A Case of Bronchiolitis Obliterans Organizing Pneumonia Syndrome with Preceding Radiation Pneumonitis after Breast-conserving Therapy

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Recent case series have demonstrated that bronchiolitis obliterans organizing pneumonia (BOOP) after radiation therapy to the breast is a distinct clinicopathological entity. Most of the investigators speculated that radiation may prime the development of BOOP through an unidentified immunological process; however, none of them showed the relationship between direct radiation injury and BOOP. We report herein a case of a 67-year-old female with BOOP following direct radiation damage confined to the irradiated area after breast-conserving therapy. This is the first case demonstrating that BOOP after breast-conserving therapy arises from direct radiation injury.

Key words: bronchiolitis obliterans organizing pneumonia – breast cancer – radiation therapy – radiation pneumonitis

INTRODUCTION

A recent meta-analysis on radiation therapy after breast-conserving surgery confirmed that it could improve both the local control rate and the survival probability (1). The most frequent complications associated with breast-conserving therapy are breast and arm edema, breast pain and subcutaneous fibrosis. Furthermore, although much less common, the morbidity of cardiopulmonary sequelae is increased by the incidental irradiation of non-target tissues in the vicinity of the breast.

The well-recognized radiation-induced lung injuries are pneumonitis and fibrosis, which occur within the radiation field. Bronchiolitis obliterans organizing pneumonia (BOOP) is a distinct clinicopathological syndrome that has been associated with a variety of underlying disorders, including infection, aspiration pneumonia, organ transplantation, drugs, collagen vascular diseases and inhalation of toxic fumes (2). It has been ~10 years since Crestani et al. (3) first reported a case of migratory BOOP after unilateral radiation therapy for breast carcinoma. To our knowledge, ~40 cases of BOOP after breast-conserving therapy have been described in the English literature (3–11). The infiltrates on chest X-ray occur ipsilateral to the irradiated side, and then spread to the outside of the radiation field including the contralateral lung in most cases. These observations suggest the association between BOOP and radiation therapy; however, none of the authors have demonstrated the relationship between direct radiation injury and BOOP. We report herein a case of BOOP following direct radiation damage confined to the irradiated area after breast-conserving therapy.

CASE REPORT

A 67-year-old female without a history of tobacco use or any significant past history including collagen vascular diseases received a quadrantectomy and sentinel node biopsy at our hospital for left upper-outer quadrant breast cancer on August 23, 2002. She received 50 Gy in 25 fractions of radiation therapy through conventional tangential field irradiation using photons with 10 Gy in five fractions of electron boost to the tumor bed from October to November 2002. She was administered anastrozole concurrently with radiation therapy, because she had hormone receptor-positive breast cancer. She was followed-up by a surgeon and radiation oncologists regularly without any significant signs of recurrence or complaints thereafter.

A routine follow-up computed tomography (CT) scan in July 2003 showed patchy consolidation confined to the radiation field (Fig. 1A). In August 2003, the patient visited us with a complaint of non-productive cough and shortness of breath. Chest X-ray film showed left pulmonary infiltrate, which was in accordance with the findings of the previous CT.
scan. She did not receive any medication at that time. She experienced progression of her symptoms with deterioration of radiological findings in October 2003, and was referred to the Department of Respiratory Medicine. Chest X-ray film showed alveolar infiltrate at the left mid-lung field (Fig. 1B) and CT scan demonstrated a dense pneumonic infiltrate with air bronchograms in the left lower lobe and resolution of a patchy consolidation in the irradiated area (Fig. 1C). Laboratory data showed mild elevation of KL-6 and C-reactive protein without signs of viral or bacterial infections or autoimmune antibodies. Pulmonary function tests demonstrated a mild obstructive ventilatory defect with marked deterioration of the diffusing capacity for carbon monoxide (Table 1). Subsequently she underwent bronchoscopy and broncho-alveolar lavage (BAL) on October 15. The result of the BAL, shown in Table 2, demonstrated an increase in total cellularity and lymphocytosis with a decrease in the CD4/CD8 ratio. Cultures of BAL effluent were negative for infectious agents.

Lung biopsy specimens from the radiographically abnormal area confirmed the diagnosis of interstitial pneumonitis without findings of granulomatous lesion or infectious agents. The patient received 30 mg/day of oral prednisolone thereafter, which resolved her symptoms and improved the findings of her imaging studies immediately (Fig. 1D).

**DISCUSSION**

Several recent reports have noted that BOOP can develop after radiation therapy for early breast cancer (3–11). A French
group reported 15 cases of BOOP after radiation therapy to the breast in 1998, which was the largest series among such reports (6). Their inclusion criteria were: (i) radiation therapy to the breast for carcinoma within 12 months; (ii) general and/or respiratory symptoms lasting for at least 2 weeks; (iii) radiographic lung infiltrates outside the radiation port; and (iv) no evidence of a specific cause. The present case fits well with their definition of BOOP after radiation therapy to the breast.

The observation that infiltrates initially appear in the irradiated side of the lung in many cases led to the notion that radiation therapy may prime the development of BOOP. However, no reports have demonstrated the direct relationship between radiation damage and BOOP. Pulmonary infiltrates have been demonstrated on chest X-rays in most cases, and whether they were confined to the irradiated area was not evident. Unilateral infiltrates were shown on CT scan in some cases, however, and they were all separate from the irradiated area. In contrast, the present case showed patchy consolidation corresponding to the tangential field on follow-up CT scan before she developed infiltrates in the extrafield. This is the first case showing that direct radiation injury contributes to the occurrence of BOOP after breast-conserving therapy.

Although many cases of BOOP are idiopathic, the mechanism by which BOOP develops after breast irradiation still remains to be determined. However, several researchers have suggested that an immunologically mediated mechanism seems most plausible. It has been suggested that radiation pneumonitis represents a form of lymphocyte-mediated hypersensitivity reaction. Investigators from Sweden have shown a clear elevation of neutrophils, mast cells, eosinophils and lymphocytes in the BAL of breast cancer patients who received radiation therapy, compared with those in healthy controls (12). In addition, an Australian group demonstrated an increase in the CD4/CD8 ratio (13). Furthermore, they found that lavage from the non-irradiated side of the lung also showed lymphocytosis without any significant differences from the irradiated side. As a result, prominent lymphocytic alveolitis has developed in both lungs after strictly unilateral thoracic irradiation. Concerning BOOP after breast-conserving therapy, Majori et al. (9) have also demonstrated a significant increase in the percentage of lymphocytes, neutrophils, eosinophils and mast cells, which was similar to that of radiation pneumonitis. Most of the lymphocytes were T cells, however, in contrast to radiation pneumonitis, among which CD4+ cells decreased and CD8+ cells increased, resulting in a reduction of the CD4/CD8 ratio. In our present case, the result of the BAL was in accordance with these findings, except for the absence of neutrophilia and eosinophilia. In contrast, one group has observed an elevation of the CD4/CD8 ratio in patients with BOOP after breast-conserving therapy (8). Further investigations are needed to resolve these discrepancies among cases.

In conclusion, we reported a case of BOOP after breast-conserving therapy following radiation pneumonitis. Although some cases have presented BOOP without any radiological findings on the irradiated side of the lung, the observation that most cases develop pulmonary infiltrates from the irradiated side of the lung suggests the contribution of radiation therapy to the occurrence of BOOP. Our case is the first to demonstrate that BOOP after breast-conserving therapy actually develops in the irradiated area and then migrates outside the area, as has been speculated by many researchers.

**References**


**Table 2.** The results of broncho-alveolar lavage

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