Bronchiolitis Obliterans*
A New Clinical-Pathologic Complication of Irradiation Pneumonitis

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A patient underwent chest irradiation for small-cell carcinoma of the left lung. Several weeks following cessation of irradiation, the patient developed hypoxemia and reticulonodular densities within the radiographic field. Open lung biopsy yielded a pathologic diagnosis consistent with radiation pneumonitis along with a previously unreported association, bronchiolitis obliterans. Bronchiolitis obliterans should be included in the pathologic description of irradiation pneumonitis.

(Chest 1990; 97:1243-44)

BOOP = bronchiolitis obliterans organizing pneumonia

Radiation injury to the lung has been described as a clinical entity for many years since this mode of therapy was initially introduced for the treatment of malignant neoplasms. The clinical spectrum of this response has been clearly delineated as having dose-time relationships, histopathologic findings, pulmonary dysfunction, and roentgenographic changes. Prophylaxis against radiation pneumonitis, and therapy of the condition when it develops, has also been investigated. Most patients who develop roentgenographic findings do not progress to symptomatic fibrosis, but sustain a self-limited pneumonitis. When dyspnea becomes severe, pulmonary function deteriorates and the roentgenographic picture worsens; steroids are frequently used with variable, but generally successful outcome. We present a case of histologically proven irradiation pneumonitis that was associated with a previously unreported finding, bronchiolitis obliterans.

CASE REPORT

A 61-year-old man was diagnosed as having small-cell carcinoma of the suprahilar area of the left lung in May 1987. He received six cycles of cyclophosphamide, doxorubicin (Adriamycin), and vincristine followed by complete remission. From Dec 7, 1987 to Jan 19, 1988 the patient received 5,600 rads to the left hilum and mediastinum. In addition, he received 1,800 rads of prophylactic brain irradiation. He was admitted to the hospital on Feb 17, 1988 because of two weeks of dyspnea, cough productive of yellow sputum, and fever.

Physical findings consisted of dyspnea with conversation. The oral temperature was 37.7°C, respiration was 40, pulse rate was 106 beats per minute, and blood pressure was 115/80 mm Hg. The lungs were clear on auscultation and percussion and no cardiac murmurs were audible. The abdomen was free of organomegaly and results of the neurologic examination were normal.

Arterial blood gas determinations while the patient breathed room air revealed a pH of 7.50, PaO₂ of 63 mm Hg, PaCO₂ of 24 mm Hg, and oxyhemoglobin saturation of 93 percent. The hemoglobin was 11.1 g/dl, hematocrit was 33 percent, and white blood cell count was 5,700/cu mm. A chest roentgenogram demonstrated bilateral fluffy infiltrates paralleling the irradiation field (Fig 1). Cultures and smears of sputum were negative for bacteria, fungi, and acid-fast bacilli.

It was believed clinically that the patient had irradiation pneumonitis because of the time frame of the onset of dyspnea, hypoxemia, and the roentgenographic findings. He was then treated with prednisone 20 mg/day and discharged from the hospital; however, he was readmitted two days later because of worsening dyspnea, hypoxemia, and interstitial densities on the chest roentgenogram. On the second hospital day an open lung biopsy was performed within the irradiation port that disclosed marked fibrosis with no evidence of a malignant neoplasm. In addition, severe bronchiolitis obliterans and thrombi within pulmonary arterioles were observed (Fig 2). The patient's respiratory status deteriorated necessitating ventilatory support through an endotracheal tube. Doppler study and impedance plethysmography of the lower extremities failed to demonstrate leg or thigh thromboses. Because of the findings of bronchiolitis obliterans, he was treated with large doses of methylprednisolone, but he could not be successfully removed from the ventilator and he subsequently died.

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Figure 1. Chest roentgenogram showing reticulonodular densities approximating irradiation port.

Figure 2. Histologic section of open lung biopsy specimen showing obliteration of bronchile (arrow) lumen by fibroblastic proliferation. Adjacent alveoli show organizing pneumonia (hematoxylin-eosin, original magnification × 40).
DISCUSSION

Extensive reviews of the pathologic findings of lung irradiation have been published, but to our knowledge, bronchiolitis obliterans has not been described as a feature. The histopathologic findings in our patient were consistent with irradiation-induced lung disease and included fibrotic changes, alveolar thickening, and microthrombi in small pulmonary vessels. Our patient was also treated with cyclophosphamide, a drug that has been associated with pulmonary disease, but bronchiolitis obliterans has not been observed as a complication with this drug (to our knowledge). It is unlikely that bronchiolitis obliterans occurred prior to irradiation therapy since preirradiation chest roentgenograms disclosed no evidence of nodular or reticulonodular patterns until shortly after irradiation therapy was terminated. The emergence of abnormal roentgen patterns corresponded to the expected time following irradiation therapy. The patient's lung biopsy specimen did demonstrate the usual described changes of radiation-induced lung disease, but the finding of bronchiolitis obliterans was surprising. Unfortunately, despite ventilatory support and large doses of corticosteroids, the patient died of respiratory failure. This is in contrast to generally adequate responses to corticosteroid therapy in both irradiation pneumonitis or bronchiolitis obliterans when they occur as separate entities.

The histopathologic picture of irradiation pneumonitis includes vascular engorgement and thrombosis of capillaries and arterioles. In addition, edema, intimal proliferation, and medial changes are found along with subintimal accumulations of lipid-laden macrophages. Other reports describe fibrin-rich alveolar deposits, hyaline membranes, thickened alveolar septae, a sparse number of inflammatory cells, focal necrosis of the bronchial mucosa, squamous metaplasia, and bronchiectasis. Several months after irradiation, dense fibrosis and anatomic alterations are noted. Of notable absence in these reports is bronchiolitis obliterans, which was a major histologic finding in our patient. Excellent reviews of bronchiolitis obliterans also fail to mention any association with irradiation. There is an extremely small likelihood that bronchiolitis obliterans and the usual findings of irradiation lung disease in our patient were separate occurrences and of differing causes. Our patient's symptoms are indistinguishable from those with bronchiolitis obliterans organizing pneumonia (BOOP). Moreover, the absence of chest auscultatory findings has been reported in 28 percent of patients with BOOP. The chest roentgen abnormalities in our patient are quite similar to those described in BOOP, except the involvement was confined to the irradiation port rather than progressing diffusely over both lung fields. Finally, microthrombi, which are a feature of irradiation pneumonitis, are not observed in BOOP; while other histologic changes are quite similar. We thus believe that bronchiolitis obliterans should be included as one of the histopathologic findings of irradiation lung disease.

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Pulmonary Function Changes in the Acute Stage of Histoplasmosis, with Follow-Up*

An Analysis of Eight Cases

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We have studied eight patients, six children and two adults, during a microepidemic of soil- and patient-proven histoplasmosis. Pulmonary function tests were performed between the 15th and 23rd days after the onset of symptoms, and repeated between the fifth and sixth, the ninth and tenth and the 15th and 22nd months afterward. Initial abnormalities were mild in seven cases and severe in one. There was a restrictive pattern in three cases and an obstructive pattern in two. The fraction of CO extraction was reduced in five cases and the diffusing capacity for CO was reduced in five of six cases so tested. Hypoxemia was present in three cases. On follow-up, the obstructive defect had disappeared by the sixth month, the restrictive pattern by the tenth month, and the diffusing defect still remained in three cases by the end of follow-up. Hypoxemia remained only in the severe case. (Chest 1990; 97:1244-45)

$Deo = steady-state diffusing capacity for carbon monoxide; Fco = fractional uptake of CO; Fico = fraction of inspired CO; FEco = fraction of expired CO

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