

Radiation Pneumonitis

Richard J Wall MD MPH and Lynn M Schnapp MD

Introduction

Radiation-induced lung injury is a serious complication following thoracic irradiation for the treatment of lung, breast, or hematologic malignancies. Two distinct lung injury patterns have been described: early radiation pneumonitis and late radiation fibrosis. Both syndromes commonly include dyspnea and cough. The chest radiograph invariably shows pulmonary infiltrates. The following case describes a patient with human immunodeficiency virus (HIV) and Hodgkin's lymphoma, who developed radiation pneumonitis after mantle radiation. The case highlights features of typical radiation pneumonitis. In addition, the case demonstrates that establishing the correct diagnosis in immunosuppressed patients requires consideration of other potential infectious and noninfectious processes.

Case Report

A 34-year-old white man presented with a 1-week history of exertional dyspnea. One week prior to presentation the patient noted the onset of nonproductive cough, wheezing, and fatigue. He attributed the symptoms to a viral illness, and treated himself conservatively with fluids and rest. Two days prior to presentation, he noted worsening breathlessness during household chores. The evening prior to presentation, he experienced dyspnea and lightheadedness while cooking dinner. After sitting down, the symptoms quickly resolved. He had no dyspnea at rest. His appetite was good and his weight was stable. He did not have fevers, chills, sweats, chest pain, pleurisy, orthopnea, edema, syncope, rash, or sick contacts. The patient worked

as a salesman in a department store. He denied tobacco, alcohol, or drug use. He did not have any recent travel, contact with animals, unusual hobbies, or inhalational exposures.

His medical history was notable for Hodgkin's disease and HIV, both of which were diagnosed 10 months prior to the current illness, when he presented with extensive lymphadenopathy of the retroperitoneum, mediastinum, axillae, and neck. Lymph node biopsy confirmed a diagnosis of nodular sclerosing Hodgkin's lymphoma (stage 3B).

The Hodgkin's disease was treated with 3 cycles of the Stanford V chemotherapy regimen (doxorubicin, vinblastine, mechlorethamine, etoposide, and bleomycin). The protocol included prednisone, 75 mg every other day. He completed the regimen 5 months prior to the current illness. Adjunctive granulocyte colony stimulating factor was intermittently given for chemotherapy-induced neutropenia. Throughout the chemotherapy period he took a double-strength trimethoprim-sulfamethoxazole (TMP-SMX) tablet daily for pneumocystis prophylaxis, and fluconazole, 100 mg daily, for fungal prophylaxis. Ten weeks prior to the current illness he completed consolidative mantle radiation therapy. He received a total dose of 36 Gy, using anterior-posterior and posterior-anterior configurations. With the exception of mild esophagitis and minimal skin erythema, he tolerated the regimen well. Two months prior to the current illness, his lymphadenopathy remained small, and he was thought to be in remission.

At the time of HIV diagnosis, his cluster of differentiation (CD4+) count was 460 cells/ μ L and his viral load was > 1 million copies/mL. Highly active anti-retroviral therapy was initiated with abacavir, lamivudine, and efavirenz. However, the patient stopped the medications within 1 week because he developed fatigue. His physicians were unaware that he had stopped the medications until 3 months prior to the current illness. When he resumed highly active anti-retroviral therapy, his CD4+ count was 84 cells/ μ L and his viral load was > 1 million copies/mL.

When he arrived in clinic, the patient looked well and was breathing comfortably, with temperature 36°C, blood pressure 133/92 mm Hg, pulse 88 beats/min, respiratory rate 12 breaths/min. Resting room-air oxygen saturation was 96%. His lungs demonstrated mild wheezing bilaterally.

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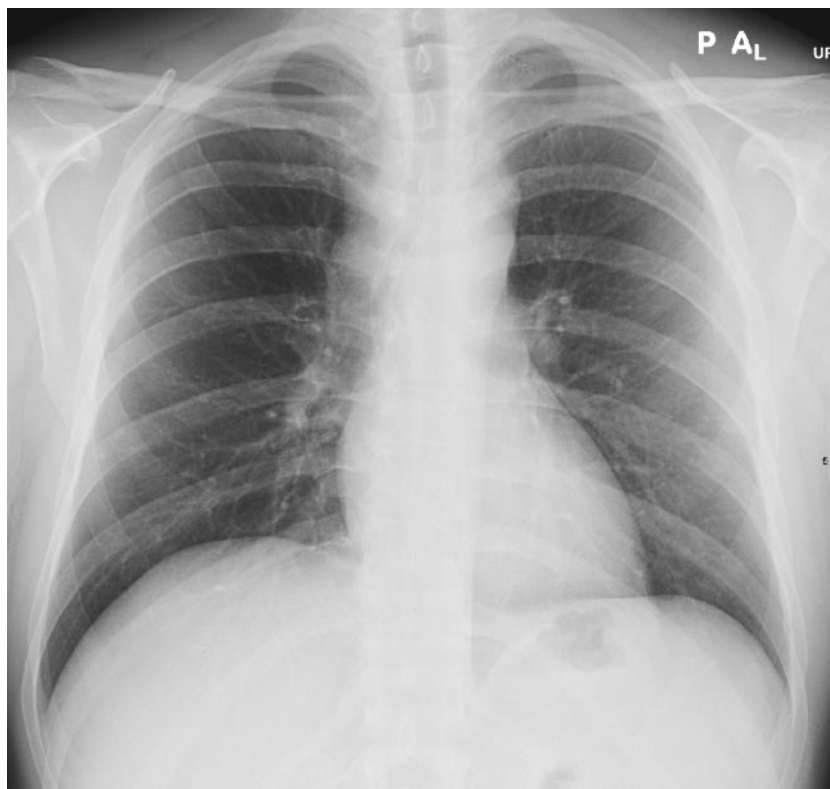


Fig. 1. Baseline chest radiograph from 7 months prior to the presentation discussed here.

ally and a prolonged expiratory phase, but no crackles or dullness. The remainder of his examination was unremarkable. He was diagnosed with post-viral bronchospasm, prescribed an albuterol inhaler, and told to follow up in 2 weeks.

The patient returned to clinic 1 week later, complaining of worsening exertional dyspnea and a nagging dry cough. He stated that the albuterol inhaler was not helping, and that he was unable to climb more than one flight of stairs without resting. He also described intermittent fevers of up to 38°C. On examination the patient was mildly dyspneic at rest, with temperature 36.5°C, blood pressure 129/74 mm Hg, pulse 104 beats/min, and respiratory rate 18 breaths/min. His room-air saturation was 96% at rest. After walking 100 m on a level surface, room-air saturation was 93% and heart rate was 128 beats/min. A detailed physical examination was otherwise normal.

A baseline radiograph (Fig. 1) from 7 months prior to this presentation was compared to a new chest radiograph (Fig. 2), which revealed bilateral perihilar opacities. The noninfectious possibilities included pulmonary edema, tumor recurrence, and radiation pneumonitis. The infectious possibilities included bacterial pneumonia, *Pneumocystis carinii* pneumonia, mycobacteria, fungi, and viral infection.

Complete blood count, electrolytes, and liver function tests were normal. Expecterated sputum revealed mixed



Fig. 2. Chest radiograph shows new bilateral perihilar infiltrates.

bacteria, but no white cells, acid-fast bacilli, or fungi. Although a sputum direct fluorescent antibody stain was negative for *P. carinii* pneumonia, he was nevertheless treated with TMP-SMX because of the high likelihood of *P. carinii* pneumonia. He was referred for bronchoscopy. Chest

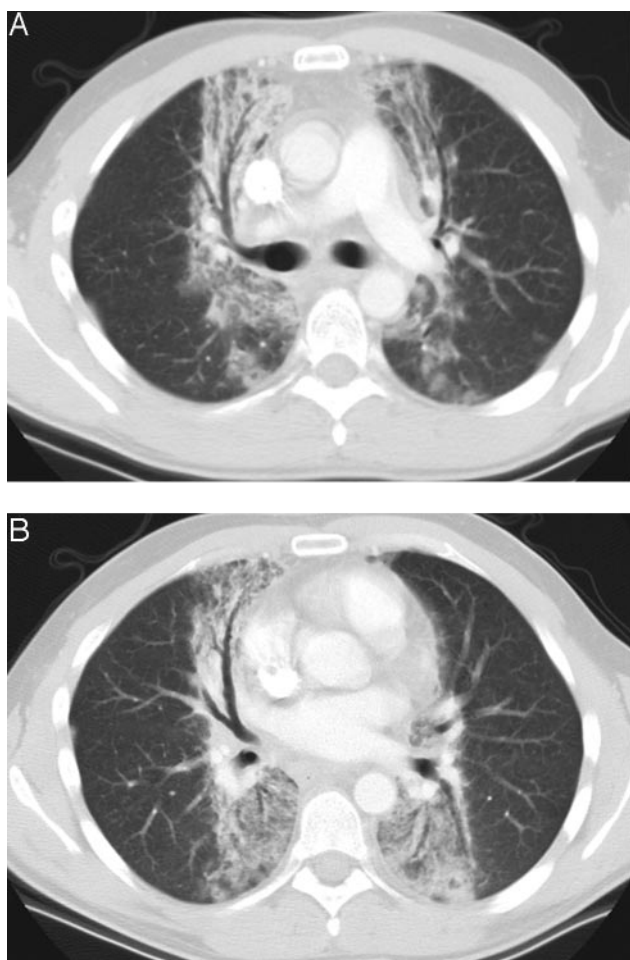


Fig. 3. These 2 sections from the chest computed tomogram show classic radiation pneumonitis. The lung fields reveal coarse perihilar reticular opacities and traction bronchiectasis. Note the straight, nonanatomic border of the opacity, which corresponds to the radiation port.

computed tomography (CT) revealed coarse perihilar opacities and traction bronchiectasis, with a straight, nonanatomic border corresponding to the radiation port (Fig. 3). A diagnosis of radiation pneumonitis was made, based on these classic findings. Bronchoscopy was cancelled and TMP-SMX was decreased to a daily prophylactic dose. When the patient returned to clinic 2 days later, he felt slightly better and agreed to conservative therapy without corticosteroids. Over the next few weeks, his cough and dyspnea resolved. Follow-up films showed resolution of the infiltrates (Fig. 4).

Discussion

This case illustrates a classic presentation of radiation pneumonitis following mediastinal irradiation. Using a common classification system,¹ our patient had grade 2

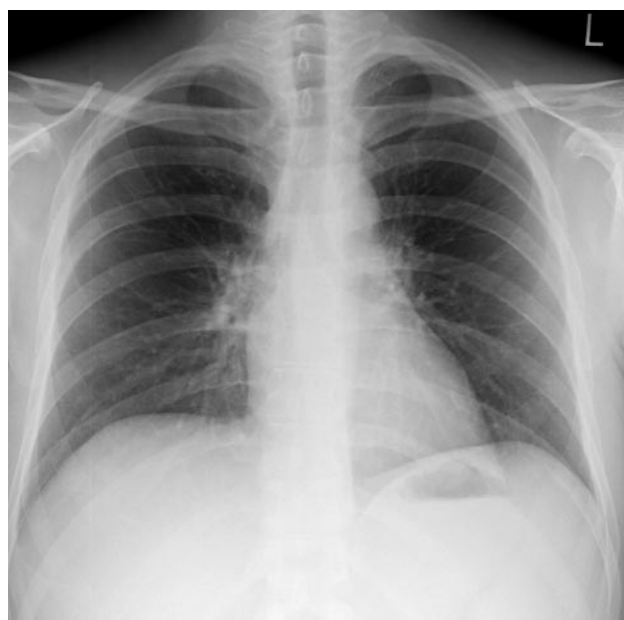


Fig. 4. Chest radiograph 5 months later shows resolving perihilar opacities.

pneumonitis. The patient developed progressive exertional dyspnea and dry cough 10 weeks after mantle radiation for Hodgkin's disease. Although the chest radiograph showed ill-defined perihilar infiltrates, the chest CT revealed classic findings of traction bronchiectasis and opacities, with a straight edge that corresponded to the radiation port. The patient improved clinically and radiographically without any treatment.

Two well-recognized clinical syndromes can occur after irradiation to the lung: radiation pneumonitis and radiation fibrosis (Table 1).

Radiation Pneumonitis

Radiation pneumonitis occurs within 6 months after radiation exposure, with a peak onset at 1–3 months. The true incidence of radiation pneumonitis is difficult to determine for a variety of reasons,² but symptomatic pneumonitis has been described in 1–37% of patients who receive thoracic radiation.^{3–5} Symptom onset is usually insidious and can mimic other diseases.⁶ Dyspnea is the most common symptom, ranging from mild to severe. The dyspnea is frequently accompanied by a dry cough and low-grade fevers. Less common symptoms include chest pain or fullness, weight loss, malaise, and fatigue. Symptoms may precede detectable changes on the radiograph. The physical examination is unreliable in radiation pneumonitis. Many patients have no abnormal chest findings, while others have crackles or a pleural rub over the area of irradiation. Dullness to percussion from a small pleural

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Table 1. Features of the 2 Types of Radiation-Induced Lung Injury

Feature	Radiation Pneumonitis	Radiation Fibrosis
Onset after radiation exposure	1–6 months	6–24 months
Radiographic findings	Ill-defined perihilar infiltrates Straight-edged parenchymal opacities that conform to the radiation port Traction bronchiectasis	Ill-defined or straight-edged fibrosis and scarring Traction bronchiectasis
Common symptoms*	Dyspnea, nonproductive cough, low-grade fever	Dyspnea, nonproductive cough
Examination findings	Usually none Less commonly Rales Friction rub Skin erythema Skin erythema	Depending on severity: Rales Dullness to percussion If secondary pulmonary hypertension: Cor pulmonale Cyanosis Clubbing Hepatomegaly
Disease course	Spontaneous resolution within 1 month Progression to fibrosis	Permanent parenchymal damage that stabilizes within 2 years after exposure

* Many patients have no symptoms, despite abnormal radiographic findings.

effusion is occasionally noted. These effusions rarely increase in size, however, and often spontaneously remit. Skin erythema may outline the radiation port, but such changes do not correlate well with the severity of pulmonary injury. Laboratory findings are nonspecific. Although the signs and symptoms of radiation pneumonitis may resolve spontaneously, many patients progress toward permanent fibrosis.

Radiation Fibrosis

Radiation fibrosis typically occurs 6–24 months after radiation exposure, and is characterized by progressive and irreversible pulmonary fibrosis.⁶ Rarely, patients may develop the syndrome earlier than 6 months. Although the fibrous process can initially worsen, the changes usually stabilize by 2 years following radiation exposure.⁷ Patients who never experience symptomatic radiation pneumonitis may present with fibrosis years later. Symptoms differ and depend on the severity of the fibrosis. Some individuals are left with permanent disability and increased susceptibility to respiratory infections. In severe cases, patients develop secondary pulmonary hypertension and cor pulmonale. Physical examination findings are variable. Abnormal breath sounds may be heard over areas with severe parenchymal damage, but the most dramatic findings occur in patients with signs of pulmonary hypertension. These patients often have evidence of chronic cor pulmonale, including cyanosis, tachypnea, hepatomegaly, and club-

bing. Fortunately, modern radiation techniques have reduced the incidence of such complications.

The molecular mechanism of radiation-induced cellular injury is incompletely understood.⁶ One theory is that ionizing radiation generates free radicals, leading to damaged bonds in various cellular structures and macromolecules such as lipids, peptides, or deoxyribonucleic acid. Cells with a high rapid turnover are at especially high risk, including bronchial epithelium and alveolar type II cells. Another theory is that radiation induces pulmonary macrophages to release proinflammatory cytokines and fibroblast mitogens, such as tumor necrosis factor alpha, interleukin 6, transforming growth factor beta, and basic fibroblast growth factor.

In animal models of radiation-induced lung injury, lungs exhibit increased capillary permeability, interstitial congestion, and a proteinaceous alveolar exudate associated with hyaline membranes.⁶ The normal respiratory epithelium is replaced by atypical flattened cells. Later, the alveolar exudate clears, fibroblasts migrate into the alveolar walls, and the interstitium is markedly thickened. Although the parenchyma is distorted, the airways usually remain unaffected.

Several risk factors impact the development of radiation-induced lung disease (Table 2). One key risk factor is the mean radiation dose administered to the lung.⁸ Radiation pneumonitis seldom occurs with doses below 30 Gy, but it is common with doses greater than 40 Gy.³ Another important factor is the volume of lung irradiated. For ex-

Table 2. Risk Factors for Radiation-Induced Lung Injury

Radiation treatment factors
Mean lung dose
Lung volume irradiated
Timing and rate of exposure
Prior irradiation
Chemotherapy
Steroid withdrawal
Pre-existing lung disease
Individual patient factors
Performance status
Female sex
Older age

ample, a fractionated dose of 30 Gy administered to 25% of total lung volume may not cause any symptoms, whereas the same dose delivered to the entire volume of both lungs would probably be fatal.⁹ The dosing schedule also plays a role; twice-daily split doses are safer than single daily doses. In general, a radiation dose is less toxic when spread out over a longer period.¹⁰ The simultaneous administration of chemotherapy with radiation can independently increase the risk of radiation-induced lung injury.¹¹ In addition, the abrupt withdrawal of steroids can trigger the development of radiation pneumonitis. A unique phenomenon called “radiation recall,” wherein the patient develops pneumonitis in a previously irradiated site following administration of chemotherapy, has been described in several cases.¹² Several patient-related factors may also increase the risk of radiation pneumonitis, including poor performance status, pre-existing lung disease, female sex, and older age.^{13,14}

The classic chest radiograph in radiation-induced lung injury shows a straight-line that conforms to the radiation port. This finding is diagnostic. In many patients, however, the infiltrates are patchy and ill defined. In addition, some patients have infiltrates outside the radiation field or within the nonirradiated lung. Chest CT is more sensitive than chest radiograph for detecting subtle lung injury, but CT should be reserved for situations when the diagnosis is uncertain. We obtained a chest CT because our patient was immunocompromised from both HIV and chemotherapy, and his radiograph was consistent with both infectious and noninfectious processes.

Bronchoalveolar lavage and transbronchial biopsy can exclude other causes of pulmonary infiltrates, but these techniques are less helpful for diagnosing radiation-induced lung injury.¹⁵ Bronchoalveolar lavage fluid usually shows an increased leukocyte count and a high CD4:CD8 ratio after thoracic irradiation. The fluid is typically lymphocytic, but otherwise nonspecific. Transbronchial biopsy specimens are too small for diagnosing radiation-induced lung injury. Pulmonary function tests following thoracic

irradiation often show reduced lung volumes, compliance, and diffusing capacity. Patients with pre-existing lung disease appear to have larger declines. The long-term effects of thoracic irradiation on pulmonary function tests are not well understood.

Prednisone is the cornerstone of treatment for radiation pneumonitis, but no prospective controlled study has demonstrated the benefit of corticosteroids. Prednisone treatment is usually initiated at a high dose (60 mg/d) for 2 weeks, with a slow taper over the next 1–3 months. Unfortunately, some patients experience a radiographic relapse upon discontinuation of the prednisone. High-dose inhaled corticosteroids have been proposed as an alternative to systemic corticosteroids, but experience with that strategy is limited to case reports.

Another promising therapy is pentoxifylline, which is a methylxanthine derivative that reduces blood viscosity and improves erythrocyte flexibility. The immunomodulating and anti-inflammatory properties of pentoxifylline were probably responsible for its benefits in a recent study.¹⁶

Azathioprine and cyclosporine have been proposed for patients who cannot tolerate systemic corticosteroids, but controlled studies have not found any efficacy with azathioprine and cyclosporine.

Amifostine is a cytoprotective agent that protects normal tissue against ionizing radiation damage by scavenging radiation-induced free radicals.¹⁷ Although results from animal studies have been promising, clinical data have not yet shown a definite protective effect in humans.

In conclusion, patients receiving thoracic irradiation are at risk for radiation-induced lung injury. Two different injury patterns have been described, based on the timing of their appearance: radiation pneumonitis and late radiation fibrosis. No proven therapies exist for treating radiation-induced lung injury, but corticosteroids are commonly used for this purpose. Many patients with radiation pneumonitis spontaneously resolve without any treatment. Several modifiable risk factors have been linked to radiation-induced lung injury, and these provide the best strategy for reducing this debilitating condition.

REFERENCES

1. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *Int J Radiat Oncol Biol Phys* 1995;31(5):1341–1346.
2. Kocak Z, Evans ES, Zhou SM, Miller KL, Folz RJ, Shafman TD, Marks LB. Challenges in defining radiation pneumonitis in patients with lung cancer. *Int J Radiat Oncol Biol Phys* 2005;62(3):635–638.
3. Movsas B, Raffin TA, Epstein AH, Link CJ Jr. Pulmonary radiation injury. *Chest* 1997;111(4):1061–1076.
4. Inoue A, Kunitoh H, Sekine I, Sumi M, Tokuyue K, Saijo N. Radiation pneumonitis in lung cancer patients: a retrospective study of risk factors and the long-term prognosis. *Int J Radiat Oncol Biol Phys* 2001;49(3):649–655.

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- Rodrigues G, Lock M, D'Souza D, Yu E, Van Dyk J. Prediction of radiation pneumonitis by dose - volume histogram parameters in lung cancer: a systematic review. *Radiother Oncol* 2004;71(2):127-138.
- Fraser RS, Muller NL, Colman N, Pare PD. Irradiation. In: Fraser and Pare's diagnosis of diseases of the chest. 4th ed. Philadelphia: WB Saunders; 1999:2592-2608.
- Park KJ, Chung JY, Chun MS, Suh JH. Radiation-induced lung disease and the impact of radiation methods on imaging features. *Radiographics* 2000;20(1):83-98.
- Hernando ML, Marks LB, Bentel GC, Zhou SM, Hollis D, Das SK, et al. Radiation-induced pulmonary toxicity: a dose-volume histogram analysis in 201 patients with lung cancer. *Int J Radiat Oncol Biol Phys* 2001;51(3):650-659.
- Rubin P, Casarett G. Clinical radiation pathology. Philadelphia: WB Saunders; 1968.
- Libshitz HI. Radiation changes in the lung. *Semin Roentgenol* 1993; 28(4):303-320.
- Byhardt RW, Scott C, Sause WT, Emami B, Komaki R, Fisher B, et al. Response, toxicity, failure patterns, and survival in five Radiation Therapy Oncology Group (RTOG) trials of sequential and/or concurrent chemotherapy and radiotherapy for locally advanced non-small-cell carcinoma of the lung. *Int J Radiat Oncol Biol Phys* 1998; 42(3):469-478.
- Azria D, Magne N, Zouhair A, Castadot P, Culine S, Ychou M, et al. Radiation recall: a well recognized but neglected phenomenon. *Cancer Treat Rev* 2005;31(7):555-570.
- Rancati T, Ceresoli GL, Gagliardi G, Schipani S, Cattaneo GM. Factors predicting radiation pneumonitis in lung cancer patients: a retrospective study. *Radiother Oncol* 2003;67(3):275-283.
- Robnett TJ, Machtay M, Vines EF, McKenna MG, Algazy KM, McKenna WG. Factors predicting severe radiation pneumonitis in patients receiving definitive chemoradiation for lung cancer. *Int J Radiat Oncol Biol Phys* 2000;48(1):89-94.
- Martin C, Romero S, Sanchez-Paya J, Massuti B, Arriero JM, Hernandez L. Bilateral lymphocytic alveolitis: a common reaction after unilateral thoracic irradiation. *Eur Respir J* 1999;13(4):727-732.
- Ozturk B, Egehan I, Atavci S, Kitapci M. Pentoxifylline in prevention of radiation-induced lung toxicity in patients with breast and lung cancer: a double-blind randomized trial. *Int J Radiat Oncol Biol Phys* 2004;58(1):213-219.
- Choi NC. Radioprotective effect of amifostine in radiation pneumonitis. *Semin Oncol* 2003;30(6 Suppl 18):10-17.



Patient receiving radiotherapy
Hospital for Joint Diseases, New York, 1952
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