Progressive Pulmonary Infiltrates in a Patient With Ovarian Cancer

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We present a case of organizing pneumonia associated with lymphangitic spread of ovarian carcinoma in a 60-year-old Hispanic female with progressive dyspnea, hypoxemia, and bilateral pulmonary infiltrates. The patient was treated with corticosteroids, and she had rapid clinical and radiographic improvement. Malignancy-associated organizing pneumonia has most often been reported in bone-marrow transplant and breast-cancer patients receiving radiation therapy. Data regarding organizing pneumonia in association with other malignancies is quite limited. *Key words: organizing pneumonia, ovarian cancer, lymphangitic metastases.* [Respir Care 2006;51(5):515–518]

Introduction

Organizing pneumonia is a rare condition, first described as a distinct clinical entity by Davison et al[1] in 1983 and Epler et al[2] in 1985. The prevalence of organizing pneumonia is estimated at 6–12 cases/100,000 admissions.[3] The classification of organizing pneumonia remains somewhat confusing; currently, organizing pneumonia without an identifiable etiology is classified as cryptogenic, whereas other causes of organizing pneumonia are classified as secondary.[3] There are a wide variety of secondary conditions associated with organizing pneumonia, including numerous pulmonary infections, toxic-fume inhalation, autoimmune conditions, medications, solid-organ transplant, Wegener's granulomatosis, chronic eosinophilic pneumonia, and hypersensitivity pneumonitis. Organizing pneumonia associated with malignancy is best described in allogenic bone-marrow transplant and breast-cancer patients following radiation therapy to the thorax.[4] Clinical presentation is subacute and includes cough, sputum production, dyspnea, and constitutional symptoms.[5,6] Crackles and wheezing are present in about a third of patients on lung examination.[3,6] Pulmonary function test results can be variable but most commonly indicate a restrictive pattern and decreased diffusing capacity.[3,6] A bronchoalveolar-lavage-fluid finding of cellular pleocytosis is common, and lung biopsy shows interstitial inflammation and polypoid masses of granulation tissue in the small airways and alveoli.[3] Treatment for symptomatic patients is corticosteroids (1 mg/kg), followed by a slow taper for up to 12 months.[3] Cyclophosphamide, azathioprine, erythromycin, and other agents have been attempted in steroid-refractory cases.[7]

Data on organizing pneumonia due to cancer other than the conditions listed above are extremely limited. In the largest case series, reported by Mokhtari et al, 43 cases were retrospectively identified at the Memorial Sloan-Kettering Cancer Center over a 7-year period.[8] Sixteen cases (37%) were associated with hematologic malignancies, and 27 (63%) with solid-organ tumors. Non-small-cell lung cancer and sarcoma were the most common associated solid-organ malignancies (10% each), and no cases were observed with ovarian cancer. The authors concluded that the type of malignancy could be correlated to clinical presentation and outcome of organizing pneumonia, with hematologic malignancies more commonly associated with important clinical symptoms, diffuse infiltrates on radiograph, and a complicated treatment course (Table 1).

Case Summary

A 60-year-old Hispanic female presented with a 6-week history of progressive dyspnea, nonproductive cough, fever, and malaise. Levofloxacin had been prescribed 1 week prior for presumed pneumonia, but there was no improve-

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Table 1. Characteristics of Patients With Organizing Pneumonia Related to Malignancy

	Chest-Radiograph Features	
	Nodular/Mass* (no. and %)	Diffuse† (no. and %)
Solid organ	22 (81)	5 (32)
Hematologic	5 (19)	11 (68)
Symptomatic	19 (68)	14 (93)
Asymptomatic	9 (32)	1 (7)
No medical treatment	19 (68)	2 (13)
Steroids	8 (28)	12 (80)
Macrolides	1 (4)	1 (7)

*$n = 28$
†$n = 15$
(Data from Reference 9.)

ment in symptoms. Her medical history was notable for stage IIIB ovarian cancer, treated with total abdominal hysterectomy and bilateral salpingo-oopherectomy. She had failed initial adjuvant treatment with paclitaxel and carboplatin, and subsequently received 3 cycles of liposomal doxorubicin, completing the last cycle 3 weeks prior to presentation. She was also receiving enoxaparin for a recent deep venous thrombosis. There was no history of tobacco use, important exposures, or travel. On physical examination the patient was tachycardic and tachypneic, with anterior crackles on lung examination. Her blood oxygen saturation (measured via pulse oximetry) was 87% on room air. While breathing oxygen at 2 L/min, arterial blood-gas values were pH 7.47, P_{aCO_2} 23 mm Hg, P_{aO_2} 65 mm Hg, and arterial oxygen saturation 93%. Chest radiograph showed bilateral mixed alveolar and interstitial infiltrates. Computed tomography of the chest revealed no venous thromboembolism and confirmed the upper-lobe-predominant infiltrates, which had progressed over several months compared to prior studies.

The patient was admitted and treated with broad-spectrum antibiotics and fluconazole (the latter to cover for coccidioidomycosis, which is endemic in our local area). Blood and urine cultures, serial sputum for acid-fast bacilli, and a purified protein derivative of tuberculin test were negative. Immunodiffusion testing for coccidioidomycosis, precipitating antibodies for common hypersensitivity pneumonitis antigens, serum immunoglobin E, and eosinophil levels were normal. Bronchoalveolar-lavage fluid showed a nonspecific cellular pleocytosis. Bronchoalveolar-lavage cultures and antigen testing for bacterial, viral, fungal, and opportunistic pathogens were unrevealing, and there was no cytologic evidence of cancer. Video-assisted thoracoscopic lung biopsy revealed lymphangitic spread of ovarian carcinoma, with surrounding areas of organizing pneumonia (Fig. 1), and subsequent testing revealed an elevated cancer antigen 125 (CA-125). The patient was treated with corticosteroids, with which she had rapid clinical and radiographic improvement (Fig. 2), followed by gemcitabine as salvage chemotherapy, with which she had a good initial clinical response.

Discussion

Our case illustrates that differentiating the radiographic appearance and clinical manifestations of organizing pneumonia based on tumor type may be less reliable than previously described. The conclusions presented by Mokhtari et al[8] are further limited by the high prevalence of concomitant chemotherapy, with associated pulmonary toxicity (15 patients, 35%), recent thoracic radiation (7 patients, 16%), and prior allogenic bone-marrow transplant (9 patients, 21%) in their case series. It is unclear if the associations described would remain if these cases were excluded from analysis.

The differential diagnosis for pulmonary infiltrates in an immunosuppressed cancer patient undergoing treatment is broad, including both infectious and noninfectious etiologies. Bacterial pneumonia is common and may be due to community-acquired pathogens or opportunistic and resistant pathogens such as *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus*, which are more commonly associated with the hospital environment.[9] Invasive fungal infections from *Aspergillus* and *Mucormycosis* species are more common in bone-marrow-transplant recipients, with reports of increasing incidence in recent years,[10] and endemic mycoses (*Histoplasma capsulatum*, *Coccidioides immitis*, and *Blastomyces dermatitidis*) must be considered in certain geographic regions.[9] Viruses have been increasingly recognized as an important cause of respiratory illness in the immunocompromised host, with influenza, parainfluenza, and respiratory syncytial virus infections showing a marked seasonal variation, whereas symptomatic cytomegalovirus infection remains largely correlated to host immune status and baseline serologic status.[9] Noninfectious causes include pulmonary edema, progression of the underlying disease with lymphangitic spread, radiation pneumonitis and fibrosis, and drug toxicity from chemotherapeutic agents.[9] Organizing pneumonia and its association with cancer are poorly understood. The prevalence of incidental organizing pneumonia in patients with resected lung cancer was recently reported to be 37%, which suggests that the incidence of this condition may be underestimated.[11]

Although lymphangitic spread, drug toxicity, and infection are the most likely etiologies of progressive infiltrates in a patient with cancer, organizing pneumonia remains an important consideration as a treatable cause of symptomatic lung disease in these individuals. In our case, infection was effectively excluded, and the time course of our pa-

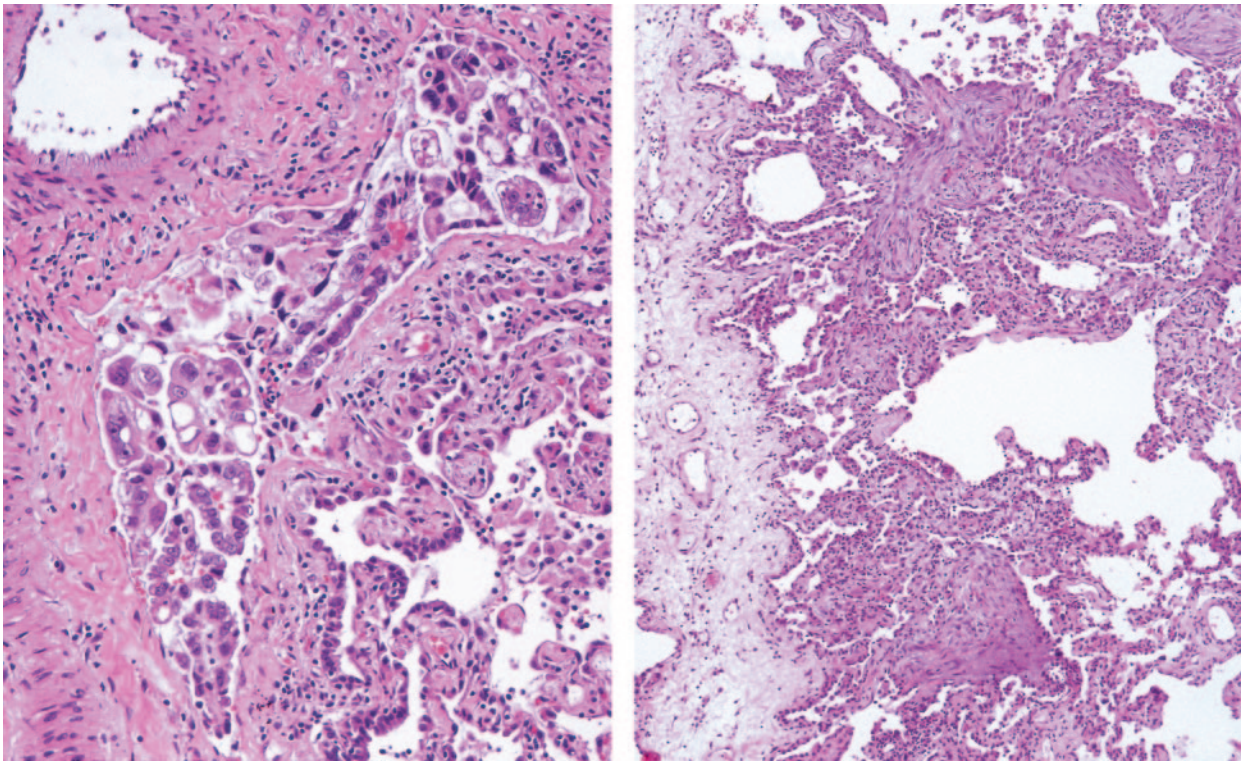

Fig. 1. Lung biopsy shows (left) lymphangitic spread of ovarian carcinoma, and (right) surrounding areas of organizing pneumonia.

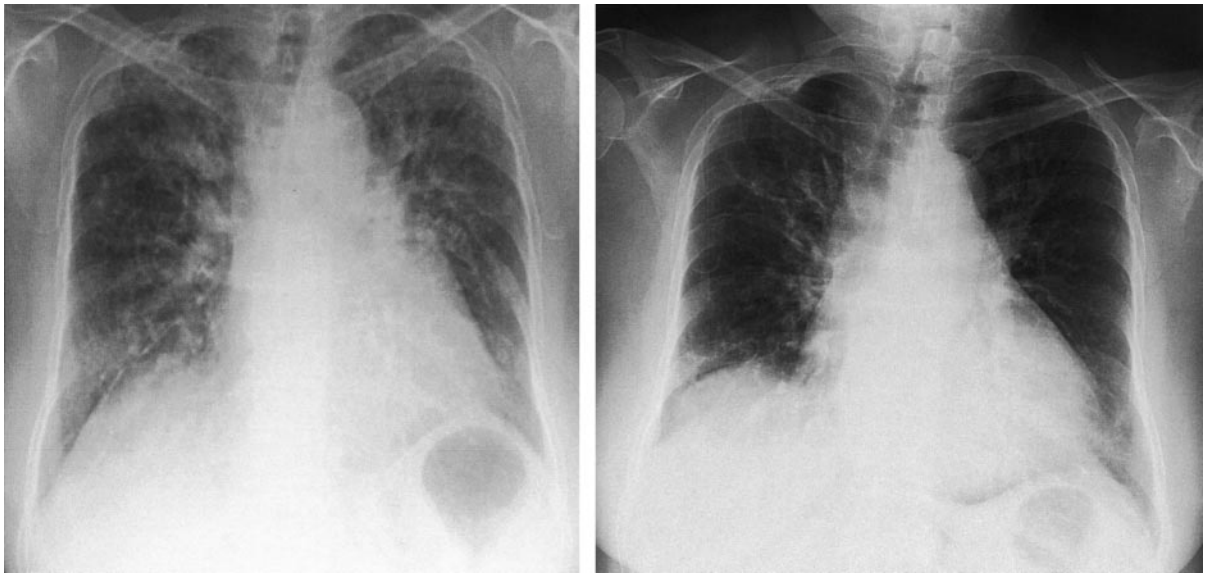

Fig. 2. Chest radiograph at baseline (left) and at 4 weeks after corticosteroid treatment (right).

tient's symptoms relative to her prior paclitaxel administration was not consistent with previous reports of pulmonary toxicity associated with this agent.[12] There are no reported cases of liposomal doxorubicin causing pulmonary toxicity (personal communication, Bristol-Myers Squibb Corporation, 2005). The biopsy evidence of cancer surrounded by organizing pneumonia, the elevated CA-125, the lack of other temporally associated exposures, and the dramatic response to corticosteroids make a strong causative argument for ovarian cancer as the most likely culprit for this patient's organizing pneumonia.

This case reaffirms the importance of establishing an early and definitive diagnosis in patients with cancer and

pulmonary infiltrates, with the potential for substantial improvement in quality of life when a reversible cause is identified. Malignancy-associated organizing pneumonia should also be considered in the differential diagnosis of patients with ovarian cancer and pulmonary infiltrates.

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