Pulmonary Veno-Occlusive Disease following Therapy for Malignant Neoplasms*

Charles M. Lombard, M.D.; Andrew Churg, M.D., F.C.C.P.; and Steven Winokur, M.D.

We report three cases of pulmonary veno-occlusive disease which developed following treatment for malignant neoplasms. Two patients received single agent BCNU chemotherapy for malignant gliomas. The third patient underwent combination radiation and chemotherapy for Hodgkin's disease. Isolated case reports of pulmonary veno-occlusive disease following therapy for malignant disease are reviewed and clinical features summarized. Pulmonary veno-occlusive disease in this setting is thought to be rare. However, the diagnosis is rarely suspected clinically and is difficult to diagnose pathologically. Therefore, the true incidence of this complication is unknown and may be higher than believed. It is important that both clinician and pathologist be aware of this entity; otherwise, elastic tissue stains may not be performed and the diagnosis missed.

Pulmonary veno-occlusive disease (PVOD) is a rare form of pulmonary disease which has multiple proposed etiologic factors including viral infections, exposure to inhaled toxins, immune complex deposition in the lung, and genetic predispositions. There have been several cases of PVOD detected following therapy for malignant neoplasms. Chemotherapeutic agents, particularly bleomycin, have been implicated as etiologic factors. We describe three cases of PVOD which followed treatment for malignancies.

CASE REPORTS

CASE 1

A 23-year-old man was diagnosed as having nodular sclerosing Hodgkin's disease following a cervical lymph node biopsy. Chest roentgenograms showed right hilar lymphadenopathy, and staging laparotomy showed involvement of the spleen and iliac lymph nodes by Hodgkin's disease. He was treated with MOPP chemotherapy for two cycles and COPP chemotherapy for one cycle. Cyclophosphamide was substituted in the regimen because of severe myelosuppression caused by the mustards. The patient then received 4,000 rads of mantle radiation therapy. There was 50 percent transmission to the right lung. He also received inverted Y radiation therapy with 4,000 rads. Following radiation therapy, he received three additional cycles of COPP chemotherapy.

The patient had no evidence of recurrent Hodgkin's disease and did well for ten years when at the age of 32, he developed gradually increasing shortness of breath over a 12-month period. The patient was admitted with accelerated progression of his dyspnea. On physical examination, the patient was in significant respiratory distress at rest. Chest examination revealed diffuse rales and rhonchi in both lung fields. Routine laboratory data were unremarkable except that arterial blood gas values on room air were as follows: pH, 7.55, P02, 55 mm Hg; and Pco2, 25 mm Hg. Chest x-ray films revealed diffuse bilateral interstitial infiltrates (Fig 1). The patient continued to suffer from rapid deterioration in respiratory status and an open lung biopsy of the left lower lobe was performed. However, the patient died one day following the procedure in respiratory failure. All cultures of lung tissue taken both at the time of the biopsy and at autopsy showed no growth.

Biopsy and Autopsy Results: At autopsy, significant pathologic findings were limited to the lung. In particular, there was no evidence of residual Hodgkin's disease and no source for possible emboli were detected. At autopsy, both lungs were diffusely firm and heavy, suggestive of the consolidative phase of an acute alveolar injury. Gross examination also revealed multiple thromboemboli in right and left pulmonary arteries and several bilateral wedge shaped infarcts. Microscopic sections of the open lung biopsy and autopsy lung were stained with hematoxylin-eosin and elastic tissue stains, and both showed similar findings. These sections showed organizing diffuse alveolar damage, areas of pulmonary infarction, and old

*From the Department of Pathology, Stanford University Medical Center, Stanford, CA; Department of Pathology, University of British Columbia, Vancouver, British Columbia; and Department of Medicine, William Beaumont Hospital, Royal Oak, MI.

Manuscript received January 19; revision accepted April 16.

Reprint requests: Dr. Lombard, Room L235, Stanford University Medical Center, Stanford 94305

Fig 1. Chest roentgenogram from case 1 with diffuse bilateral interstitial infiltrates.
organizing and more recent pulmonary thromboemboli. Numerous hemosiderin-laden macrophages were present. The pulmonary arteries showed hypertensive changes including medial hypertrophy and intimal thickening. In addition to the striking changes in the pulmonary arteries, there were multiple veno-occlusive lesions in both large and small pulmonary veins. Many of these lesions had the appearance of organizing thrombi (Fig 2). In addition, there were numerous dilated thin walled vessels which in some areas resembled angiomatoid malformations (Fig 3). The case was interpreted as PVOD with marked pulmonary artery hypertensive change, probable extensive in-situ pulmonary artery thrombus formation, widespread pulmonary infarcts, and organizing diffuse alveolar damage.

Case 2

A 17-year-old woman was admitted to the hospital with left temporal headaches and complaints of numbness and clumsiness of the right hand and face. Physical examination revealed an obese young woman with right hemiparesis, hemianesthesia, and hyperreflexia. A computerized tomographic study of the brain demonstrated a pontine mass. The patient was treated with brainstem radiation (5,500 rads) followed by BCNU administered at six-week cycles over six months to a total dose of 1,270 mg (550 mg/m²). Four months after completing BCNU therapy, the patient noted the onset of shortness of breath which progressed to the point where she could walk only a few steps without stopping. On admission to the hospital,
she was noted to be in mild respiratory distress at rest with a respiratory rate of 20. However, minimal exertion produced marked respiratory distress with cyanosis. The remainder of the physical examination was unremarkable. Routine laboratory studies were unremarkable. On room air, the patient's arterial blood gas values were as follows: pH, 7.48; PaO₂, 45 mm Hg; and PaCO₂, 32 mm Hg. Chest roentgenograms showed vague infiltrates at the lung bases as well as mild cardiac enlargement. An open lung biopsy was performed and was initially interpreted as showing pulmonary fibrosis, most likely secondary to the BCNU chemotherapy. The patient rapidly deteriorated and died six weeks after the biopsy. No autopsy was obtained.

**Biopsy Results:** Microscopic sections were again examined with hematoxylin-eosin, as well as elastic tissue stains. Patchy interstitial fibrosis was identified, which in rare areas was sufficient to have caused mild distortion of the normal pulmonary architecture. The areas of interstitial fibrosis were accompanied by a mild interstitial chronic inflammatory infiltrate composed of lymphocytes, histiocytes, and numerous plasma cells. Hemosiderin-laden macrophages were present within alveolar spaces (Fig 4). A mononuclear venulitis was present in randomly scattered pulmonary veins. The walls of these small veins were infiltrated by lymphocytes and plasma cells (Fig 5). These inflamed vessels generally had patent lumens. However, in some, the walls appeared thickened and sclerotic. Other similar sized veins showed partial and complete fibrous obliteratorive lesions characteristic of PVOD without an inflammatory infiltrate (Fig 5). Pulmonary arteries were unremarkable. On first review, the occlusive lesions in small pulmonary veins were not detected, and the biopsy was interpreted as consistent with BCNU-induced pulmonary fibrosis. However, when the subtle changes of PVOD were detected in case 3, this case was reexamined and careful evaluation of small pulmonary veins with elastic tissue stains demonstrated the changes of PVOD.

**CASE 3**

A 21-year-old white woman first presented with complaints of headache, nausea, and vomiting. She was found to have a right homonymous hemianopsia, and a mass in the left occipital lobe. Biopsy results yielded a diagnosis of high grade astrocytoma. Postoperatively, she was treated with cranial radiation, dexamethasone, and BCNU. The BCNU was administered every six weeks to a total dose of 1,620 mg (953 mg/m²) over a period of six months.

Shortly after completing BCNU chemotherapy, the patient was admitted to the hospital with complaints of a nonproductive cough and shortness of breath without fever, chills, or sweats. A chest roentgenogram showed basilar infiltrates, and the patient was treated with antibiotics without improvement. Two weeks later, the chest roentgenogram showed unchanged pulmonary infiltrates, but cardiac enlargement was now present. On readmission, the patient was in
significant respiratory distress with a respiratory rate of 40. Rales and decreased breath sounds were noted over both lung bases. Cardiac examination demonstrated a loud S2. Tender hepatomegaly was noted on palpation of the abdomen. The remainder of the physical examination results were within normal limits. Laboratory studies were generally unremarkable except for mild anemia. There was no evidence of a coagulopathy, and all blood and sputum culture results were negative. Arterial blood gas values on room air were as follows: pH 7.40, PaO₂ 31 mm Hg, and PaCO₂ 35 mm Hg. Chest x-ray films showed cardiomegaly, bilateral pleural effusions, accentuated pulmonary vascular markings, Kerley B lines, and bibasilar infiltrates.

Right heart catheterization was performed. The pulmonary artery pressure was 56/24 mm Hg, and the wedge pressure varied from 3 to 8 mm Hg. Cardiac output was 4.5 L/minute. A contrast study revealed no evidence for a cardiac shunt. Two dimensional echocardiograms showed a moderately-sized pericardial effusion, enlargement of the right atrium and ventricle, a normal left ventricle and paradoxic motion of the interventricular septum consistent with right ventricular overload. The left atrium and mitral valve appeared normal. A clinical diagnosis of pulmonary veno-occlusive disease was made, but the patient's unstable condition precluded confirmation by open lung biopsy. She continued to deteriorate and died approximately one month after admission.

Autopsy Findings: The autopsy was restricted to a large lung biopsy. Grossly, the lung appeared unremarkable. Microscopic sections were stained with hematoxylin-eosin, as well as elastic tissue stains. Overall lung architecture was well preserved. There were patchy areas of mild interstitial fibrosis. These areas also showed a mild mononuclear interstitial inflammatory infiltrate. Multiple veno-occlusive lesions composed of fibrous tissue were identified in small pulmonary venules. These lesions appeared similar to those illustrated for case 2. No recent fibrin thrombi were found in pulmonary veins. There was no evidence of a venulitis. No significant change was seen in the pulmonary arteries. Scattered hemosiderin-laden macrophages were present within alveolar spaces. The amount of fibrosis present was minimal and insufficient to explain the respiratory difficulties this patient suffered. The diagnosis of PVOD was made.

DISCUSSION

Two of the cases we report received BCNU as a single chemotherapeutic agent for the treatment of malignant gliomas. BCNU has been reported to cause pulmonary fibrosis in such patients. The incidence of pulmonary fibrosis is dose related with an incidence as high as 50 percent with cumulative doses of BCNU of 1,500 mg per m². There have been no reports of PVOD associated with BCNU chemotherapy. Although both of the patients we report had patchy areas of interstitial fibrosis, it was only mild and was insufficient to account for the severe respiratory failure that these patients suffered. The pathologic changes of primary importance in both cases were the occlusive lesions in small pulmonary venules. In separating lesions of PVOD from venosclerotic lesions of other forms of fibrosing alveolitis, it is essential to demonstrate occlusive lesions in areas away from significant pulmonary fibrosis. In our cases, these occlusive lesions were widespread; however, they were subtle and difficult to detect without elastic tissue stains. One of the cases was originally diagnosed as pulmonary fibrosis presumably secondary to BCNU chemotherapy. It was only on review of the case with the specific diagnosis of PVOD in mind that the numerous, though inconspicuous, veno-occlusive lesions were identified. These lesions were demonstrated to be hemodynamically significant in the one patient who underwent cardiac catheterization where pulmonary hypertension was documented.

Our third case occurred in a patient treated with combination radiation and chemotherapy for Hodgkin's disease. Unlike the other two patients, this patient had both angiomatoid-like malformations, as well as severe pulmonary arterial change in addition to the pulmonary veno-occlusive lesions. Similar angiomatoid lesions have been described in PVOD and may represent dilated bronchial veins. In our experience, the extent of the pulmonary artery lesions in this case was unusual for PVOD. However, Waagenvoort and co-workers have reported that both arterial and venous changes occur in about 50 percent of cases of PVOD. The arterial lesions that they describe are also severe in some cases. Pulmonary artery thromboembolism is described in some of their cases and they attribute this to in-situ thrombus formation.

PVOD associated with Hodgkin's disease has been previously reported. But that case is not likely to be an example of chemotherapy-related disease because the signs and symptoms of PVOD preceded the administration of cytotoxic chemotherapy. Our case is remarkable for the ten-year disease-free interval between the radiation/chemotherapy and the onset of symptoms referable to PVOD, and we cannot exclude the possibility that the PVOD was unrelated to the patient's history of treated Hodgkin's disease. Of the drugs used to treat Hodgkin's disease in this patient, cyclophosphamide is the one most associated with pulmonary toxicity. Cyclophosphamide induces pulmonary fibrosis in less than 1 percent of patients treated with this drug. No clear relationship between pulmonary fibrosis and cumulative dose of this drug has been established. Of importance with respect to the long latency period between symptoms of PVOD and the chemotherapy regimen in this case is the observation that in cyclophosphamide-induced pulmonary fibrosis the interval between onset of symptoms and chemotherapy ranges from two weeks to 13 years.

This patient was treated with radiation therapy in addition to chemotherapy. Is it possible that the radiation may have played an etiologic role in the patient's PVOD? Radiation induces pathologic changes in both arteries and veins. Furthermore, radiation is known to cause hepatic veno-occlusive disease. Nevertheless, we know of no report identifying it as the etiologic factor in PVOD. However, there are two case reports of patients who received thoracic radiation and subsequently developed PVOD. In one, the patient received irradiation for thymic enlargement in
Table 1—Cases of PVOD Following Therapy for Malignant Neoplasms

<table>
<thead>
<tr>
<th>Malignant Neoplasm</th>
<th>Chemotherapy</th>
<th>Radiation Therapy</th>
<th>Interval between Treatment—PVOD</th>
<th>Survival from Onset PVOD</th>
<th>Clinical Diagnosis</th>
<th>Original Pathologic Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hodgkins disease*</td>
<td>MOP, COP chemotherapy</td>
<td>Mantle and inverted Y</td>
<td>10 yr</td>
<td>12 mo</td>
<td>ARDS</td>
<td>PVOD</td>
</tr>
<tr>
<td>Glioma*</td>
<td>BCNU</td>
<td>Brain</td>
<td>10 mo</td>
<td>3⅓ mo</td>
<td>Fibrosis</td>
<td>Fibrosis</td>
</tr>
<tr>
<td>Glioma*</td>
<td>BCNU</td>
<td>Brain</td>
<td>6 mo</td>
<td>2 mo</td>
<td>PVOD</td>
<td>PVOD</td>
</tr>
<tr>
<td>Non-Hodgkins' lymphoma</td>
<td>Bleomycin Vincristine</td>
<td>—</td>
<td>3⅓ mo</td>
<td>1 wk</td>
<td>Fibrosis</td>
<td>PVOD</td>
</tr>
<tr>
<td>Non-Hodgkins' lymphoma</td>
<td>Chlorambucil Vincristine VP16-213</td>
<td>—</td>
<td>?</td>
<td>&lt;3 mo</td>
<td>Fibrosing alveolitis</td>
<td>Fibrosing alveolitis</td>
</tr>
<tr>
<td>Squamous carcinoma*</td>
<td>Adriamycin Bleomycin Mitomycin C Cis platinum</td>
<td>Pelvis</td>
<td>6 mo</td>
<td>3 mo</td>
<td>Fibrosis</td>
<td>PVOD</td>
</tr>
<tr>
<td>Uterine cervix</td>
<td>Mitomycin C Cis platinum</td>
<td>Pelvis</td>
<td>3 mo</td>
<td>?</td>
<td>PVOD</td>
<td></td>
</tr>
<tr>
<td>Squamous carcinoma*</td>
<td>Adriamycin Bleomycin Mitomycin C Cis platinum Vinblastine</td>
<td>Pelvis</td>
<td>3 mo</td>
<td>?</td>
<td>PVOD</td>
<td></td>
</tr>
<tr>
<td>Uterine cervix</td>
<td>Mitomycin C Cis platinum</td>
<td>Pelvis</td>
<td>3 mo</td>
<td>?</td>
<td>PVOD</td>
<td></td>
</tr>
<tr>
<td>Acute lymphocytic leukemia* (Bone marrow transplant)</td>
<td>Vincristine Cytosine arabinoside Daunorubicin Methotrexate</td>
<td>Total body irradiation</td>
<td>1⅓ mo</td>
<td>?</td>
<td>Interstitial pneumonia</td>
<td>PVOD</td>
</tr>
<tr>
<td>Gastric adenocarcinoma</td>
<td>S-Fluorouracil Doxorubicin Mitomycin C</td>
<td>—</td>
<td>15 mo</td>
<td>3 mo</td>
<td>?</td>
<td>PVOD</td>
</tr>
</tbody>
</table>

*Our currently reported cases.

Bleomycin has been implicated as the etiologic agent in a previous report, and four of the patients summarized in Table 1 were treated with this drug. Mitomycin C has been reported to cause hepatic veno-occlusive disease and the hemolytic uremic syndrome. Three patients with PVOD were treated with this drug, and none had the hemolytic-uremic syndrome. Two of these patients were also treated with bleomycin, and this makes assignment of pathogenic significance difficult in these cases. Clinical features of note are that in all but one case, the interval between initiation of chemotherapy and onset of PVOD was less than one year. As in PVOD in general, the clinical course from onset of symptoms to death with respiratory failure is short.

The pathogenesis of PVOD following therapy for malignancies is unknown. Hypotheses proposed include the following: (1) the chemotherapeutic agents are causally related to PVOD, and (2) the underlying malignancy is in some way related to the PVOD. Our cases lend support to the first hypothesis. Gliomas are not known to be associated with a hypercoagulable state or with circulating immune complexes, two proposed mechanisms for the pathogenesis of PVOD. In addition, gliomas and other brain tumors have not been reported in association with PVOD. Our patient with Hodgkin’s disease had been free of disease for ten...
years when he developed PVOD. Thus, it is unlikely that the underlying malignancy was causally related to PVOD in our three cases. The possibility remains that the PVOD in these cases is merely coincidental and unrelated to either the underlying malignancy or the therapy. However, the increasing number of reported cases of PVOD following chemotherapy suggests otherwise.

How chemotherapy induces PVOD is unclear. The veno-occlusive disease seen in our case 2 is similar to that seen in other cases of PVOD. Whether it is related to the pathogenesis of the occlusive lesions or is a secondary phenomenon is unknown. Experimental models have shown that bleomycin causes endothelial damage. It is possible that this damage plays a role in the pathogenesis of PVOD. Mitomycin has been reported to be associated with microangiopathic hemolytic anemia and widespread intravascular coagulation. Patients treated with this drug may develop the hemolytic-uremic syndrome and pulmonary hypertension. The cases of PVOD we report had no evidence of microangiopathic hemolytic anemia, disseminated intravascular coagulation, or veno-occlusive lesions outside of the lung. Thus, they are distinctly different from the reported cases of mitomycin-associated hemolytic-uremic syndrome with lung disease as part of a systemic abnormality in intravascular coagulation. However, the pathogenesis of pulmonary hypertension in these two clinical situations may be similar. In PVOD, thrombotic occlusion of small pulmonary venules has been postulated to be the etiology of the pathologic changes. In one case of mitomycin-associated microangiopathic hemolytic anemia and pulmonary hypertension microthrombi in small pulmonary vessels were identified as the pathologic change accounting for the hypertension.

Pulmonary veno-occlusive disease is a rare cause of pulmonary hypertension. The infrequency with which it is reported in association with chemotherapy suggests that it is a rare complication. However, the clinical diagnosis of PVOD is difficult. In seven of the eight cases reported (Table 1), the clinical diagnosis was not suspected. The pathologic diagnosis of PVOD is similarly difficult. Two of the eight cases reported were misdiagnosed initially as pulmonary fibrosis and the veno-occlusive lesions were overlooked. The difficulty in identifying veno-occlusive lesions and the importance of elastic stains in their identification has been repeatedly stressed. We suspect that the true incidence of PVOD related to chemotherapy is underestimated. A thorough review of cases initially diagnosed as chemotherapy-related pulmonary fibrosis with special attention paid to the possibility of PVOD might reveal additional cases.

ACKNOWLEDGMENT: We wish to thank Dr. Steven Duncan, Stanford University Medical Center, for the referral of one patient.

REFERENCES

7 Knight BK, Rose AG. Pulmonary veno-occlusive disease after chemotherapy. Thorax 1985; 40:874-75
13 Ellis DA, Capewell SJ. Pulmonary veno-occlusive disease after chemotherapy (Correspondence). Thorax 1986; 41:415-416
14 Rose AG. Pulmonary veno-occlusive disease after chemotherapy (Correspondence). Thorax 1986; 41:416