artery, and if alveolar oxygen falls, continued perfusion with pulmonary arterial blood would cause interstitial hypoxia by equilibration with mixed systemic venous blood in the pulmonary artery, at a much lower oxygen tension than that of the alveoli. The demonstration in our patient that bronchial gas was hypoxic, and that ipsilateral pulmonary vasoconstriction was present, supports the inference that lung interstitium derives much or most of its oxygen from the alveolus, and that the vasoconstriction prevents interstitial hypoxia. The inference that alveolar interstitium derives oxygen from alveolar air also helps explain how it often survives pulmonary embolism, and would suggest, further, that when infarction occurs, an element of bronchial obstruction may well be present.

The locus of vasoconstriction in the pulmonary arterial tree is at a very peripheral level. In the cat,9 quick-freezing of the hypoxic lung shows constriction of arteries of 0.2 mm diameter. In the coati mundi, a small South American mammal whose lungs have interlobular septa preventing collateral ventilation, it can be shown10 that the phenomenon demonstrated in our patient for the whole lung also occurs in individual lobules. Lobular blood flow in this animal decreased within minutes as alveolar Po2 falls. Segmental and lobular bronchial obstruction in man likewise leads to pulmonary vasoconstriction, deflecting blood from nonventilated areas wherever they occur. The most common clinical example of this is seen in perfusion scans of patients with chronic obstructive airway disease, whose perfusion defects match their ventilatory defects.5,11

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Adult Respiratory Distress Syndrome Related to Ampicillin Sensitivity*


A patient with the adult respiratory distress syndrome was found to have an alveolar allergic reaction demonstrated by transbronchial lung biopsy. The clinical course and subsequent skin test reactivity suggested ampicillin as the cause. This is an unusual presentation of ampicillin allergy, and drug sensitivity is suggested as another cause of the adult respiratory distress syndrome.

The clinical picture of marked respiratory distress, diffuse pulmonary infiltration on x-ray examination, impaired effective pulmonary compliance, marked impairment in oxygen transport in spite of ventilatory assistance, and pulmonary congestion, arises from unrelated pulmonary insults and has been termed the adult respiratory distress syndrome.1 It is an important and common medical emergency and is likely to occur in all hospitals dealing in respiratory care. Our patient had features consistent with this entity and the clinical findings suggested ampicillin sensitivity as the cause.

CASE REPORT

A 17-year-old white woman was initially evaluated for signs and symptoms of a urinary tract infection which consisted of dysuria, urgency, frequency, lower abdominal pain, and fever. Microscopic examination of the urine showed 20 to 30 white blood cells per high power field. Her WBC was 15,000/cu mm, with 84 neutrophils, 2 bandforms, 4 monocytes, and 10 lymphocytes. She was started on a regimen of ampicillin, 250 mg every six hours, which was discontinued after three days because of the development of a generalized erythematous rash. Cephalexin, 250 mg every six hours, was substituted. On the fifth day after the initial physician contact, and two days of cephalexin therapy...
apy, she was hospitalized with persistent fever, abdominal pain, and urticaria.

On admission to the hospital, the patient was noted to have temperature elevation, a generalized urticarial rash, lower abdominal pain, and tender bilateral adnexal thickening on pelvic examination suggesting salpingitis. Pertinent laboratory studies included a WBC of 28,400/cu mm, with 71 neutrophils, 6 bandforms, 6 monocytes, 5 lymphocytes, and 12 eosinophils, and a culdocentesis which revealed 20 ml of serosanguinous fluid on Gram stain demonstrated a few white blood cells and no organisms. A cell block subsequently revealed the white blood cells were predominantly eosinophils. On the sixth day after her initial physician contact, and three days after stopping ampicillin therapy, her temperature remained elevated at 39.2° C, and rales were heard over both lungs posteriorly. A chest x-ray film demonstrated diffuse infiltrates bilaterally. The WBC was 34,400/cu mm, with a 38 percent eosinophilia. An arterial blood gas evaluation on room air revealed a PaO2 of 32 mm Hg, and the patient required oxygen provided by a rebreather mask with an inspired oxygen concentration (FiO2) of 60 percent to obtain a PaO2 of 38 mm Hg. Cultures of urine and blood were obtained because of suspected sepsis which subsequently were all negative. Because of the severity of the patient's illness and the question of infection, she was started on a regimen of kanamycin, 1 gm intramuscularly, followed by 0.5 gm every 12 hours, and erythromycin, 0.5 gm every six hours intravenously, on her second hospital day.

On the eighth day following her initial physician contact, and five days after ampicillin was discontinued, the patient was intubated and placed on a Bennett MA-1 respirator. At this time, an arterial PaO2 (FiO2 90 percent) was 53 mm Hg. Static compliance (tidal volume 500 ml) was 40 cm of water. A chest x-ray film revealed progression of the alveolar process (Fig 1) and a transbronchial forceps biopsy was obtained from the lower lobe of the patient's right lung.

**Figure 1.** Taken at the time of intubation, this demonstrates diffuse parenchymal infiltration bilaterally.

**Figure 2.** Transbronchial lung biopsy specimen showing eosinophilic cellular alveolar exudate.

Intravenous administration of hydrocortisone, 1 gm every six hours, clindamycin, 600 mg every six hours, and isoniazid, 300 mg per nasogastric tube daily, were begun. An arterial PaO2 of 85 mm Hg (FiO2, 50 percent) was achieved after furosemide, 40 mg intravenously, and positive end expiratory pressure (PEEP) of 5 cm H2O were instituted.

On the ninth day after initial physician contact, and the fourth day of hospitalization, rapid improvement in ventilation, fever, and chest roentgenographic findings were noted. The patient was afebrile, and pulmonary compliance fell to 18 cm to H2O. The arterial PaO2 (FiO2 40 percent) was 75 mm Hg without PEEP. There was no evidence of infection by examination of the urine, blood, and bronchial washings. The lung biopsy specimen revealed alveoli filled with histiocytes, eosinophils, and neutrophils consistent with an alveolar allergic reaction (Fig 2).

On the tenth day after physician contact, and seven days after ampicillin therapy was discontinued, the patient was extubated. Arterial PaO2 (FiO2 21 percent) was 80 mm Hg. The chest x-ray film was normal. The patient remained afebrile but with continued urticaria and pruritus. Hydroxyzine, 25 mg every six hours, and diphenhydramine, 25 mg at night, were instituated with control of the patient's urticaria. She was discharged on the ninth day after admission on a regimen of prednisone, 10 mg four times a day. This was slowly tapered over the next two months.

When off all medication, the patient was skin tested with penicillin G benzathine, 1,000 and 10,000 units per ml ampicillin, 0.25 mg/ml, cephalothin, 1 mg/ml, the major determinant benzylpenicilloly S X 10^-8 M and the alkaline hydrolysis product of K penicillin G 1 X 10^-2 M and ampicillin 1 X 10^-2 M. The patient's only positive skin test was on intradermal testing to ampicillin, 0.25 mg/ml, with a wheel and flare observed within 20 minutes. In addition, pulmonary function tests at that time which included a single breath carbon monoxide diffusing capacity were normal.

**Discussion**

The lungs are a common site of allergic manifestations, and many substances inhaled, ingested, or injected can cause these reactions. Pulmonary infiltration and eosinophilia has been reported following penicillin therapy. These reactions have usually followed parental administration of the drug and have varied in their pulmonary presentation from transient infiltrates to infiltrates which resolve slowly over a number of
months. Liebow and Carrington described diffuse alveolar damage with predominantly small mononuclear infiltrates and hyaline membrane formation in a patient who received both penicillin and streptomycin. However, none of the reports to date has presented clinical features of the adult respiratory distress syndrome, and in most cases, a lung biopsy specimen was not obtained.

The immunologic basis for these reactions has not been determined, but positive immediate skin tests demonstrating IgE antibody to penicillin have been noted in some patients. Reichlin and associates described such a case. Molina and associates reported pulmonary infiltration with a 53 percent peripheral blood eosinophilia in a patient who had received a penicillin suppository and orally administered ampicillin. A positive immediate skin test was noted to penicilloylpolylysine-PPL without a delayed response. In addition, lymphoblastic transformation occurred in the presence of phytohemagglutinin and penicillin G but not ampicillin. In this patient, the left basilar infiltrate resolved slowly over nine months.

The adult respiratory distress syndrome has been observed in association with drug overdose. Methadone and colchicine are two examples. Pulmonary edema has been reported as a severe allergic reaction to hydrochlorthiazide. In all these situations, the adult respiratory distress syndrome has followed medication being used in greater than therapeutic doses.

This case report has several unique features. It reports the development of the adult respiratory distress syndrome following the administration of ampicillin in therapeutic doses. The diagnosis of pulmonary infiltrates with eosinophilia with primary involvement of the alveoli is supported by lung biopsy findings. In addition to the pulmonary manifestations, the patient had other manifestations suggesting an immunologic reaction such as urticaria, eosinophilia, and a positive skin test to ampicillin. Although it is felt by many that re-introduction of a drug is necessary to document the reaction as being due to the drug in question, this patient's illness was so severe that re-administration of the drug to a skin test-positive individual was believed not to be warranted.

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