patients who did not respond to nitroprusside treatment for reducing pulmonary hypertension prior to cardiac transplantation. These patients were given a bolus of amrinone (0.75 mg/kg) followed by a prolonged continuous infusion (25 μg/kg/min) for 48 h; 89 percent of these patients responded to the therapy evidenced by a decrease in PCWP, right atrial pressure, systemic vascular resistance (SVR), and PVR.* In our two documented patients who had severe pulmonary hypertension and biventricular failure, the administration of amrinone brought about the dramatic change in the pulmonary indices. The PAP decreased by 20 percent and 23 percent while the PVR decreased by about 40 percent and 67 percent, respectively. We are aware that in case 2, because of the initial large V wave, the mean height of the A wave or the diastolic pressure of the PCWP should be used to calculate the PVR. Unfortunately, PCWP was not recorded; therefore, pulmonary arterial diastolic pressure was used in the PVR calculation. This probably underestimates the absolute severity of PVR, but the relative change in PVR remains valid. The resultant lower pulmonary resistance and pressure improved the right ventricular performance and reduced the wall stress of the right side of the heart, thus improving the left ventricular function and systemic BP.

In conclusion, we demonstrated that the addition of amrinone can be life-saving in patients with severe pulmonary hypertension and biventricular failure following complicated valvular heart surgery, not responding to conventional β-adrenergic (isoproterenol or dopamine) and vasodilator (nitroglycerin) drug therapy. A loading dose of amrinone, 1 to 1.5 mg/kg, followed by 25 μg/kg/min infusion increased the mean BP by 49 to 51 percent, CI by 36 to 37 percent, and decreased mean PAP by 20 to 23 percent, PVR by 40 to 67 percent, and HR by 13 to 22 percent in the moribund patients.

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Pneumonitis Complicating Low-dose Methotrexate Therapy for Rheumatoid Arthritis*

Discrepancies Between Lung Biopsy and Bronchoalveolar Lavage Findings

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Two very similar cases of drug-induced pneumonitis complicating treatment of rheumatoid arthritis with low-dose methotrexate are presented. Diagnosis was suggested by clinical history and findings, but the bronchoalveolar lavage showed a high percentage of neutrophils, an unusual feature in methotrexate-induced pneumonitis. Transbronchial lung biopsies (TBB) confirmed the diagnosis by showing interstitial lymphocytic infiltrate with microgranulomas. Although histologic findings are not strictly pathognomonic, when a differential diagnosis has to be made with infectious and rheumatoid lung disease, TBB appears to be of great promise.

(Chest 1993; 104:1620-83)

BAL = bronchoalveolar lavage; RA = rheumatoid arthritis; TBB = transbronchial lung biopsy

Weekly low-dose methotrexate sodium administration (5 to 15 mg) is used in the treatment of rheumatoid arthritis (RA) refractory to conventional antirheumatic drugs.† The dosages used are much lower than those used in the treatment of malignancies so that severe toxic reactions are infrequently reported.‡ Methotrexate-related interstitial pneumonitis, however, has been described.⁴ We report two cases of methotrexate-induced pneumonitis after low-dose therapy for RA in which transbronchial lung biopsy (TBB) was highly contributive to the diagnosis.

CASE REPORTS

CASE 1

This 68-year-old woman was a nonsmoker and had no history of respiratory disease. In 1967, she developed severe RA which required treatment with salazopyrine, salicylates, and corticosteroids.

In July 1991, treatment with salicylates and corticosteroids was stopped because of slight impairment of renal function and osteoporosis. Starting on July 15, 1991, methotrexate sodium (10 mg/wk) was administered orally with improvement of articular complaints. She received the last dose the day before her admission. From the end of September 1991, she recurrently complained of cough and fever, and these complaints progressively increased until admission on October 31, 1991. She had no articular symptoms. Examination revealed an ill-appearing woman with severe respiratory distress and fever. Dry inspiratory crackles were heard in both lungs. A chest radiograph (Fig 1, top) and computed tomography scan (Fig 1, bottom) showed massive interstitial infiltration of both lungs. Lung function tests showed a severe restrictive ventilatory impairment (Table 1). While she was breathing room air, the PaO2 value was 37.2 mm Hg, PaCO2, 20 mm Hg, and arterial pH, 7.50. The white blood cell count was 4,000/mm3, with 81 percent neutrophils.

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Pneumonitis Complicating Low-dose Methotrexate Therapy (Leduc et al)
Table 1—Lung Function Test Results

<table>
<thead>
<tr>
<th>Case</th>
<th>Predicted Values</th>
<th>Before Methotrexate Treatment</th>
<th>At Admission</th>
<th>Two Months After Admission</th>
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<td>6.50</td>
<td>24.00</td>
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</table>

11 percent lymphocytes, 6 percent monocytes, and 2 percent basophils. The serum creatinine value was 1.8 mg/100 ml (normal, 0.5 to 1.2 mg/100 ml). Fiberoptic bronchoscopy was performed on the admission day and was normal. Bronchoalveolar lavage was performed in the right middle lobe (with 3/50-ml aliquots) and the cell count was 260 × 10⁸/ml with 31 percent neutrophils, 5 percent lymphocytes, and 64 percent macrophages. Stains and cultures for aerobic and anaerobic bacteria including Legionella, fungi, acid-fast organisms, virus, and Pneumocystis carinii were negative. No rise in viral or Mycoplasma titers was noted. Methotrexate was withdrawn and symptomatic treatment given. Because the clinical situation did not improve in the following 48 h, TBB was performed in the right upper and lower lobes. The biopsy specimens showed an extensive lymphocytic interstitial infiltrate with granuloma formation (Fig 2). Corticotherapy was started (methylprednisolone, 2 mg/kg/d) because of persistent hypoxemia. Clinical improvement occurred after 48 h, and the patient was discharged from the hospital 15 days after admission. At that time, PaO₂ with the patient breathing room air was 75 mm Hg, and pulmonary infiltrates had completely disappeared on the chest x-ray film. Pulmonary function tests also improved (Table 1).

Case 2

A 73-year-old woman with RA was admitted to the hospital in December 1991 with a presumptive diagnosis of pneumonia.

In 1983, she had developed erosive symmetrical polyarthritis. Rest, physical therapy, gold salts, salicylates, penicillamine, and low-dose prednisone failed to control her progressive arthritis.

In July 1991, oral treatment with methotrexate sodium (7.5 mg/wk) was initiated with progressive improvement of joint complaints. The patient was a nonsmoker and had no history of lung disease. Four weeks prior to admission, she developed progressively increasing breathlessness and a dry cough. She had taken the last dose of methotrexate on the admission day. She was admitted with tachypnea (30 breaths per minute). She had no fever. Inspiratory crackles were heard in both lungs. While she received oxygen (2 L/min), the PaO₂ was 60 mm Hg; PaCO₂, 31.8 mm Hg; pH, 7.53. The white blood cell count was 17.500/mm³, with 89 percent neutrophils, 3 percent lymphocytes, 6 percent monocytes, and 2 percent basophils. The serum creatinine value was 1.8 mg/100 ml (normal, 0.5 to 1.2 mg/100 ml). Fiberoptic bronchoscopy was performed on the admission day and was normal. Bronchoalveolar lavage was performed in the right middle lobe (with 3/50-ml aliquots) and the cell count was 260 × 10⁸/ml with 31 percent neutrophils, 5 percent lymphocytes, and 64 percent macrophages. Stains and cultures for aerobic and anaerobic bacteria including Legionella, fungi, acid-fast organisms, virus, and Pneumocystis carinii were negative. No rise in viral or Mycoplasma titers was noted. Methotrexate was withdrawn and symptomatic treatment given. Because the clinical situation did not improve in the following 48 h, TBB was performed in the right upper and lower lobes. The biopsy specimens showed an extensive lymphocytic interstitial infiltrate with granuloma formation (Fig 2). Corticotherapy was started (methylprednisolone, 2 mg/kg/d) because of persistent hypoxemia. Clinical improvement occurred after 48 h, and the patient was discharged from the hospital 15 days after admission. At that time, PaO₂ with the patient breathing room air was 75 mm Hg, and pulmonary infiltrates had completely disappeared on the chest x-ray film. Pulmonary function tests also improved (Table 1).

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percent lymphocytes, 6 percent monocytes, and 2 percent eosinophils. The sedimentation rate was 100 mm/h.

A chest radiograph and computed tomography scan showed diffuse interstitial infiltrates in both lungs with patchy confluent lesions in the two upper lobes. Pulmonary function tests indicated a moderate restrictive ventilatory impairment (Table I). Fiberoptic bronchoscopy was normal.

Bronchoalveolar lavage fluid from the right middle lobe contained 420 × 10^6 nucleated cells/ml, with 70 percent neutrophils, 6 percent lymphocytes, and 24 percent macrophages. Stains and culture showed the presence of a few colonies (2 × 10^3/ml) of Haemophilus influenzae, and treatment consisted of administration of trimethoprim and sulfamethoxazole (trimethoprim, 8 mg/kg/d; sulfamethoxazole, 40 mg/kg/d intravenously) after stopping methotrexate therapy. Forty-eight hours later, the patient remained severely hypoxemic. Then TBB was performed in the right upper lobe. Pathologic examination showed a massive interstitial lymphocytic infiltrate with granuloma formation (Fig 3). Treatment with intravenously administered methylprednisolone, 2 mg/kg/d, was begun. The patient rapidly improved. Concomitantly, the infiltrates evidenced on chest roentgenogram, resolved. Ten days later, at discharge, arterial blood gases with the patient breathing room air were PaO_2, 74 mm Hg; PaCO_2, 29 mm Hg; and pH, 7.46. Lung function tests confirmed clinical improvement (Table I).

**DISCUSSION**

Evidence is accumulating that low-dose methotrexate is an effective therapy to control RA refractory to more conventional treatment. Common adverse reactions from low-dose methotrexate treatment include an increase in serum transaminase activity, nausea, and diarrhea. The incidence of interstitial pneumonitis is lower than 5 percent in the patients receiving this low-dose regimen for RA. Although methotrexate pneumonitis is generally considered as a hypersensitivity reaction, contribution of a direct cytotoxic effect is not excluded, since the exact mechanism of lung injury remains controversial. That it can develop with low doses and that there is a wide range of delay between drug intake and onset of disease (15 days to 5 years) supports the hypersensitivity hypothesis.

The clinical history and radiologic findings in our two patients were consistent with the diagnosis of methotrexate-induced lung disease. In both cases, TBB assessed the diagnosis: massive interstitial infiltrate by lymphocytes and granuloma formation, the classic histologic feature of methotrexate-induced pneumonitis.

A very striking observation was the coexistence, in both cases, of a neutrophilic alveolitis with a well-demonstrated lymphocytic and granulomatous lung infiltration. The bronchoalveolar lavage (BAL) cell abnormality associated with hypersensitivity pneumonitis at the granulomatous stage classically is an elevated lymphocyte count; lymphocytic alveolitis usually is found in BAL fluid samples from patients with methotrexate-induced lung disease. Our lavage findings contrasted with previous data, particularly those of White et al, who systematically found in their six cases of methotrexate-induced lung disease a lymphocytic alveolitis with BAL lymphocyte count over 20 percent and a neutrophil count under 10 percent.

We have no definite explanation for the discrepancy between lavage findings and lung biopsies. Since the computed tomographic scan confirmed diffuse involvement of both lungs, it is difficult to ascribe local differences in the alveolar cell populations. Also, it is difficult to attribute a role to the short delay (less than 45 h) between the two diagnostic procedures in these subacute diseases. Neutrophilic alveolitis has been associated with rheumatoid lung and this might interfere with BAL results in our cases; most reported cases of methotrexate-induced lung diseases with lymphocytic alveolitis are complications of malignancies without obvious underlying lung diseases. It must, however, be underlined that lesions of rheumatoid lung were not detected in the biopsy specimens.

Since methotrexate withdrawal together with high-dose steroid treatment has been proposed to accelerate recovery of this disease, it appears important to recognize rapidly methotrexate-induced pneumonia (especially in critically ill patients). The dramatic improvement observed in our two patients tends to confirm the beneficial role of early steroid administration in this disease.

In patients treated with methotrexate for RA who present with interstitial pneumonia, differential diagnosis of methotrexate-induced toxicity has to be made with rheumatoid lung disease and opportunistic lung infections (P carinii, etc). In this particular clinical setting, histopathologic findings are specific enough to allow the diagnosis of methotrexate-induced pneumonitis. Since our data suggest that BAL findings are not always contributive to the diagnosis of methotrexate-induced disease and because it is a less invasive method to obtain lung tissue than open-lung biopsy, TBB appears to be a very interesting procedure for diagnosis in such cases.

**REFERENCES**


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**Figure 3.** Histologic pattern showing lymphocytic interstitial infiltrate with a small nonnecrotic granuloma.
Extradural Hematopoietic Tumors of the Posterior Mediastinum Related to Asymptomatic Refractory Anemia*

Vincent Thomas De Montpréville, M.D.; Elisabeth M. Dulmet, M.D.; Alain R. Chapelier, M.D.; Philippe G. Dartevelle, M.D.; and Jeanne M. Verley, M.D.

Two asymptomatic paravertebral thoracic masses occurred in a 65-year-old patient with isolated macrocytosis. The largest one measured 8 cm and was surgically resected with a presumptive diagnosis of schwannoma. This thoracic mass was hemorrhagic, encapsulated, and composed of fat and hematopoietic tissue. While extradural hematopoietic tumors usually occur in patients with severe chronic hemolytic anemia, our report suggests that such lesions must be considered in the differential diagnosis of posterior mediastinal mass in patients without clinically evident anemia.

(Chest 1993; 104:1623-24)

*From the Departments of Surgical Pathology (Drs. Thomas De Montpréville, Dulmet, and Verley) and Thoracic and Vascular Surgery and Heart-Lung Transplantation (Drs. Chapelier and Dartevelle), Marie Lannelongue Surgical Center (Université Paris-Sud), Le Plessis-Robinson, France.

Extradural hematopoietic tumors (EMHTs) that resemble myelolipomas may occur when the normal function of bone marrow is disturbed. In the posterior mediastinum, EMHTs are usually associated with chronic congenital hemolytic anemia. These tumors present as asymptomatic, unilateral, or bilateral paraspinal masses.

A single case of mediastinal EMHTs associated with macrocytosis related to vitamin deficiency has been reported. This report presents the first case (to our knowledge) associated with primary refractory anemia that was confirmed by histologic examination of the surgically removed mass.

CASE REPORT

A 65-year-old man was referred to the Marie Lannelongue Hospital for a right femoral bypass. He had a history of partial gastrectomy at the age of 25 years and had smoked one pack of cigarettes a day for 45 years.

A right paravertebral thoracic mass was incidentally discovered on preoperative chest radiographs. The lesion was already present on systematic radiographs performed 2 years before. The patient was not investigated further at that time. He had no thoracic symptom, no fever, and no weight loss.

Laboratory findings included the following: a WBC count of 8 x 10^9/L with neutrophils 65 percent, lymphocytes 29 percent, and monocytes 6 percent; an erythrocyte count of 3.35 x 10^12/L with hemoglobin concentration of 127 g/L, hematocrit of 37 percent, and mean corpuscular volume of 110 fl; and a platelet count of 250 x 10^9/L. Other pertinent laboratory serum values were as follows: normal creatinine and liver chemistry studies, total bilirubin of 22 μmol/L (N<20), free bilirubin of 20 μmol/L, vitamin B12 of 353 ng/L (N>130), and folate of 2.8 μg/L (N>1.8).

Fiberoptic bronchoscopy revealed no lesion and aortography showed no argument for pulmonary sequestration. Computed tomography showed two paravertebral masses at the T9 level (Fig 1). The right mass and the left measured 8 and 3.5 cm, respectively. These tumors had a smooth margination and were composed of areas of low density suggestive of fat deposition and of regions of water density. There was no calcification. The bones were normal and not eroded.

FIGURE 1. Computed tomographic scan of the chest showing the two round paravertebral masses containing fat.