Radiation-Induced Pulmonary Veno-occlusive Disease*

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Late occurrence of radiation-induced pulmonary pneumonitis and fibrosis is well documented. We report an unusual case of radiation induced veno-occlusive disease (VOD) occurring six years following mantle irradiation for Hodgkin's lymphoma. The patient developed severe pulmonary hypertension and cor pulmonale. A left lung transplantation was performed successfully and pathologic examination of the explanted lung showed severe changes compatible with VOD. In the absence of exposure to alternate therapeutic or toxic agents that may cause VOD, it is likely that radiation caused damage to the venular endothelium and caused progressive obliteration of the pulmonary vessels. Review of the literature reveals only a few similar reports of VOD mostly following radiation for bone marrow transplantation. We conclude that previous irradiation (even several years earlier) should be considered as a possible cause of pulmonary VOD. (Chest 1993; 104:1282-84)

BMT = bone marrow transplantation; VOD = veno-occlusive disease

Pneumonitis and fibrosis are well-known complications of lung irradiation.1-5 The damage is usually dose dependent and confined to the port of direct injury.6-7 It usually occurs 2 to 3 months after irradiation but late occurrence of pulmonary injury, happening up to several years after radiation, is well described.8 Pulmonary vasculopathy is a well-recognized feature of radiation injury, but it is seldom of major clinical significance.9-10 We report an unusual case of pulmonary veno-occlusive disease (VOD) and fibrosis occurring six years after radiation and manifesting with severe pulmonary hypertension. A single lung transplantation was performed successfully enabling us to examine the pathologic changes in the explanted lung.

CASE REPORT

A 42-year-old woman was admitted to the Hadassah University Hospital, Jerusalem, in April 1990, with progressive dyspnea. Six years prior to hospital admission, she was diagnosed as having Hodgkin's lymphoma by a cervical lymph node biopsy specimen. Staging, which included splenectomy, revealed that the disease was IIIA due to splenic involvement with no involvement of the mediastinum. The patient received 3,600 rad (3.6 Gy) in a mantle distribution with no additional chemotherapy. Follow-up examinations showed no evidence of disease and the patient remained in complete remission ever since. At the time of hospital admission, there was no evidence of infection or of pulmonary relapse of the lymphoma. She was hypoxicemic with a \( \text{PaO}_2 \) of 65 mm Hg and a \( \text{PaCO}_2 \) of 30 mm Hg. Pulmonary function tests showed mild restriction with \( \text{FEV}_1 \) of 80 percent predicted, \( \text{FEV}_1/\text{FVC} \) ratio of 90 percent, TLC of 80 percent, and Dco of 82 percent predicted. Chest radiographs showed a mild increase in the interstitial markings. Ventilation-perfusion scan showed matched defects at both apices and pulmonary angiogram was negative for pulmonary embolism, although vessels at both apices seemed to be significantly narrowed. With the presumed diagnosis of radiation pneumonitis, the patient was given a trial with corticosteroids (80 mg of prednisone) with no response and the steroid therapy was discontinued. The patient's condition continued to deteriorate and she was placed on a regimen of home oxygen therapy. Eight months later, she was admitted again for severe respiratory failure (\( \text{PaO}_2 \) of 45 mm Hg and \( \text{PaCO}_2 \) of 29 mm Hg). Chest radiographs (Fig 1) showed bilateral pleural effusions with interstitial and alveolar infiltrates. Echocardiogram showed severe pulmonary hypertension with dilated right ventricle and good left ventricular function. She was intubated and a transbronchial biopsy specimen showed severe interstitial fibrosis. The patient was treated with diuretics and broad-spectrum antibiotics and was extubated five days later. She was discharged from the hospital after three weeks with high-flow...

Figure 1. Chest radiography of patient showing diffuse alveolar edema and bilateral pleural effusion.

Figure 2. Lung section showing extensive interstitial fibrosis with thickening of interalveolar septa. Alveolar spaces are filled with hemosiderin-laden macrophages (top left). Note intimal thickening of venules (bottom) (hematoxylin eosin, x 400).

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oxygen (6 L/m). Two months later she was admitted again with large pleural effusions that proved to be transudates. Cardiac catheterization showed good left ventricular function with severe pulmonary hypertension (pulmonary artery pressure, 95/33; mean, 65 mm Hg) and normal wedge pressure (8 mm Hg). Her cardiac output was 3.3 L/m. Radionuclide ventriculography (multiple gated acquisition) disclosed a left ventricular ejection fraction of 55 percent with good wall motion and dilated right ventricle with right ventricular ejection fraction of 20 percent. In August 1991, a suitable donor was found in Erasme Hospital in Brussels and a left lung transplant was performed. The postoperative course was complicated by recurrent infections with Staphylococcus aureus, cytomegalovirus, and Aspergillus fumigatus of which she died six months after transplantation. Autopsy was not performed at the request of the family.

**Pathologic Examination**

Macroscopically, the left lung was heavy and the cut surface was firm and gray with areas of irregular consolidation interspersed with zones of normal aeration.

Microscopically (Fig 2), the lung showed patchy foci of interstitial fibrosis with some confluence into large irregular fibrotic areas. The interstitium was markedly thickened with widening of the alveolar septa by mononuclear cellular infiltrate and collagenous material. The alveolar spaces were filled with numerous hemosiderin-laden macrophages.

The most striking pathologic feature was that seen in the blood vessels. Numerous large veins and small pulmonary venules were obliterated. On some occasions, near total occlusion of the vessels was seen (Fig 3). On others, recanalization was seen with fibrous septa crossing the lumen, resulting in cavernous-like spaces. The muscular pulmonary arteries also showed marked hypertrophy of their walls, sometimes containing thrombi. Fibrinoid necrosis, arteritis, or plexiform lesions were not seen. Elastin van Gieson stain demonstrated an accumulation of elastic fibers and smooth muscle fibers in the venular walls.

These microscopic findings were consistent with pulmonary VOD.

**DISCUSSION**

Radiation injury can occur late postirradiation and deterioration in lung function has been noted as late as ten years after injury. However, this type of deterioration is slow and progressive over years. Early reports have pointed out that radiation can cause vasculopathy with intimal damage in both arterioles and venules. In our case, the pattern was atypical with a stormy course and within several months a rapid decline in lung function was observed. The clinical picture was typical for VOD and manifested with severe pulmonary hypertension and florid pulmonary venous congestion with a persistent normal pulmonary artery occlusion (wedge) pressure.

Veno-occlusive diseases of the lung is an unexplained phenomenon that is associated with multiple mechanisms of injury. Viral infections, genetic factors, toxins (Crotalaria flacca), dietary drugs (Aminorex), contraceptives, and cytotoxic chemotherapeutic agents (busulfan, cyclophosphamide) are all associated with VOD.

The association between radiation and VOD is less clear. Lombard et al summarized the literature on VOD complicating therapy for various malignant neoplasms. In this report, the authors emphasized the association between VOD and the chemotherapy regimen, in particular mitomycin C and bleomycin. However, if one looks carefully at the report, six of those nine patients received radiotherapy as well, although in four the radiation field did not include the lungs. Similarly, Butler et al described a young child who received cranial radiation for neuroblastoma at infancy and 13 years later developed fatal pulmonary hypertension. In this case, however, autopsy was not performed and VOD was not clearly proven. Capewell et al described a patient with Hodgkin's lymphoma who developed VOD at the time of the diagnosis of lymphoma prior to any therapy. In all other cases mentioned above, including ours, no evidence of the malignant process was found at the time of appearance of the VOD which was remote from the initial disease (from 3 months to 10 years).

Recently, with the introduction of bone marrow transplantation (BMT), an association between pulmonary VOD and BMT has been noted. In most cases, conditioning was carried out with cytotoxic chemotherapy as well as total body irradiation. Hepatic VOD has also been reported following irradiation, mostly in the setting of BMT. In one report, pulmonary VOD was found in association with hepatic VOD after BMT and with pulmonary fibrosis. Pulmonary VOD was seen in 71 percent of patients having both pulmonary fibrosis and hepatic VOD. Piedbois et al reported that in patients receiving high single-dose irradiation as conditioning for BMT, 45 percent developed pulmonary fibrosis and 10 percent of those developed VOD of the liver. It seems that both the pulmonary and hepatic veins are sensitive to various noxious agents, radiation for one, that lead to intimal injury and obliteration of the venular lumen.

We cannot exclude the possibility that the VOD seen in our patient was a coincidental finding or related to the lymphoma itself. In the absence of chemotherapy or active lymphoma and in view of the association with irradiation in other reports, we believe it is highly likely that the VOD was caused by the previous irradiation.

In conclusion, we present a case of pulmonary VOD that may be associated with previous mantle irradiation for Hodgkin's lymphoma. This rare complication is now seen more frequently following irradiation prior to BMT and should be added to the growing list of toxic agents causing pulmonary (as well as hepatic) VOD.

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**FIGURE 3.** Section showing a typical venule with intimal proliferation and near obliteration of lumen. (elastin stain, ×400).
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Confirmation of Anomalous Origin of the Right Coronary Artery From the Left Sinus of Valsalva With Magnetic Resonance Imaging*

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Anomalous origin of the right coronary artery from the left sinus of Valsalva is a rare but clinically significant congenital abnormality, difficult to diagnose angiographically. We describe a patient in whom magnetic resonance imaging was used to delineate the anomalous course of the right coronary artery following angiographic demonstration limited by technical considerations. (Chest 1993; 104:1284-86)

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