A Man With Interstitial Pneumonia and Pancytopenia During Radiotherapy*

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A 61-year-old man with carcinoma of the lung presented with a 1-week history of worsening dyspnea, nonproductive cough, and fever (ie, temperature of up to 39°C) while still receiving radiotherapy. Six months earlier, he had received a diagnosis of stage IV non-small cell carcinoma. He had received six courses of chemotherapy, which included cisplatin and etoposide, with partial response. Chemotherapy was followed by radiotherapy to the mediastinum and right middle lobe. The total dose was 5,400 cGy, consisting of 4,140 cGy in 23 fractions, and a boost to the tumor bed of 1,260 cGy in 7 fractions. Toward the end of his radiotherapy, the patient began experiencing worsening dyspnea associated with fever and dry cough. His medications included oral dexamethasone, 2 mg daily, which was started in preparation for radiotherapy to the brain.

**Physical Findings**

A physical examination revealed a pale, dyspneic, and cachectic man. His temperature was 38.5°C, heart rate was 105 beats/min, and oxygen saturation was 90% while the patient was breathing 100% oxygen by facemask. Scattered end-inspiratory crackles were heard all over the lung fields. The rest of the physical examination findings were within normal limits.

**Laboratory Findings**

A chest radiograph (Fig 1) revealed bilateral interstitial infiltrates. Laboratory results were remarkable for pancytopenia, and hemoglobin concentration was 8.1 g/dL, WBC count was 2,925 cells/µL, and platelet concentration was 67,500 cells/µL. Within 24 h, the patient developed severe hypoxemic respiratory failure requiring mechanical ventilation. A CT scan of the chest (Fig 2) demonstrated diffuse bilateral interstitial changes with ground-glass opacities, mostly in the upper lobes. Alveolointerstitial changes could be appreciated at the lower lobes. Therapy with levofloxacin was initiated. The results of BAL were noncontributory, and the results of Gram-staining and cultures were negative, with no malignant cells being demonstrated to be present. There was a predominance of CD4 lymphocytes in the BAL fluid, and the CD4/CD8 ratio was 1:1.

**What diagnostic study should be performed to confirm this patient’s diagnosis?**

Figure 1. A postintubation chest radiograph is shown. Bilateral diffuse interstitial infiltrates can be seen. The right lower lobe is relatively spared, and there are no masses or mediastinal lymphadenopathy. The heart is not enlarged, and there are no signs of pulmonary congestion.

Figure 2. A contrast-enhanced CT scan of the chest. Severe diffuse bilateral interstitial changes with ground glass appearance are seen. Bullous emphysema in the left upper lobe is also present. No masses or lymph nodes can be seen.
Diagnosis: A lung biopsy confirmed the diagnosis of sporadic radiation pneumonitis

Diffuse pulmonary infiltrates due to interstitial lung disease is one of the most common and serious complications in patients with a compromised immune system. The mortality rate varies between 15% and 90%, depending on the underlying disease, the severity of lung involvement, and the total impairment of host defenses. An evaluation of the immunocompromised host with diffuse pulmonary infiltrates can be difficult, frustrating, and time-consuming. Opportunistic and bacterial infections are the most common cause of such pulmonary infiltrates and must be distinguished from other conditions such as drug reactions, radiation pneumonitis (RP), the recurrence of malignant disease, volume overload, and pulmonary hemorrhage, among others. The complexity of and potential fatality from the condition mandates aggressive evaluation and quick identification of the underlying process. Moreover, it is practically impossible to address all the diagnostic possibilities with empiric treatment. In view of the diversity of etiologies, the nonspecific nature of the clinical and radiologic findings, and the low yield of noninvasive procedures, invasive diagnostic methods often are required. The least invasive procedure that may provide useful information is BAL. Unfortunately, some disorders that occur predominantly in the interstitium require the performance of more invasive techniques, such as transbronchial biopsy (TBB) or even open lung biopsy (OLB), which seems to be well-tolerated even in critically ill patients. However, outcome studies have been unable to show convincingly an impact on overall survival for this invasive approach. Although the guidelines for the management of immunocompromised patients with pulmonary infiltrates have been developed, they may be predicated on data from a single institution or may depend on diagnostic procedures and laboratory support that are not necessarily available to physicians in all locations. Therefore, an individualized approach should be tailored to each patient, considering all the pertinent clinical data that would dictate the extent and pace of additional interventions.

We suggest that the first step in managing these patients is a quick noninvasive workup including sputum and blood cultures, relevant serologic tests, chest radiograph, and CT scan followed by BAL. Typically, therapy with broad-spectrum antibiotics will be initiated based on clinical characteristics and epidemiologic considerations such as age, clinical context, fever, sputum analysis, Gram-stain, WBC count, and radiologic findings. We would not recommend starting empiric therapy without making this initial diagnostic effort. If the patient fails to improve within 48 to 72 h, our approach would be to proceed to either TBB or OLB, depending on the clinical circumstances.

RP is a distinct clinical entity that may complicate radiation therapy in intrathoracic organs. The incidence and severity of this complication is influenced by a variety of factors including the total dose of irradiation, dose fractioning, the lung volume subjected to irradiation, and preexisting lung disease. Current data suggest that the following two separate mechanisms are involved: (1) classic RP, which is a consequence of the direct effects of radiation on the lung, releasing cytokines from injured pulmonary parenchyma within the field of radiation; and (2) sporadic RP, which is characterized by bilateral lymphocytic alveolitis, occurring in regions of the lung outside of the radiation fields. Typically, classic RP occurs from 3 to 6 months after the beginning of treatment and is related to the dose and extent of the lung area irradiated. Sporadic RP occurs in only 5 to 10% of patients in an unpredictable manner. In the majority of patients, it is characterized by early onset (usually 2 to 6 weeks after the completion of therapy) and complete recovery.

This patient presented with early-onset symptoms and pancytopenia, both of which are uncharacteristic of sporadic RP. Previous research has suggested that cellular interaction between lung parenchymal cells and circulating immune cells, mediated through a variety of proinflammatory cytokines (ie, interleukin-1α and interleukin-6), chemokines, and adhesion molecules, is the primary mechanism for radiation-induced lung injury. This process results in lymphocytic alveolitis outside of the radiation field. The predominance of CD4 lymphocytes in the BAL fluid and biopsy specimens of patients with sporadic RP, as seen in the patient who is under discussion, provides additional support for the concept of an immunologically mediated response. The time course and severity of disease in the case presented are distinctly unusual, suggesting that sporadic RP may develop very early, even during the course of therapy, and at times may lead to severe respiratory failure.

The most common laboratory finding in patients with RP is peripheral polymorphonuclear leukocytosis. Indeed, pancytopenia has not been previously reported. The prompt resolution of the pancytopenia in response to therapy with steroids suggests immune system-mediated bone marrow suppression. Thus, sporadic RP may have systemic implications that extend beyond the affected lungs.

The present patient experienced interstitial pneumonitis while receiving radiation therapy. An open left lung biopsy, which was performed on the
third day, revealed interstitial edema, thickening of the alveolar walls due to fibrosis, and diffuse alveolar damage features that were consistent with irradiation-induced lung injury (Fig 3). There was no predominance of CD4 lymphocytes. There was no evidence of an infectious or malignant process. Moreover, chemotherapy had concluded 4 months prior to his hospital admission, making drug-induced lung injury an unlikely possibility. The clinical context and course, as well as the histopathologic features, confirm the diagnosis of sporadic RP.

Therapy with IV methylprednisolone, 2 mg/kg/d, was initiated, and therapy with antibiotics was stopped. Within 3 days, a remarkable improvement was noticed. He was quickly weaned off the ventilator and was successfully extubated. By the fourth day of steroid therapy, the chest radiograph findings normalized and the pancytopenia resolved. He was discharged from the hospital 10 days after his admission.

**Clinical Pearls**

1. The diagnostic approach to an immunocompromised patient with bilateral pulmonary infiltrates must be quick, based on the clinical context and local resources.
2. The low yield of noninvasive procedures and the nonspecific nature of the clinical and radiologic findings often dictate an invasive approach that includes BAL followed by either TBB or OLB.

3. Sporadic and classic RP are distinct clinical entities with different mechanisms and clinical presentations.
4. Bilateral interstitial infiltrates appearing during radiation therapy could be a manifestation of sporadic RP.
5. Both the pulmonary infiltrates and pancytopenia associated with sporadic RP may respond to corticosteroid therapy.

**Selected Readings**


