Radiation-Induced Bronchiolitis Obliterans Organizing Pneumonia: A Case Report and Literature Review

Adedayo A. Onitilo, MD, MSCR, FACP 1
Aryal Govinda, MD 2
Jessica Engel, MSN 3

1Department of Hematology/Oncology, Marshfield Clinic Weston Center, Weston, Wisconsin; 2Department of Internal/Hospital Medicine, Marshfield Clinic, Marshfield, Wisconsin; 3Department of Oncology, Marshfield Clinic at Ministry St. Michael’s Hospital, Stevens Point, Wisconsin

Introduction

Bronchiolitis obliterans organizing pneumonia (BOOP) is defined histopathologically by the presence of a mass of granulation tissue in the bronchiolar lumen, alveolar ducts, and lung alveoli, along with varying degrees of interstitial infiltrate by mononuclear cells and, occasionally, by neutrophils.1,2 Radiographically, radiation-induced BOOP is characterized by pulmonary infiltrates that occur outside of the radiation field.3 BOOP is most often described as idiopathic, but it may also occur secondary to connective tissue disease, medication use, infection, aspiration, and inhalation of toxic fumes.1,3 Risk factors for radiation-induced BOOP have been reported in the literature and include age >50 years and concurrent endocrine therapy in patients with breast cancer treated with breast-conservative therapy.4,5 We report the case of a relatively young woman who developed radiation-induced BOOP while receiving tamoxifen for only 4 months.

Case Report

A 42-year-old woman presented with a new fever and non-productive cough for 3 weeks. The patient was diagnosed with right-sided pneumonia and treated with azithromycin. Symptoms did not improve. The patient had been diagnosed 4 months prior with right breast, low grade, estrogen receptor–positive and progesterone receptor–negative ductal carcinoma in situ (DCIS). Treatment for DCIS included lumpectomy and endocrine therapy with tamoxifen. She was also treated with radiation therapy to the right breast for 25 sessions, at a total dose of 5,000 cGy. Radiation therapy was completed 2 months before the patient present with pneumonia. The patient had a 3-pack-year history of smoking 20 years prior, and her paternal grandfather died of asbestos-related lung disease.

Physical examination was significant for a temperature of 100°F. Chest x-ray (CXR) showed right middle lobe and partial right lower lobe infiltrate (Figure 1A). Computed tomography (CT) of the chest revealed dense consolidation with air bronchogram in the right middle and lower lobe of the lung (Figure 1B). The patient was started on levofloxacin for pneumonia. Laboratory data, including basic metabolic panel, complete blood count, and liver function tests, were within normal limits. Bronchoscopy was performed and bronchial wash was negative for any organism, including bacteria and fungus.

The patient did not have any improvement in symptoms after completing the 10-day course of levofloxacin. Repeat CXR after 2 weeks showed worsening infiltrates. She was referred to a pulmonologist and underwent a second bronchoscopy with bronchoalveolar lavage (BAL). BAL cell count was 1,095, with differential showing 29% neutrophils, 6% lymphocytes, 27% monocytes, and 38% eosinophils. BAL was negative for Gram-stain, culture, acid-fast bacilli, and malignant cells. Transbronchial biopsy was most consistent with organizing pneumonia. The patient was started on a tapering course of oral prednisone. Her symptoms improved significantly, and repeat CXR after 4 weeks of prednisone showed near complete resolution of the pulmonary infiltrates (Figure 2A).

The patient was off prednisone for 4 days when symptoms reappeared. Repeat CXR showed new infiltrate in the right upper and lower lobe (Figure 2B). Laboratory testing was negative for anti-neutrophilic cytoplasmic antibody (ANCA) and anti-neutrophilic antibody (ANA), and C-reactive protein was elevated. To further evaluate her nonresolving pneumonia, the patient underwent video-assisted thoracic surgery and lung biopsy. The lung biopsy was reported as non-neoplastic lung tissue, with histopathologic changes compatible with bronchiolitis obliterans and organizing pneumonia. Based on presentation, history of radiation to the right breast, and pathologic findings on lung biopsy, she was diagnosed with BOOP. She was restarted on oral prednisone 60 mg daily with a very slow taper. Marked clinical improvement was observed, and CXR after 6 months showed complete resolution of pulmonary infiltrates (Figure 2C). At 8 months post-diagnosis of radiation-induced BOOP, the patient continues on low-dose prednisone 10 mg daily.
Pulmonary toxicity in the form of radiation pneumonitis is a well-known side effect of radiation therapy in breast cancer patients. In radiation pneumonitis, toxicity occurs through direct injury to the lung in the irradiated field. Radiation-induced BOOP is a distinct syndrome believed to occur following injury from radiation therapy outside the field of irradiation. BOOP was first reported in 1985 by Epler and associates. In 1995, Crestani and colleagues introduced criteria for the diagnosis of radiation-induced BOOP, including 1) radiotherapy to the breast within the last 12 months, 2) general and/or respiratory symptoms for 2 weeks or more, 3) radiographic lung infiltrates outside the radiation port, and 4) no evidence of a specific cause.

In the last decade, reports and studies of radiation-induced BOOP have increased, but the mechanism by which radiation induces injury in nonirradiated portions of the lung remains unclear. It has been postulated that a radiation-primed, autoimmune mechanism may be responsible for the development of radiation-induced BOOP.

The incidence of radiation-induced BOOP in breast cancer patients treated with radiation therapy after breast-conservative surgery ranges from 1.8–2.5%. In 2008, Ogo and coworkers reported survey results of patients with radiation-induced BOOP after breast-conservative therapy in Japan. It included 37 patients, the largest number of BOOP patients reported in the literature thus far. Patient age ranged from 41–75 years, and 78% of patients were older than 50 years. Major clinical symptoms included cough (68%), fever (41%), sputum production (16%), chest pain (5%), chest pressure sensation (5%), dyspnea (3%), and general fatigue (3%). The mean duration post-irradiation to the appearance of a pulmonary finding was 4.2 months. In 2009, Katayama and associates published a similar study that sought to find factors associated with radiation-induced BOOP in breast cancer patients treated with radiotherapy after breast-conservative surgery. A total of 16 patients ranging in age from 44–74 years were included, with 93% of patients older than 50 years. The interval from completion of radiotherapy to occurrence of any symptoms ranged from 2.3–7.9 months (median, 3.8 months). Pulmonary findings were unilateral in 62% of patients and bilateral in 48%. Ninety-three percent of patients were treated with endocrine therapy, and
62% were undergoing endocrine therapy concurrently with radiation treatment. The authors concluded that age greater than 50 years and endocrine therapy were associated with increased risk for developing radiation-induced BOOP in patients treated with breast-conservative therapy for breast cancer. The patient in our report was relatively young in terms of age at presentation. She also developed symptoms 2 months after completion of radiotherapy. Cough is the predominant symptom in the larger, aforementioned studies, and it was the initial symptom of radiation-induced BOOP in our patient, who later developed a fever. She received tamoxifen for 4 months, which may have increased the risk for developing radiation-induced BOOP. Radiologically, infiltrates were unilateral.

Diagnosis of radiation-induced BOOP is usually made using the criteria mentioned earlier, as outlined by Crestani and colleagues. Histopathologic diagnosis is made either by bronchoscopy and transbronchial biopsy or thorascopic lung biopsy. In the absence of steroid treatment, the symptoms of radiation-induced BOOP may disappear gradually over time. In a single study of 12 patients with radiation-induced BOOP symptoms disappeared completely in all patients within approximately 12 months in the absence of steroid treatment. Radiation-induced BOOP responds dramatically to steroid therapy, but relapses are common when steroids are stopped or tapered. This was demonstrated clearly in the present case. The patient was treated for 4 weeks with a tapering course of oral prednisone. She returned with development of pulmonary infiltrate on CXR only 4 days after the prednisone was stopped. For this reason, longer courses of steroids may be considered to prevent relapse. In the literature, patients are reported to continue on steroids for periods ranging from 1 week to 3.7 days after the prednisone was stopped. For this reason, radiologic resolution of pulmonary infiltrates was obtained following a 4-week tapering course of oral prednisone after breast-conserving therapy. Radiation-induced BOOP in patients treated with breast-conserving therapy for early breast cancer: radiation-induced lung toxicity. Int J Radiat Oncol Biol Phys. 2000;40:751-755.


11. Onitiilo and associates describe an interesting case of a 42-year-old woman who presented with cough and fever 2 weeks after she completed adjuvant radiation therapy for breast cancer. Radiologic studies and clinical presentation were consistent with pneumonia, but antibiotic therapy was not successful. A bronchoscopy with transbronchial biopsy showed a pattern of organizing pneumonia. Clinical and radiologic resolution of pulmonary infiltrates was obtained following a 4-week tapering course of oral prednisone. How-
ever, new pulmonary infiltrates and symptoms developed only 4 days after prednisone treatment was stopped. Video-assisted thoracic (VAT) lung biopsy confirmed the diagnosis of bronchiolitis obliterans organizing pneumonia (BOOP). A diagnosis of radiation-induced BOOP was made and the patient was restarted on a long course of oral prednisone, with complete resolution of the pulmonary infiltrates.

**Discussion**

BOOP was first described in 1985 by Epler and colleagues as a distinct entity with clinical, imaging, and prognostic features different from those of obliteratorive bronchiolitis and usual interstitial pneumonia/idiopathic pulmonary fibrosis (UIP/IPF). BOOP is characterized by an excessive proliferation of granulation tissue plugs within small airways and alveolar ducts, and is associated with chronic inflammation in the surrounding alveoli. Characteristically, distal airways and alveoli are involved simultaneously. Most cases of BOOP have no obvious cause and are referred to as primary, idiopathic, or cryptogenic BOOP. Other related etiologies include a variety of underlying disorders, such as infection, aspiration pneumonitis, acute respiratory distress syndrome, organ transplantation, collagen vascular diseases, hypersensitivity pneumonitis, toxic fume inhalation, and, rarely, chemotherapy or radiotherapy.

Radiation pneumonitis (RP) represents the most frequent pattern of radiation lung toxicity, and is recognized as a potential complication in the treatment of patients with breast cancer. One of its most characteristic features is that the pathologic and radiologic changes are confined to the outline of the fields of radiation. Occasionally, radiologic shadows extend beyond the radiation port, but these are less marked than those within the radiation port. Two distinct clinical stages have been recognized: an early transient radiation pneumonitis, which occurs approximately 4–12 weeks after completion of radiotherapy, and a later chronic radiation fibrosis, which occurs at least 9 months after treatment. The injury of RP is often clinically silent and reversible. The extent and severity of injury are related to the volume of lung irradiated, the total amount of radiation delivered, the rate of delivery (shorter time between treatments is associated with more injury), concomitant chemotherapy, and concurrent use of corticosteroids.

**Radiation-induced BOOP**

Radiation-induced BOOP was recognized as a distinct entity in 1995 after Crestani and coworkers and Bayle and associates independently reported on 3 patients who developed a clinicopathologic syndrome identical to idiopathic BOOP after radiation therapy for breast cancer. Of note, the 3 patients developed migratory pulmonary infiltrates that extended outside the field of irradiation. Today, radiation-induced BOOP is a well-recognized syndrome. Clinical manifestations are identical to those of idiopathic BOOP, although some patients may not have respiratory symptoms. It usually occurs 3–6 months after radiotherapy. The incidence of radiation-induced BOOP syndrome after breast cancer treatment ranges from approximately 1.8–2.9%. While RP is known to be a direct effect of irradiation, the underlying mechanism by which radiation-induced BOOP syndrome develops remains unclear. The occurrence of pulmonary infiltrates outside the radiation port and the frequent migratory pattern has suggested that radiation may have an indirect effect as a trigger of an autoimmune process.

Several reports have investigated risk factors for the development of lung injury due to radiation. Most studies focus on factors related to RP, but risk factors for radiation-induced BOOP have also been reported. Due to differences in dosing, schedules, agents, and timing with radiotherapy within these studies, the exact role of chemotherapy and endocrine therapy is difficult to interpret. In a retrospective study involving 702 patients, Katayama and colleagues evaluated factors associated with radiation-induced BOOP. They found that age (≥50 years) and concurrent endocrine therapy were significantly associated with BOOP in both univariate and multivariate analysis. However, chemotherapy, central lung distance (CLD), and irradiation of the supravacular region were not associated with radiation-induced BOOP. Kubo and coworkers evaluated risk factors of RP in 413 patients with breast cancer after whole breast irradiation following breast-conserving surgery. Eighty-four patients (21%) were diagnosed with RP, whereas radiation-induced BOOP was observed in 12 patients (2.9%). Multivariate analysis of factors associated with radiation-induced BOOP detected a significant difference only in CLD (>1.8 cm). In another study, Ogo and associates found that age (≥50 years) and concurrent endocrine therapy could promote the development of radiation-induced BOOP.

**Diagnosis of Radiation-Induced BOOP**

A diagnosis of radiation-induced BOOP should be considered in breast cancer patients who present after the end of adjuvant radiation therapy (typically after 3–4 months) with febrile flu-like illness and chest x-ray (CXR) showing bilateral patchy infiltrates that are not responsive to a typical course of antibiotics.

In 1998, Crestani and colleagues identified 4 criteria for diagnosing radiation-induced BOOP (radiotherapy to the breast within the last 12 months, general and/or respiratory symptoms for 2 weeks or more, radiographic lung infiltrates outside the radiation port, and no evidence of a specific cause). Symptoms can be minimal, and asymptomatic patients may be identified when chest radiographs
are performed during follow-up for breast cancer. Most patients have fever, nonproductive cough, crackles, and mild shortness of breath. A typical chest radiograph shows bilateral patchy (alveolar) infiltrates that are almost always outside the radiation filed, while cavities and effusions are rarely seen. Generally, the infiltrates gradually enlarge from their original site or new infiltrates appear as the clinical course progresses. However, migratory or “mobile” pulmonary infiltrates have been reported in 10–25% of patients. Chest computed tomography shows findings similar to chest radiography, with bilateral areas of consolidation and ground glass opacities with a peripheral location, although unilateral BOOP has also been reported. Bronchoscopy and bronchial wash for infection (bacterial, mycobacterium, virus, and fungus) and neoplastic cells are often performed. Bronchoalveolar lavage cell count shows an increase in lymphocytes, mast cells, CD3 and CD8 cells, and a decrease in CD4 cells and the CD4-CD8 ratio. In some cases, transbronchial lung biopsy reveals a pattern of organizing pneumonia; however, VAT is the established technique for diagnosing BOOP.

**Treatment of Radiation-Induced BOOP**

Although radiation-induced BOOP responds dramatically to steroid therapy, relapses often occur while tapering the dose or after stopping treatment. Prednisone is usually administered at a dose of 1 mg/kg/d (60 mg/d) for 1–3 months, then 40 mg/d for 3 months, then 10–20 mg/d or every other day, for a total of 1 year. A shorter treatment period of 6 months may also be used in certain situations, but is associated with disease recurrence in up to a third of patients. In the 5 largest studies of radiation-induced BOOP published to date, the median time of steroid therapy was approximately 1 year. Compared with other types of secondary BOOP, the prognosis of radiation-induced BOOP is excellent. Under certain circumstances, patients with minor or no symptoms can be monitored and treated at a later time, if needed.

In a retrospective analysis of 616 patients who underwent breast-conserving therapy for breast cancer, 12 patients developed BOOP; 6 of these patients were asymptomatic and the other 6 patients had only fever and cough. Of note, all patients had gradual resolution of symptoms and pulmonary lesions without the use of steroids. Thus, it may be beneficial to consider these patients as candidates for a conservative approach in order to avoid the toxicity of prolonged steroid treatments.

**Conclusion**

The case reported by Onitilo and colleagues highlights the importance of the differential diagnosis in the management of lung infiltrates, especially in breast cancer patients after radiation therapy. Breast cancer patients should have careful follow-up after completion of radiation therapy, and respiratory symptoms should be investigated thoroughly. Clinicians should be aware of radiation-induced BOOP when managing a patient with pulmonary infiltrates after radiotherapy, especially if lung lobes outside the radiation port are involved or the infiltrates are migratory. Infectious and neoplastic causes should be reasonably excluded, and, whenever possible, a pulmonary biopsy should be obtained (transbronchial or VAT) in order to confirm BOOP. Patients with minor or no symptoms can be managed without specific therapy and treated at a later time, if needed. Patients with moderate or severe symptoms should receive prednisone for 1 year. Shorter courses of prednisone may be sufficient in some cases, but recurrence of BOOP can occur in up to a third of these patients.

**References**