Twenty-six patients with various lung diseases who had received oxaliplatin therapy at Mayo Clinic in Rochester, MN from January 2000 to December 2006 were identified. Three of these patients had radiologic evidence of interstitial lung disease before undergoing oxaliplatin therapy. We examined the medical records and imaging studies of these three patients to further define their clinical presentation, radiological and functional characteristics, and clinical outcome.
Results: All three patients experienced symptomatic and radiologic worsening of their interstitial lung disease following oxaliplatin administration. One of these patients died from refractory respiratory failure; the remaining two patients stabilized after the discontinuation of oxaliplatin therapy and have since shown modest improvement in pulmonary symptoms and lung function. There were no other potential causes identified for the unexpected progression of their lung disease other than the temporal relationship to oxaliplatin therapy.
Conclusions: Treatment with oxaliplatin, in the setting of a pre-existing interstitial lung disease, may be associated with respiratory deterioration. It is unknown whether this is

Abbreviations: CRC, colorectal cancer; FOLFOX, chemotherapy regimen using oxaliplatin, leucovorin and fluorouracil; ILD, intersitial lung disease; HRCT, high resolution computed tomographic; PFT, pulmonary function tests; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; TLC, total lung capacity; DLCO, diffusing capacity of carbon monoxide; CTD, connective tissue disease; CTA, computed tomographic angiography

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mediated by acceleration of the underlying parenchymal disease or by a superimposed acute lung injury caused by oxaliplatin.
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Introduction

Oxaliplatin is a platinum derivative chemotherapeutic agent approved by the Food and Drug Administration in 2002 for the treatment of metastatic colorectal cancer (CRC). Since this approval, an oxaliplatin-based regimen that includes fluorouracil and leucovorin (FOLFOX) has become first-line therapy for treatment of metastatic CRC. Randomized controlled trials have shown significantly greater response rates and disease-free survival using FOLFOX when compared with fluorouracil and leucovorin alone, and superior results to a regimen of irinotecan combined with fluorouracil and leucovorin.[1–4] The initial studies examining the toxicities of oxaliplatin showed hematologic, gastrointestinal and neurologic complications but no pulmonary complications.[5] More recently, there have been reports of patients developing interstitial lung diseases (ILD),[6–8] acute lung injury,[9] eosinophilic lung disease,[10] hypersensitivity reactions and wheezing associated with oxaliplatin infusion.[5,11]

We recently encountered a patient who suffered fatal progression of ILD associated with oxaliplatin therapy. We subsequently conducted a computer-aided search to identify other patients with ILD seen at Mayo Clinic in Rochester, MN from January 2000 to December 2006 and received oxaliplatin therapy. This search yielded 26 patients with various lung diseases who were treated with oxaliplatin therapy for their CRC. Only three of these 26 patients had radiologic evidence of ILD prior to administration of oxaliplatin therapy and all developed symptomatic and radiologic worsening of their ILD after initiation of FOLFOX regimen in the treatment of metastatic CRC.

Case 1

A 71-year-old man with a history of mild bibasilar pulmonary infiltrates consisting of subpleural, reticular opacities on high-resolution computed tomographic (HRCT) scan, was diagnosed with CRC in 2005. Pulmonary infiltrates were first noted in 1999 when the patient was asymptomatic. Pulmonary function tests (PFT) revealed only minimal abnormalities consisting of a mildly reduced forced vital capacity (FVC) of 3.47 L (74% predicted) and forced expiratory volume in 1 s (FEV_1) of 2.77 L (77% predicted) with normal total lung capacity (TLC) 5.70 L (83% predicted) and diffusing capacity (DLCO) 23.1 ml CO/mmHg/min (84% predicted). There was no history of relevant exposures and evaluation for potential causes of ILD, including serologic testing for connective tissue disease (CTD), was unrevealing with negative rheumatoid factor, anti-cyclic citrullinated peptide antibody, antinuclear antibody, and antibody to extractable nuclear antigen. There was no evidence of radiologic or symptomatic progression on repeated evaluations between 1999 and 2005 and no lung biopsy was performed.

The patient underwent resection of the primary CRC lesion and subsequently six cycles of FOLFOX therapy beginning in 2005. His chemotherapy regimen included intravenous oxaliplatin 180 mg, leucovorin 860 mg and fluorouracil 5130 mg per cycle. No complications were noted through the first five cycles of FOLFOX therapy; however, his sixth cycle of oxaliplatin infusion was interrupted because of acute dyspnea and cough. Chest radiography revealed new parenchymal infiltrates. These abnormalities were thought to represent a hypersensitivity reaction to oxaliplatin and were treated with oral methylprednisolone starting at 24 mg orally daily and tapering by 4 mg per day over 5 days. His symptoms and radiographic infiltrates improved. Three weeks following this episode, he again noted increasing exertional dyspnea along with fever ($T = 39.0\,^{\circ}C$). He was found to be profoundly hypoxemic (oxygen saturation 70–75% on room air at rest) and was hospitalized for further management.

On admission, he was tachypneic with respiratory rates in the high 30's and required supplemental oxygen via a nonrebreather mask with a fractional concentration of inspired oxygen (FiO_2) of 1.0. Despite the high FiO_2, his arterial blood gas study showed a pH of 7.43, PCo_2 of 27, PO_2 of 58 and oxygen saturation of 88%. Other laboratory data included hemoglobin 12.8 mg/dL, leukocytes $13.9 \times 10^9\,L^{-1}$ and a normal platelet count. An electrocardiogram demonstrated normal sinus rhythm without signs of ischemia. An echocardiogram showed normal left ventricular ejection fraction of 55%, mild (grade 1/4) diastolic dysfunction, and a mildly elevated estimated right ventricular systolic pressure of 44 mmHg. Computed tomographic angiography (CTA) was negative for pulmonary embolism but showed extensive new areas of ground-glass opacities bilaterally (Figure 1).

Multiple blood, sputum, and urine cultures failed to demonstrate any infection. Bronchoscopy with bronchoalveolar lavage also did not identify any infectious agent. Following bronchoscopy, his oxygenation worsened further and he required endotracheal intubation with mechanical ventilatory support. He was empirically treated with vancomycin, levofloxacin and meropenem as well as high-dose corticosteroids (intravenous methyprednisolone 250 mg per day for 14 days), but continued to worsen. Another chest CT scan was performed and demonstrated an increased amount of fibrotic-appearing infiltrates as well as the ground-glass opacities. Maintaining adequate oxygenation with mechanical ventilation became increasingly difficult for which inhaled nitric oxide, high-frequency oscillator ventilation as well as prone positioning were instituted with only limited and transient benefit. He ultimately succumbed to refractory respiratory failure after 30 days of mechanical ventilation. An autopsy request was declined.

Case 2

The second patient is a 77-year-old woman who was diagnosed with CRC in February 2006 at an outside

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