A 63-year-old man with progressive dyspnea was referred for consideration of open lung biopsy of a persistent interstitial infiltrate (Fig 1). He had initially presented to an outside hospital 6 months previously with bilateral hilar adenopathy. A left thoracotomy was performed, and biopsy specimens revealed poorly differentiated small cell lung carcinoma. Two months after presentation, he was given chemotherapy with cisplatin (later carboplatin) and etoposide (VP16-213), and granulocyte colony stimulating factor to prevent neutropenia. Three cycles of these agents were given. However, a repeat CT scan of his chest revealed persistent hilar fullness and an enlarging left lower lobe mass. Accordingly, 3½ months after presentation, radiation treatments to his mediastinum were started, and a total of 50 Gy was given over 6 weeks.

Four weeks prior to the current admission, the patient developed fever, chills, nonproductive cough, and shortness of breath. Chest radiographs revealed a left-sided infiltrate, and a regimen of antibiotics was initiated for a presumed pneumonia. His symptoms persisted, however. Another chest CT scan revealed left hilar adenopathy and bilateral interstitial infiltrates. Corticosteroid therapy was begun, without appreciable effect. Bronchoscopy with transbronchial biopsy was performed, which revealed metaplasia with tumor cells. No Pneumocystis organisms were identified, but he was treated with trimethoprim-sulfamethoxazole against this possibility. During this period, the patient had defervesced but continued to complain of dyspnea and a dry, hacking cough. His pulmonary infiltrates persisted, and he also developed mild hypoxemia. Open lung biopsy was recommended for diagnosis, and he was transferred to a tertiary care center for consideration for this procedure. Pulmonary consultation was requested, and his radiographs were reviewed.

*From the Veterans Affairs Medical Center, Eastern Virginia Medical School, Hampton.

Reprint requests: Dr. Gentry, VA Medical Center, Hampton, VA 23667
Diagnosis: Acute radiation pneumonitis

The capacity for ionizing radiation to injure normal lungs and pleura has been known since the early 1920s and has proved the major limitation to radiation therapy for neoplastic disease of the chest.\(^1\) Clinical pneumonitis can be seen in as many as 15 percent of patients receiving radiation, although radiographic features are present in a much larger proportion.\(^2\) The mechanism by which ionizing radiation causes injury is not entirely clear but is likely related, at least in part, to the development of toxic free radicals. These free radicals can cause breakage of covalent bonds within structural macromolecules, and if the damage is sufficiently severe, lead to cell death within several hours. Free radicals also can damage cell DNA, leading to genetic mutations and abnormal or ineffective mitoses which also can cause cell death, even after several cell divisions.\(^3\)

Clinically, radiation pneumonitis is characterized by the gradual development of cough and shortness of breath. Dyspnea may become quite severe and can be associated with tachypnea, cyanosis, and signs of acute cor pulmonale.\(^1\) Fever often is present and may be low-grade or high and spiking. Sputum is present inconstantly and usually is scant. Frank hemoptysis is rare, but mild staining or streaking of sputum with blood is not uncommon. Pulmonary function tests show lung restriction and decreased diffusing capacity. Arterial blood gases often show hypoxemia and an increased alveolar-arterial gradient of oxygen. Other laboratory values are generally nonspecific.\(^1,2\)

Of all diagnostic tests, the chest radiograph is undoubtedly the most crucial. The most common initial finding is a diffuse haziness in the affected area, which gives way to patchy alveolar infiltrates. Air bronchograms are a frequent occurrence. The hallmark of radiation pneumonitis, however, is the straight, sharp edge of the infiltrate, corresponding to the boundary of the radiation port (Fig 2).\(^4\) As in this case, the nonanatomic distribution of the infiltrate often provides a major clue to its etiology. It has been reported that radiographic changes, sometimes extensive in nature, can occasionally be found outside the radiation port.\(^5\) The etiology of these changes is unclear, but may be related to lymphatic obstruction, "stray" radiation, or release of inflammatory mediators. When compared to the primary infiltrates, however, these abnormalities generally are minor.\(^1\)

Radiation pneumonitis is usually recognized within 2 to 6 months following the end of treatment, although onset as early as 2 weeks has been reported.\(^1,4\) In the case described here, the onset was somewhat earlier, with symptoms beginning at about the time of the final treatment. This accelerated course could be related to previously administered chemotherapy. A number of chemotherapeutic agents, including actinomycin D, cyclophosphamide, vincristine, and bleomycin, have been shown to potentiate adverse effects of radiation on the lung.\(^6,8\) None of the agents used in this patient have been associated with increased incidence of radiation pneumonitis. However, cisplatin has been reported to increase the sensitivity of intestinal crypt cells to external beam radiation.\(^9\)

No therapy has been shown definitively to improve the course of radiation pneumonitis. Studies in rodents have demonstrated improvement in various physiologic parameters following administration of corticosteroids,\(^10\) but reports of efficacy in humans have been mixed. It is noteworthy that this patient received steroids, but showed no apparent response. Nevertheless, in severe cases of radiation pneumonitis, most authorities recommend the institution of steroid therapy at a dose of at least 60 mg/d of prednisone, or its equivalent.\(^1,2\) This dose should be tapered slowly, since cases have been reported of "rebound" pneumonitis, occurring following withdrawal of corticosteroid therapy.\(^11\)

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