Pulmonary Fibrosis After Pegylated Liposomal Doxorubicin in a Patient With Uterine Papillary Serous Carcinoma

Introduction

Uterine papillary serous carcinoma (UPSC) is an aggressive histopathologic variant of uterine cancer. UPSC accounts for less than 15% of all endometrial cancers and is more common in African American women than white women.¹ Unlike more common forms of endometrial cancer, for which cure is common, the 5-year disease-specific survival rate and overall survival rate have been reported as 55% and 30%, respectively.² Treatments include comprehensive surgical staging, cytoreduction, radiation, and chemotherapy. Chemotherapies that have shown the best activity are mainly platinum and taxane based and include paclitaxel, carboplatin, and cisplatin.³ Patients with recurrent UPSC are unlikely to be successfully treated with surgery or radiation as salvage treatment, and have a less favorable response rate to chemotherapy or hormonal therapy than patients with endometrioid histology.⁴ Potential chemotherapy regimens for recurrent UPSC include cisplatin, cyclophosphamide, topotecan, doxorubicin, and pegylated liposomal doxorubicin (Doxil; Janssen Pharmaceuticals, Beerse, Belgium).⁵

Doxorubicin is an anthracycline antibiotic that works by intercalating DNA and is used to treat solid tumors, leukemia, and lymphoma. Doxorubicin's use is limited by cardiac toxicity, dose-dependent congestive heart failure, and cardiomyopathy. Pegylated liposomal doxorubicin is a liposome-encapsulated form of doxorubicin. The most common toxicities of pegylated liposomal doxorubicin are myelosuppression (65%), palmar-plantar erythrodysesthesia (51%), nausea (46%), and stomatitis (41%). There is theoretical concern that patients taking pegylated liposomal doxorubicin may suffer from cardiac toxicity. However, to our knowledge, cardiomyopathy and/or pulmonary toxicity attributed to the liposomal pegylated form of doxorubicin has never been reported. There are also no reported cases of pulmonary fibrosis after receipt of pegylated liposomal doxorubicin, to our knowledge.

Case Report

A 57-year-old woman presented with UPSC in October 2009. She underwent surgical staging including total abdominal hysterectomy, bilateral salpingo-oophorectomy, bilateral pelvic and para-aortic lymphadenectomy, omentectomy, and washings for peritoneal cytology. The final surgical stage was IIIA by virtue of positive peritoneal cytology. The tumor invaded 14% of the myometrial thickness. In accordance with a clinical protocol at our institution (Montefiore Medical Center, New York, NY), the patient received three cycles of adjuvant carboplatin and paclitaxel followed by brachytherapy and three additional cycles of carboplatin and paclitaxel after the brachytherapy. Post-treatment computed tomography (CT) showed no ev-

idence of disease and her cancer antigen-125 (CA-125) level was 30.8 U/mL.

Six months after completion of her primary therapy, the patient presented with new ascites, and evaluation of peritoneal fluid revealed recurrent UPSC. A 20-cm lesion developed on the patient's anterior abdominal wall at the site of the needle entry for the paracentesis. Her CA-125 level increased to 134 U/mL. She was treated with six cycles of pegylated liposomal doxorubicin at a dose of 40 mg/m², and received 59 to 60 mg intravenously for six doses. After six cycles, a repeat surveillance CT showed no evidence of disease, the anterior abdominal wall lesion had resolved, and the CA-125 level decreased to 13 U/mL.

The patient's chemotherapy course was uneventful except for hospitalization 3 days before her last cycle. She presented to the emergency department (ED) and was admitted for fever and cough. After a negative work-up, she was discharged home with a diagnosis of an upper respiratory viral infection. The patient returned later that month with the same complaints. She was treated with intravenous antibiotics in the ED and discharged again with a course of moxifloxacin for presumed pneumonia. She returned to the ED 2 weeks later with similar complaints after completion of the course of antibiotics, with persistent fevers and chills, chest pain, shortness of breath, and a nonproductive cough. The patient was admitted for evaluation, and a chest CT at that time was significant for diffuse airspace disease throughout both lungs (Fig 1; A, anterior; P, posterior). The differential diagnosis included pulmonary edema, multifocal pneumonia, and acute respiratory distress syndrome. The chest CT was negative for

Fig 1.

pulmonary embolus, and the CT of the abdomen and pelvis was negative for intra-abdominal disease or abscess. Lower-extremity Doppler ultrasound evaluation was negative for deep vein thrombosis. She was started on methylprednisolone and intravenous antibiotics. A transthoracic echocardiogram was consistent with mild pulmonary hypertension, and bronchoscopy was nondiagnostic.

One month after admission the patient was transferred to the surgical intensive care unit for hypoxic respiratory failure. Chest x-ray showed worsening bilateral interstitial infiltrates consistent with a progressive pulmonary process. Eleven days after the intensive care unit admission, the patient required intubation because of severe respiratory distress. Video-assisted thoracic surgery was performed and the biopsy demonstrated diffuse alveolar disease (interstitial alveolitis), likely secondary to drug toxicity, without any sign of lymphangitic spread of the malignancy. Empiric antibiotics were continued until all cultures were negative, and 10 days later, a tracheostomy tube was placed. The patient was discharged to a subacute rehabilitation facility. Before discharge she had an acute left middle cerebral artery infarct with right hemiplegia and global aphasia.

Six weeks later the patient was readmitted with acute renal failure, and bilateral percutaneous nephrostomies were placed. The hospitalization was complicated by urinary tract infection, colonic infection with *Clostridium difficile*, and partial small bowel obstruction. At that time the patient's pulmonary status had improved sufficiently that the tracheotomy was removed. Six weeks after admission the patient died as a result of disseminated sepsis, with blood cultures positive for *Pseudomonas*.

The autopsy demonstrated findings that were consistent with diffuse pulmonary fibrosis; specifically, the pleural surfaces were dull, with numerous thick fibrous adhesions, and the parenchyma was diffusely consolidated. There was widely metastatic recurrent UPSC with involvement of the pelvis, para-aortic, and mediastinal lymph nodes, liver, pancreas, and kidneys.

Discussion

Cryptogenic fibrosing alveolitis, also referred to as idiopathic pulmonary fibrosis (IPF), is a chronic progressive fibrotic disorder of the lower respiratory tract that usually affects adults older than age 40 years. Histopathologic characteristics that are associated with IPF include abnormal proliferation of mesenchymal cells, varying levels of fibrosis, overproduction and disorganized deposits of collagen and extracellular matrix, distorted pulmonary architecture, and subepithelial fibrotic foci (or fibroblast foci).⁶ The cause of IPF is unknown; however, risk factors include cigarette smoking, infection, environmental pollutants, chronic aspiration, and drugs.

Diagnosis may be difficult, and up to 10% of chest radiographs will be normal. Symptoms may include shortness of breath, particularly with exertion, chronic dry hacking cough, fatigue and weakness, chest discomfort, and loss of appetite/rapid weight loss. High-resolution computed tomography may show typical changes, including reticular opacities in basal and peripheral distribution, traction bronchiectasis, honeycombing (clustered airspaces 3 to 10 mm in diameter) in subpleural location, and ground-glass opacities. Video-assisted thoracoscopic surgery or open lung biopsy is indicated to confirm the clinical diagnosis. Although IPF is incurable, treatment includes a combination of supportive care (supplemental oxygen, pulmonary rehabilitation), immunosuppressive/antioxidant therapy, and referral for possible lung transplantation.⁷ Combination therapy including a systemic gluco-

corticoid, azathioprine, and *N*-acetylcysteine is a regimen that has been used, although the duration of this therapy is unknown.⁷ IPF has a poor prognosis and only 20% to 30% of patients live for 5 years after diagnosis.⁸ Factors associated with a shortened survival time include older age at presentation, excessive cigarette smoking, lower body mass index, pulmonary hypertension, and emphysema. Comorbid diseases and adverse effects of therapy may also cause a shortened survival.

Chemotherapies including paclitaxel, docetaxel, and bleomycin have been reported to cause pulmonary toxicity. Reactions to paclitaxel and docetaxel are usually acute and occur within the first 10 to 15 minutes of infusion of the chemotherapy. The patient may experience dyspnea, urticaria, and hypotension. Paclitaxel has been linked to acute diffuse interstitial pneumonia, subacute diffuse interstitial pneumonia, pulmonary opacities with peripheral eosinophilia, and acute noncardiogenic pulmonary edema.⁹ Docetaxel has been linked to acute or subacute diffuse interstitial pneumonia, acute permeability edema (with or without a pattern of adult respiratory distress syndrome), and pleural effusions.⁹ Interstitial pneumonitis caused by taxanes is hypothesized to be an immune-mediated delayed hypersensitivity reaction.⁹ Rarely, interstitial lung disease can occur with chronic chemotherapy dosing and may progress to pulmonary fibrosis.⁷ Approximately 1% to 4% of patients who receive conventional-dose paclitaxel or docetaxel every 3 weeks develop grade 3 or 4 pneumonitis.⁷ Bleomycin is an antitumor antibiotic that is known to cause lung injury, fibrosing alveolitis, or interstitial pulmonary fibrosis.¹⁰ The hypothesized mechanism involves oxidative damage, deficiency of the deactivating enzyme bleomycin hydrolase, genetic susceptibility, and an amplification of inflammatory cytokines. Bleomycin hydrolase is active in all tissues except the skin and the lungs, which may explain toxicity specific to the lungs. Risk factors for acquiring bleomycin-induced lung injury include age, cumulative drug dose, decreased renal function, the severity of the malignancy at presentation, and use of radiation therapy.¹⁰ To our knowledge, pulmonary fibrosis has never been reported in the literature as a consequence of pegylated liposomal doxorubicin therapy.

In conclusion, the prognosis for patients with recurrent UPSC is poor. We believe that our patient developed pulmonary fibrosis as a result of exposure to pegylated liposomal doxorubicin, although this has not been previously reported in the literature, to our knowledge. Although the patient received paclitaxel, which is known to cause pulmonary toxicity, the development of pulmonary fibrosis occurred more than 12 months after her exposure to paclitaxel. The median time to development of pulmonary fibrosis after receipt of agents has been reported to be 4 months.¹⁰ Earlier evaluation with pulmonary function testing or diffusing capacity of the lung for carbon monoxide may have prevented administration of the last dose and reduced pulmonary morbidity. We believe that oncologists prescribing these drugs should thoroughly evaluate their patients for any signs or symptoms of pulmonary toxicity.

Nicole S. Nevadunsky, Chinyere Mbagwu, Nina Mizrahi, Elizabeth Burton, and Gary L. Goldberg

Montefiore Medical Center, Albert Einstein College of Medicine, New York, NY

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

REFERENCES

1. Wright JD, Fiorelli J, Schiff PB, et al: Racial disparities for uterine corpus tumors: Changes in clinical characteristics and treatment over time. *Cancer* 115:1276-1285, 2009
2. Hamilton CA, Cheung MK, Osann K, et al: The effect of adjuvant chemotherapy versus whole abdominopelvic radiation on the survival of patients with advanced stage uterine papillary serous carcinoma. *Gynecol Oncol* 103:679-683, 2006
3. Fader AN, Drake RD, O'Malley DM, et al: Platinum/taxane-based chemotherapy with or without radiation therapy favorably impacts survival outcomes in stage I uterine papillary serous carcinoma. *Cancer* 115:2119-2127, 2009
4. Muggia FM, Blessing JA, Sorosky J, et al: Phase II trial of the pegylated liposomal doxorubicin in previously treated metastatic endometrial cancer: A Gynecologic Oncology Group study. *J Clin Oncol* 20:2360-2364, 2002
5. McMeekin D, Filiaci V, Thigpen J, et al: The relationship between histology and outcome in advanced and recurrent endometrial cancer patients participating in first-line chemotherapy trials: A Gynecologic Oncology Group study. *Gynecol Oncol* 106:16-22, 2007
6. Crystal RG, Bitterman PB, Rennard SI, et al: Interstitial lung diseases of unknown cause: Disorders characterized by chronic inflammation of the lower respiratory tract (first of two parts). *N Engl J Med* 310:154-166, 1984
7. Raghu G, Collard HR, Egan JJ, et al: An official ATS/ERS/JRS/ALAT statement: Idiopathic pulmonary fibrosis—Evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med* 183:788-824, 2011
8. Orens JB, Estenne M, Arcasoy S, et al: International guidelines for the selection of lung transplant candidates: 2006 update—A consensus report from the Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant* 25:745-755, 2006
9. Gross TJ, Hunninghake GW: Idiopathic pulmonary fibrosis. *N Engl J Med* 345:517-525, 2001
10. O'Sullivan JM, Huddart RA, Norman AR, et al: Predicting the risk of bleomycin lung toxicity in patients with germ-cell tumours. *Ann Oncol* 14:91-96, 2003

DOI: 10.1200/JCO.2012.44.5767; published online ahead of print at www.jco.org on January 28, 2013