

Pneumocystis Carinii Pneumonia: Percutaneous Lung Biopsy and Review of Literature*

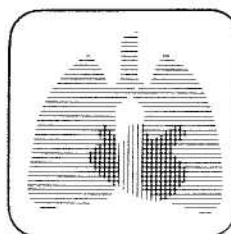
*Michael L. Cohen, M.D.,** and Earle B. Weiss, M.D.,
F.C.C.P.†*

In patients with impaired immune defenses, unusual organisms such as *Pneumocystis carinii* may be responsible for fatal diffuse interstitial pneumonia. Inasmuch as relatively specific therapy is available, a precise diag-

*From the Lung Station (Tufts), Tufts Medical Service, Boston City Hospital, Boston, Massachusetts.

**Research Fellow, Lung Station (Tufts), Present address Pulmonary Division, Salem Hospital, Salem, Massachusetts.

†Associate Professor of Medicine, Tufts University School of Medicine; Physician-in-Charge, Pulmonary Physiology Section, Lung Station (Tufts), Boston City Hospital; Research Associate, Lung Station (Tufts), Boston City Hospital.



Vol. 60, p. 195-199

August 1971 Issue

Reprinted from **CHEST**

Pneumocystis Carinii Pneumonia: Percutaneous Lung Biopsy and Review of Literature*

*Michael L. Cohen, M.D.,** and Earle B. Weiss, M.D.,
F.C.C.P.†*

In patients with impaired immune defenses, unusual organisms such as *Pneumocystis carinii* may be responsible for fatal diffuse interstitial pneumonia. Inasmuch as relatively specific therapy is available, a precise diag-

*From the Lung Station (Tufts), Tufts Medical Service, Boston City Hospital, Boston, Massachusetts.

**Research Fellow, Lung Station (Tufts), Present address Pulmonary Division, Salem Hospital, Salem, Massachusetts.

†Associate Professor of Medicine, Tufts University School of Medicine; Physician-in-Charge, Pulmonary Physiology Section, Lung Station (Tufts), Boston City Hospital; Research Associate, Lung Station (Tufts), Boston City Hospital.

nosis must be established in all instances. The present case supports the role of percutaneous lung biopsy for this purpose. The toxicity of pentamidine isethionate and a review of the current literature is presented.

Pneumocystis carinii appears to be a disease of increasing incidence. Previously described in premature and debilitated infants, or children with hypogammaglobulinemia, *P. carinii* pneumonia has since been discovered in transplant patients receiving immunosuppressive therapy,¹⁻³ patients with hematopoietic and lymphoreticular malignancies receiving adrenal corticosteroids or cytotoxic agents,⁴⁻⁶ and patients with immunoglobulin deficiencies.^{7,8} Untreated, this disease is usually fatal. Recent reports of successful treatment of *P. carinii* pneumonia with pentamidine isethionate, indicate that a specific diagnosis is mandatory. In the appropriate clinical setting and where the usual diagnostic modalities are unrevealing, the percutaneous needle biopsy of the lung may play a significant role.

CASE REPORT

A 34-year-old woman underwent cadaveric renal transplantation on November 24, 1968, because of end-stage chronic glomerulonephritis. Bilateral nephrectomy and splenectomy had been performed on October 29, 1968. Immunosuppressive therapy consisted of azathioprine (Imuran), prednisone, antilymphocyte serum and local irradiation. The development of hypertension required admission two months later. The recumbent blood pressure was poorly controlled despite methyldopa, hydralazine, spironolactone, and guanethidine; renal function, however, was not impaired (creatinine 0.8 mg percent). A spiking fever to 105° F developed on the 109th posttransplant day (March 15, 1969); however physical examination and numerous laboratory studies failed to reveal its source. A few days later the patient became dyspneic, the respiratory rate was 52/minute, rales were audible over the left-lower lobe, and a chest x-ray picture showed bilateral pulmonary congestion suggestive of pulmonary edema. The PaO₂ was 38 mm Hg, Paco₂ 20 mm Hg, and pH 7.46. Two days later the chest x-ray film revealed progressive opacification (Fig 1).

A needle biopsy (Franklin modification of the Vim-Silver-

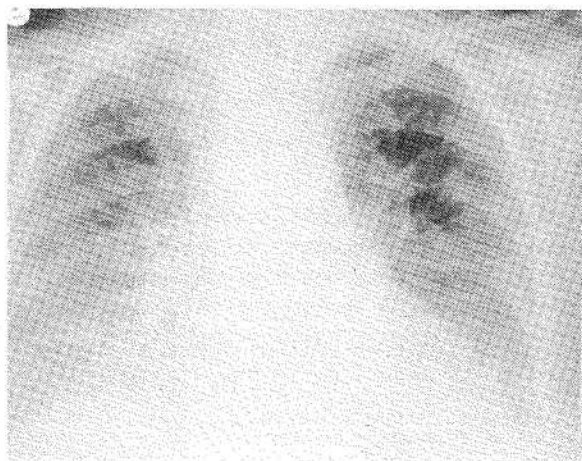


FIGURE 1. Chest roentgenogram on day of percutaneous lung biopsy revealing bilateral intra-alveolar infiltration pattern.

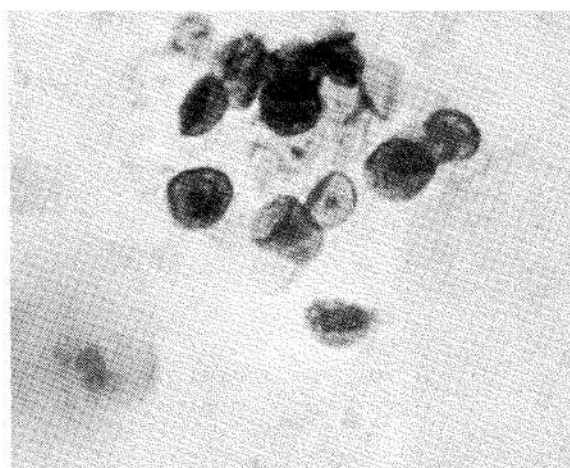


FIGURE 2. Toluidine blue stain of tissue imprint obtained from percutaneous lung biopsy. *P. carinii* cysts appear as dark round bodies 1 to 5 micron size. An internal structure can be seen within some cysts. $\times 1000$.

man) of the right lung was performed on March 20, 1969 with transient hemoptysis (5 to 10 ml) as the sole complication. Tissue imprints and fixed sections, when stained with methenamine silver and Graw's modified toluidene blue, revealed *P. carinii* cysts (Fig 2). Pentamidine, 4 mg/kg was administered for four days, then increased to 8 mg/kg for four additional days.

On March 30, 1969 the patient developed oliguria; an infusion IVP and a renal arteriogram suggested renal rejection. Peritoneal dialysis was instituted, pentamidine and Imuran were discontinued, and prednisone, which had been tapered to a maintenance dosage of 20 mg, was now increased. Although she continued a spiking febrile course, the chest x-ray improved significantly with reduction in dyspnea and tachypnea. Nine days later she suffered a cerebrovascular accident, remaining comatose until her death.

At postmortem examination, the lungs revealed acute bronchopneumonia; however, there was no evidence of interstitial pneumonitis, nor were *P. carinii* identified. There was infarction of the transplanted kidney, with diffuse thrombosis of small arterioles and venules consistent with a hyperacute rejection of the type seen in patients with preformed anti-white cell antibody. Although this patient had preformed antibody to over 90 percent of randomly selected donors, she did not have antibody to the donor used for transplantation.

DISCUSSION

Pneumocystis carinii was described in the European literature in the 1940's, as occurring primarily in premature and debilitated infants,⁹ but is now recognized as a pathogen causing diffuse interstitial pneumonia in patients with altered immune mechanisms. Goodell and co-workers¹⁰ estimated that *P. carinii* comprised a minimum of 44 percent of cases with diffuse interstitial pneumonias in patients with neoplastic disease who were receiving immunosuppressive therapy. Rifkind and colleagues² and Hill and co-workers³ called attention to this organism as a factor in the death of renal transplant patients, and LeClair¹¹ recently described three cases of *P. carinii* pneumonia among cardiac transplant recipients.

We have encountered three cases of *P. carinii* pneu-

Table 1—Summary of Literature—Cases of *P. Carinii* Proved by Lung Biopsy and Successfully Treated.

Reference	Age*	Disease	Medications	Biopsy + Complications	Treatment	Complications	Follow-up
28	7.5 months	Hypogammaglobulinemia	—	Open— Not stated	Pentamidine	Not stated	X-ray unchanged p 3 months
				Open (5 mos later)— Tension pneumothorax 1 wk after biopsy			
8	2	Hypogammaglobulinemia	—	Open— Not stated	Pentamidine + Gammaglobulin	Not stated	2 years
16	8	Hypogammaglobulinemia	—	Open— Not stated	Hydroxystilbamidine, Pentamidine	Megaloblastic marrow	3 years
25	10	ALL**	Methotrexate Vincristine Prednisone	Open— Not stated	Hydroxystilbamidine, D/C Methotrexate	Not stated	16 months
7	14	ALL**	Methotrexate	Open— Not stated	Pentamidine	Not stated	10 months
5	14	ALL**	X-ray, Prednisone, 6-M-P, Methotrexate	Needle— Hemothorax, mild	Pentamidine	Hypoglycemia	Not stated
4	20	ALL**	Vincristine Prednisone	Needle— Not stated	Pentamidine	Transient oliguria	Clear x-ray at 13 days
26	46	CLL†	Chlorambucil Prednisone	Open— Extreme dyspnea	Pentamidine, Steroids	Not stated	8 months. Autopsy showed no pneumocystis
4	50	Malignant lymphohistiocytoma	Cyclophosphamide Vinblastine Prednisone	Needle— Not stated	Pentamidine, D/C Prednisone	Papules with slough Renal tubular dysfunction	Clear x-ray at 1 month
5	50	CML‡	Busulfan	Open— Not stated	Pentamidine	Hypoglycemia Painful, weeping injection site	1 year
27	53	CLL†	Chlorambucil Prednisone	Open— Not stated	Amphotericin, Steroids	Not stated	Clear x-ray
16	57	CLL†	Prednisone Chlorambucil	Open— "Respiratory distress"	Pentamidine	Not stated	"Improved discharged"
23	8	ALL**	6-MP Amphotericin Vincristine Prednisone	Needle— Not stated	Pentamidine	Not stated	"Improved" x-ray resolution
20	58	Mycosis fungoides	Amphotericin	Needle— Not stated	Pentamidine	None	Complete clearing at 2 months
12	49	Renal transplant	Azathioprine Prednisone	Needle— Hemoptysis (5 to 10 ml)	Pentamidine	None	Well after 14 months
Present case	34	Renal transplant	Azathioprine Prednisone	Needle— Hemoptysis (5 to 10 ml)	Pentamidine	None	Died after 1 month No evidence of <i>p carinii</i> at postmortem exam

*Age in years.

**Acute lymphocytic leukemia.

†Chronic lymphocytic leukemia.

‡Chronic myelogenous leukemia.

monia in renal transplant patients on immunosuppressive therapy, antilymphocytic serum, prednisone and Imuran in a one-year period. One case was diagnosed at postmortem, the other two by percutaneous needle lung biopsy and were treated with pentamidine. The present case was successfully treated for *P. carinii* pneumonia based upon clinical and radiographic criteria. Although she died one month after treatment, there was no evidence of pulmonary *P. carinii* by detailed postmortem examination. Our third case¹² is alive and well 16 months after therapy; his chest x-ray remains clear, and the transplanted kidney functions adequately.

In the English literature, 14 other biopsy proved cases of *P. carinii* pneumonia have been successfully treated (Table 1); five of these were established by needle biopsy of the lung, and 12 were treated with pentamidine isethionate.

Pentamidine isethionate, a diamidine with trypanasomacidal activity and utilized since 1941 in the treatment of African sleeping sickness and leishmaniasis, is potentially nephrotoxic. Western and Schultz¹³ state that hundreds of thousands of patients have been treated with this drug without a recorded instance of permanent renal damage. In the French literature,¹⁴ four cases of transient azotemia were reported in patients treated for African sleeping sickness; however, it was suggested that this was due to a protein catabolic effect rather than renal injury. DeVita and associates,⁴ reported a case of transient renal impairment possibly related to a doubling of the dose of pentamidine for four days; and a second case that experienced one day of oliguria with full recovery; nephrotoxic antibiotics, however, may have been added factors.

Because of the precarious function of transplanted kidneys, potentially nephrotoxic drugs should be limited. Our previously reported case¹² received 4 mg/kg of pentamidine for 14 days, without any renal damage as measured by conventional renal function tests. The present patient received 4 mg/kg for four days, then 8 mg/kg for an additional four days. Although she became oliguric after completion of her treatment, postmortem examination implicated the oliguria to a hyperacute rejection phenomenon rather than to pentamidine toxicity.¹⁵

Pentamidine is usually administered intramuscularly at a dose of 4 mg/kg for ten days. It occasionally causes pain at the injection site, and sterile abscesses and tissue slough have been reported.⁵ Other complications include vomiting, dizziness, hypotension, tachycardia, hypoglycemia, and one possible case of a megaloblastic bone marrow by an antifolate effect.¹⁶

In patients with altered or with suppressed immune defense mechanisms it is mandatory to establish the specific etiology of any pneumonia to provide specific therapy, and thereby to avoid complications of toxicity of empirical therapy. *P. carinii* may, at times, be recoverable from the sputum, blood, or pleural fluid; however, a significant number of cases remain undetected by these conventional means. Ivady and co-workers,¹⁷ based upon a vast pediatric experience, advocated aspiration of

tracheal mucus through a laryngoscope. Since the organisms rarely appear in the sputum,¹⁸ lung biopsy is another approach available to establish this diagnosis. These patients are frequently critically ill, with severe hypoxemia, and therefore may be poor surgical candidates. Following open lung biopsy, assisted ventilation may be required because of severe postoperative respiratory distress.¹⁶ Although Robbins mentions a death due to a nondecompressable pneumothorax following needle aspiration of a lung infected with *P. carinii*, others have successfully employed needle biopsy with only minor complications, providing there are no contraindications to the procedure (*ie* bleeding diathesis).^{5,19,20}

Rifkind and colleagues⁶ reported the arterial blood gas data in five patients. Oxyhemoglobin saturation values ranged from 90.5 percent to 44.5 percent while the partial pressures of CO₂ were normal or low. As demonstrated in the present case, clinical progression is associated with increasingly severe hypoxemia. While unclarified at present, the mechanism of hypoxemia appears to be due to a diffusion defect and/or veno-arterial shunting.

For needle lung biopsy the most densely involved area is selected from conventional chest roentgenograms. Since diffuse disease is frequently present, the biopsy is performed in the right lower lobe to avoid cardiac trauma. Oxygen is routinely provided. After 0.5 to 1.0 mg atropine IV, local anesthesia (1 percent lidocaine, [1 percent Xylocaine]) to the parietal pleura is followed by a 0.5 cm skin incision through which the biopsy is conducted employing a Franklin modification of the Vim-Silverman needle. Vital signs and chest x-ray are monitored over the next 24 hours.

Processing of the biopsy specimen is of utmost importance. The resulting tissue is divided as follows: one-third in 10 percent formalin for sections, one-third homogenized with sterile saline for culture, and one-third touched to several glass slides for touch imprint which may then be treated with Gram's, acid fast, or Wright's stains. We routinely make touch imprints of the biopsy material in addition to fixed sections since it is not infrequent that such tissue imprints reveal many more pneumocystis organisms.^{5,8,9,21} The 4-micron size spherical, intra-alveolar cysts stain readily with Gomori's methenamine silver or Grawe's modification of the toluidene blue stain.²²

We have successfully utilized the Franklin-Silverman needle in two renal transplant patients, with transient hemoptysis (5 to 10 ml) as the sole complication. Additionally, in some 40 cases with a variety of diffuse and local pulmonary diseases, it is well demonstrated that needle biopsy is a rapid diagnostic modality with limited morbidity and mortality for resolving difficult causes of diffuse pneumonopathies, particularly in critically ill patients.^{23,24}

REFERENCES

- 1 Hill RB Jr, Rowlands DT Jr, Rifkind D: Infectious pulmonary disease in patients receiving immunosuppressive therapy for organ transplantation. *New Eng J Med* 271: 1021, 1964

- 2 Rifkind D, Marchioro TL, Schneck SA, et al: Systemic fungal infections complicating renal transplantation and immunosuppressive therapy. *Amer J Med* 43:28, 1967
- 3 Hill RB Jr, Dahrling BE, Starzl TE, et al: Death after transplantation (editorial) *Amer J Med* 42:327, 1967
- 4 DeVita VT, Emmer M, Levine A, et al: *Pneumocystis carinii* pneumonia. *New Eng J Med* 280:287, 1969
- 5 Lillehei JP, Funke JL, Drage CW, et al: *Pneumocystis carinii* pneumonia. *JAMA* 206:596, 1968
- 6 Rifkind D, Faris TD, Hill RB Jr: *Pneumocystis carinii* pneumonia. *Ann Intern Med* 65:943, 1966
- 7 Einzig S, Hong R, Sharp HL: Successful treatment of *pneumocystis carinii* in an immunologically deficient acute lymphatic leukemia patient. *Cancer* 23:658, 1969
- 8 Marshall WC, Weston HJ, Bodian M: *Pneumocystis carinii* pneumonia and congenital hypogammaglobulinemia. *Arch Dis Child* 39:18, 1964
- 9 Gajdusek DC: *Pneumocystis carinii*—etiologic agent of interstitial plasma cell pneumonia of premature and young infants. *Pediatrics* 19:543, 1957
- 10 Goodell B, Jacobs JB, Powell RD, et al: *Pneumocystis carinii*: The spectrum of diffuse interstitial pneumonia in patients with neoplastic disease. *Ann Intern Med* 72:337, 1970
- 11 LeClair RE: Transplantation pneumonia, associated with *pneumocystis carinii*, among recipients of cardiac transplants. *Amer Rev Resp Dis* 100:874, 1969
- 12 Cohen ML, Weiss EB, Monaco AP: Successful treatment of *pneumocystis carinii* and nocardia asteroides in a renal transplant patient. *Amer J Med* 50:269, 1971
- 13 Western KA, Schultz MG: Pentamidine nontoxicity. *Ann Intern Med* 70:234, 1969
- 14 Payet M, Sankale M: Transitory hyperazotemia during the treatment of human African trypanosomiasis by diamidines. *Bull Soc Path Exot* 53:690, 1960
- 15 Williams GM, Hume DM, Hudson RP Jr, et al: "Hyperacute" renal-homograft rejection in man. *New Eng J Med* 279:611, 1968
- 16 Robbins JB: *Pneumocystis carinii* pneumonitis—a review. *Pediatr Res* 1:131, 1967
- 17 Ivady G, Paldy L, Koltay M, et al: *Pneumocystis carinii* pneumonia (letter to the editor). *Lancet* 1:616-617, 1967
- 18 Erchul JW, Williams LP, Meighan PP: *Pneumocystis carinii* in hypopharyngeal material. *New Eng J Med* 267:926, 1962
- 19 Mulligan WJ, Krause FD, Morningstar W, et al: *Pneumocystis carinii* infestation. *Ohio State Med J* 64:1017, 1968
- 20 Jacobs JB, Vogel C, Powell RD, et al: Needle biopsy in *Pneumocystis carinii* pneumonia. *Radiology* 93:525, 1969
- 21 Burke BA, Korvetz LJ, Good RA: Occurrence of *Pneumocystis carinii* in children with agammaglobulinemia. *Pediatrics* 28:196, 1961
- 22 Chalvardjian AM, Grawe LA: A new procedure for the identification of *Pneumocystis carinii* cysts in tissue sections and smears. *J Clin Path* 16:383, 1963
- 23 Krumholz RA, Manfredi F, Weg JC, et al: Needle biopsy of the lung. *Ann Intern Med* 65:293, 1966
- 24 Youmans CR Jr, Middleton JM, Derrick JR, et al: Percutaneous needle biopsy of the lung for diffuse parenchymal disease. *Dis Chest* 54:25, 1968
- 25 Moore, DL, Carnahan CE, Mills SD, et al: *Pneumocystis carinii* pneumonitis complicating leukemia. *Mayo Clin Proc* 44:162, 1969
- 26 Smith E, Gaspar IA: Pentamidine treatment of *Pneumocystis carinii* pneumonia in an adult with lymphatic leukemia. *Amer J Med* 44:626, 1968
- 27 Schultz JC, Ross SW, Abernathy RS: Diagnosis of *Pneumocystis carinii* pneumonia in an adult with survival. *Amer Rev Resp Dis* 93:943, 1966
- 28 Patterson JH, Lindsey IL, Edwards ES: *Pneumocystis carinii* pneumonia and altered host resistance: Treatment of one patient with pentamidine isethionate. *Pediatrics* 38:388, 1966

Reprint requests: Dr. Weiss, Lung Station (Tufts), Boston City Hospital, Boston 02118