genuous group of patients with BG. These patients are not asthmatic, have little or no blood or tissue eosinophilia, and usually do not have mucoid impaction or noninvasive fungi in the airways. The pathogenesis of BG in this second group is largely unknown, and multiple etiologic agents are likely. Our case falls into this second group.

We believe that the bronchocentric granulomas in our patient are a manifestation of infection with *Mycobacterium tuberculosis*. This conclusion is supported by the positive sputum culture for *M tuberculosis* and the clinical and radiographic improvement which followed antituberculosis chemotherapy. Failure to demonstrate mycobacteria in the lung biopsy specimen may be accounted for by the thirteen days of antituberculosis chemotherapy the patient received prior to the lung biopsy. Pathologic findings in our patient's lung biopsy are characteristic of the lesions of BG described by Liebow and are unlike typical tuberculous granulomas. Our patient had roentgenographic evidence of a roundworm infestation. However, no worms were identified in multiple post-treatment stool specimens, by endoscopy, or in the lung biopsy specimen. Pulmonary infection with Ascaris and Toxocara species can produce granulomatous lesions in the lungs, but peripheral eosinophilia and demonstration of larvae in lung tissue would be expected. Therefore, we do not believe that the bronchocentric granulomatous lesions in our patient were the result of parasitic infiltration of the lungs.

The pathologic pattern of BG in the nonasthmatic patient has been associated with fungal and mycobacterial infection, but not with culture-proven tuberculosis. Ulbright and Katzenstein reported that 14 of 86 resected solitary pulmonary granulomas demonstrated the pathologic pattern of BG. Acid-fast bacilli were seen on the Ziehl-Neelsen stain in eight of the 14 specimens with BG, but detailed culture results were not reported. Duncan-Myers and Katzenstein reported four additional nonasthmatic patients with pathologic features of BG who were eventually proven to have infection. Rare acid-fast bacilli were demonstrated on stain in two, one of which grew *M intracellulare* on culture. Two additional case reports describe patients with BG on lung biopsy and atypical mycobacteria cultured from sputum or lung biopsy.

In conclusion, we report a patient with BG which we believe is a manifestation of tuberculosis. BG is most commonly one of the histologic manifestations of allergic bronchopulmonary aspergillosis. Other agents, including infectious agents, almost certainly can produce the same pathologic pattern. It is important to consider tuberculosis and other infections whenever BG is diagnosed on lung biopsy, particularly if the patient is nonasthmatic. Corticosteroids and cytotoxic drugs have been used in the treatment of some patients with BG, and failure to consider and diagnose an infectious etiology for BG could result in further dissemination of infection.

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Pulmonary Hypertension, Hemolytic Anemia, and Renal Failure*

A Mitomycin-Associated Syndrome

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After treatment with mitomycin C, a patient developed pulmonary hypertension with interstitial infiltrates, microangiopathic hemolytic anemia, systemic hypertension, and renal failure with the nephrotic syndrome. Open lung biopsy documented intracapillary fibrin thrombi in the pulmonary vasculature. Renal biopsy documented glomerular and arteriolar changes that were most consistent with a thrombotic-thrombocytopenic-like process. Treatment with corticosteroids, fresh-frozen plasma, and total plasma exchange was ineffective. The patient died six months after the onset. When mitomycin-C therapy is given, the clinician should be aware of the pulmonary, renal, and microangiopathic changes that can be associated with such therapy.

Mitomycin C (MMC) is an alkylating agent commonly used in the chemotherapy of gastrointestinal cancer, breast cancer, and other solid tumors. In this case report, we detail the course of a patient who became dyspneic while being treated with MMC. She rapidly developed pulmonary and systemic hypertension, interstitial pulmonary infiltrates, microangiopathic hemolytic anemia, and azotemia with the nephrotic syndrome. We believe this distinct syndrome can be attributed to MMC therapy.

CASE REPORT

A 46-year-old white woman was initially seen by us in early June 1984. In July 1983, a localized grade 2 adenocarcinoma of the colon, infiltrating to the serosal surface but without nodal metastasis, was resected. There was no known evidence of pulmonary or renal disease at this time, although the patient was a current smoker of 20

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Pulmonary Hypertension, Anemia and Renal Failure (McCarthy, Staats)
From August 1983 through February 1984, she received five courses of chemotherapy, each consisting of 5-fluorouracil (5-FU) and MMC (total dosage: 5-FU = 7.5 g or 4.2 g/M² BSA; MMC = 75 mg or 42 mg/M² BSA). Onset of dyspnea and cough were noted after the third course of chemotherapy. A presumptive diagnosis of bronchitis was made, but the patient did not improve with oral antibiotic treatment. Serum creatinine value in February 1984 was normal. Her dyspnea worsened, and the patient developed generalized myalgias and arthralgias. In April 1984, right-sided cardiac catheterization revealed right atrial pressure of 13 mm Hg, pulmonary artery pressure of 75/38 mm Hg, and pulmonary artery wedge pressure of 12 mm Hg. The patient was treated with nifedipine, hydralazine, warfarin, and prednisone (30 mg twice a day). At that time, the serum creatinine level was 1.5 mg/dl; 24-hour urine protein excretion was 8.7 g; and the hemoglobin level was 9.4 g/dl. Four units of packed red blood cells were transfused within the next two months. Symptoms progressed and by early June 1984, the patient required continuous nasal oxygen.

Upon admission to our institution in late June 1984, the physical examination showed an afibrile cushingoid woman with systemic blood pressure of 156/110 mm Hg. Cyanosis and clubbing of the nail beds were evident. Diffuse wheezes, bibasilar rales, and pitting edema were present. The second pulmonary sound was increased. Generalized petechiae and purpura were noted.

Review of the serial chest roentgenograms from February 1984 showed progressive cardiac enlargement and bilateral interstitial infiltrates. Her admission film is shown in Figure 1. Pulmonary function testing showed mild restriction (total lung capacity, 88 percent of predicted), moderate airway obstruction (FEV1/FVC ratio, 83 percent of predicted), and a reduced diffusing capacity (38 percent of predicted). On 4 L/min of nasal oxygen, the PaO₂ was 62 mm Hg, the PaCO₂ was 31 mm Hg; and the pH was 7.48. Sputum cytology was negative. Sector echocardiogram and Doppler examination revealed right ventricular enlargement, with an estimated right ventricular pressure of 80 mm Hg; the left ventricle was normal.

The creatinine level was 4.2 mg/dl, and urinalysis disclosed 0.1 percent glucose, grade 4 proteinuria, grade 3 microhematuria, and oval fat bodies. The 24-hour urine protein excretion was 11.2 g. The serum albumin level was 2.4 g/dl. Normal kidneys were noted on ultrasound examination.

The hemoglobin level was 10.3 g/dl; leukocytes, 11,500/cu mm; and platelets, 64,000/cu mm. The prothrombin time was 10.8 s (normal, 10.4 to 12.1) with an activated partial thromboplastin time of 24.0 s (normal, 25 to 38). Fibrin split products were 10 to 40 µg/ml (normal, <10), and the level of fibrinogen was mildly elevated at 488 mg/dl (normal, 190 to 365 mg/dl). The serum haptoglobin concentration was 0 (normal, 38 to 270 mg/dl). A blood smear revealed schistocytes and nucleated red cells. The reticulocyte count was 4.6 percent. Bone marrow aspirate and biopsy were nondiagnostic. A computed tomographic scan of the chest and abdomen showed a diffuse pulmonary infiltrate; mediastinal or abdominal lymphadenopathy was not noted.

The patient received bronchodilator drugs, supplemental oxygen, diuretics, fresh-frozen plasma (2 units/day), and 5 units of platelet concentrate. Her urinary output remained stable at 1,600 to 2,200 ml/day. However, during the one week of hospitalization, the creatinine level increased to 4.8 mg/dl, the hemoglobin level decreased to 8.0 g/dl, and she became increasingly hypoxic. Because of clinical deterioration, open-lung and renal biopsies were done.

Light microscopic examination of the lungs revealed focal intra-
alveolar hemorrhages without cellular changes of cytotoxicity. Intrapulmonary thrombi were noted (Fig 2). No evidence of cancer was seen.

Renal biopsy findings revealed an acute and chronic microangiopathy with involvement of glomeruli, arterioles, and ischemic tubular changes most consistent with a thrombotic-thrombocytopenic-purpura-like process (Fig 3).

Eighteen hours after operation, the patient suffered a generalized seizure and respiratory arrest. A computed tomographic scan of the head showed low attenuation in the left temporal lobe. The patient remained comatose despite treatment with fresh-frozen plasma infusions 1 total plasma exchange. Serial electroencephalograms documented progressive anoxic/ischemic encephalopathy. The patient died five days after operation. A postmortem examination was not performed.

DISCUSSION

Pulmonary toxicity related to MMC can take several forms; acute interstitial pneumonitis after a single dose, diffuse interstitial fibrosis, and diffuse alveolar damage. The use of high concentrations of oxygen in patients previously exposed to MMC may predispose to interstitial fibrosis. Acute, fatal, noncardiogenic pulmonary edema and coexisting hemolytic anemia and pulmonary edema have also been described. Pulmonary hypertension is rarely documented and is probably due to pulmonary arterial endothelial proliferation and intracapillary thrombi.

Clinical nephrotoxicity is an infrequent side effect of MMC therapy, but renal histologic changes have been well documented in both experimental animals and patients exposed to MMC. Renal biopsy specimens in patients with a microangiopathic hemolytic anemia demonstrate hyaline thrombi, swollen endothelial cells, and endothelial proliferation within glomeruli. Systemic hypertension due to renal vascular involvement can be seen. The nephrotic syndrome itself has not been emphasized to be associated with MMC nephrotoxicity, although both low-grade and occasional high-grade qualitative proteinuria have been noted.

Microangiopathic hemolytic anemia may occur after MMC therapy. Problems in diagnosis can arise because disseminated carcinomatosis can lead to similar findings. Blood transfusions may exacerbate the hemolytic anemia due to MMC. The fact that 5-FU is often used in combination with MMC raises the possibility of a synergistic effect of these drugs. Hemolytic anemia is presumably due to a change in the vascular endothelium. This vascular damage may be related to an immunologic aberration, as suggested by the findings of elevated platelet-associated IgG and immune complexes in studies of other chemotherapy-associated microangiopathic hemolytic anemias.

The symptom complex found in our patient—that is, pulmonary hypertension with interstitial infiltrates, microangiopathic hemolytic anemia, systemic hypertension, and progressive renal failure associated with the nephrotic syndrome—is rare. Although the total dose of MMC in reported cases has been greater than 10 mg/M², there is no clear dosage relationship. Symptoms can start after the third or fourth course of MMC and up to ten or 11 months after completion of chemotherapy. Our patient's course and case reports reveal that treatment with corticosteroids, heparin, platelet inhibitors, or plasma infusions has been unsuccessful. Dialysis seems to have no effect except to supply exogenous renal function. Total plasma exchange may benefit the hematologic abnormalities. There is also a report of reversal of the renal failure with plasmapheresis therapy. In general, few patients have survived these sequelae of MMC.

Clinicians should be aware of MMC-associated syndromes. We recommend that patients treated with MMC receive frequent monitoring of peripheral blood counts, pulmonary status, renal function, and blood pressure. Because of delayed reactions, observation should continue for up to one year after discontinuation of MMC.

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Acute right-to-left intracardiac shunt through a patent foramen ovale has been described previously in critically ill patients and after pneumonectomy. Any process which can increase right atrial pressure, such as a pulmonary embolus and the use of positive end-expiratory pressure (PEEP), may lead to the development of a right-to-left intracardiac shunt through a patent foramen ovale; however, such an association has not been described previously in a patient with the adult respiratory distress syndrome (ARDS).

This report describes a patient with ARDS who developed a right-to-left shunt through a patent foramen ovale, causing significant hypoxemia which was not corrected by a high fractional concentration of oxygen in the inspired gas (FIO2) and PEEP. The diagnosis was confirmed at the time of cardiac catheterization, with dramatic improvement in the arterial blood gas levels following cardiac surgery.

**Case Report**

A 49-year-old black woman with no known pulmonary or cardiac disease was diagnosed as having adenocarcinoma of the endometrium and was treated with radium implants. She was readmitted six weeks later with chills and fever, and a cildocentesis revealed purulent material consistent with a pelvic abscess. A total abdominal hysterectomy with oophorectomy and drainage of the pelvic abscess was performed. Immediately after extubation in the recovery room, the patient developed acute respiratory distress and hypotension, necessitating reintubation and mechanical ventilation. A chest x-ray film revealed bilateral diffuse alveolar infiltrates, and rales were heard bilaterally. The clinical picture was consistent with ARDS secondary to sepsis and hypotension. Treatment with an FIO2 of 0.60 to 0.70 and PEEP of 20 cm H2O was continued for the next 48 hours. The patient’s condition improved clinically, and the chest x-ray film showed complete clearing; however, the hypoxemia persisted, and on the fourth postoperative day, severe hypoxemia was present. The arterial oxygen pressure (PaO2) was 40 mm Hg with FIO2 of 1.0 and PEEP of 25 cm H2O. At this time, lowering the PEEP from 25 cm H2O to 15 cm H2O did not affect the PaO2 (Fig 1). The pulmonary artery pressure was persistently elevated (Table I). The discordance in the clinical picture and the magnitude of the right-to-left shunt led us to suspect a possible intracardiac shunt.

Since the chest x-ray film finding had returned to normal, a perfusion lung scan with radioactive technetium-labelled albumin was done, and it disclosed no perfusion defects; however, contrast material rapidly appeared in both kidneys, a finding consistent with a right-to-left shunt. M-mode and cross-sectional echocardiograms were performed with 10 ml of physiologic saline solution as contrast material. The saline solution was injected through a central line, and saline echoes immediately appeared in the left atrium, indicating a right-to-left intracardiac shunt. This was confirmed by cardiac catheterization (Table I). The patient underwent surgery, and an atrial septal defect secondary to a patent foramen ovale was corrected. After surgery, arterial blood gas levels were markedly improved with the PaO2 400 mm Hg with FIO2 1.0. Two days later, the patient had a cardiac arrest and died.

**Discussion**

Patent foramen ovale is reported to be present in 20 to 25 percent of normal individuals. The unique nature of this membranous structure allows it to function as a unidirectional valve, opening from right-to-left. Normally, left atrial pressures are higher than the right atrial pressures, which prevents any flow of blood across the foramen; however, an increase in right atrial pressure, as may occur in clinical

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**Persistent Hypoxemia due to Patent Foramen Ovale in a Patient with Adult Respiratory Distress Syndrome**

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This report describes a patient in the recovery phase of the adult respiratory distress syndrome in whom the persistence of severe hypoxemia was not corrected by a high fractional concentration of oxygen in the inspired gas and positive end-expiratory pressure. A right-to-left intracardiac shunt was diagnosed by M-mode and cross-sectional echocardiography with saline injection, and the presence of a patent foramen ovale was confirmed at the time of cardiac surgery.

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