PNEUMOCYSTIS CARINII PNEUMONIA FOLLOWING 5-FLUOROURACIL ADMINISTRATION

Robert Hardy, MD, Clinton Cummings, MD, Marquetta Faulkner, MD, and Ifeanyi Obianyo, MD
Nashville, Tennessee

A 54-year-old man who had been treated with monthly courses of 5-fluorouracil for one year developed Pneumocystis carinii pneumonia. No evidence of significant, permanent, immunologic impairment was evident one year after the patient became infected. An infection associated with 5-fluorouracil treatment is implicated.

Pneumocystis carinii pneumonitis has recently become a significant epidemiologic and acute medical problem in certain risk groups. Most cases in the past have occurred in immunocompromised patients.[1-3] More recently, the acquired immunodeficiency syndrome (AIDS) has developed in homosexual men and in certain other high-risk groups.[4-6]

Though cancer chemotherapy is known to cause depression of the immune system, 5-fluorouracil is among the least immunosuppressive antimetabolites when used in normal cytotoxic dosages. The following is a report of the development of Pneumocystis carinii in a married, heterosexual man who had received an intermittent dose of 5-fluorouracil therapy adjunctively for colon cancer. No previous cases of 5-fluorouracil-associated immunosuppression and Pneumocystis carinii penumonia have been reported.

From the Department of Internal Medicine, Meharry Medical College, Nashville, Tennessee. Requests for reprints should be addressed to Dr. Robert Hardy, Department of Internal Medicine, Meharry Medical College, 1005 D. B. Todd Boulevard, Nashville, TN 37208.

CASE REPORT

On August 13, 1981, F. R., a 54-year-old black heterosexual man, was admitted to G. W. Hubbard Hospital of Meharry Medical College with a complaint of dyspnea and back pain. The patient is married, and was vacationing in Nashville, Tennessee. F. R. had undergone a left hemicolectomy in September 1980, for a Dukes C cancer of the sigmoid colon. Subsequently, he had been treated with five-day courses of 5-fluorouracil every 28 days.

His past medical history was positive for hypertension, angina pectoris, and gout, for which he took nitroglycerin, a beta-adrenergic blocker, hydrochlorothiazide, and allopurinol. F. R. smoked one-half pack of cigarettes per day.

His back pain was interscapular, nonpleuritic, nonradiating, aching, and intermittent. He had experienced some dyspnea during the week prior to admission but this had intensified on the day of admission. He also developed a moderate hacking cough productive of scant sputum. He denied any chills or fever.

The patient's vital signs were: temperature 38.2 °C (100.8 °F), pulse rate 120/min, respiratory rate 24/min, and his blood pressure was 160/100 mmHg. F. R. was a well-developed and muscular middle-aged black man who appeared to be in mild respiratory distress. There were no skin or mucosal lesions present. He had no lymphadenopathy. He had a prominent fourth heart sound. His chest was symmetrical and breath sounds were bronchovesicular in quality; no rales were detected. There was no hepatosplenomegaly. There was also a well-healed midline vertical

scar. The remainder of his physical examination was normal.

Laboratory tests and studies of electrolytes, blood counts, and liver function were normal. His white blood cell count ranged from 4.5 to 7.5 $\times$ $10^3/\mu L$. His total globulin was 3.6 g/dL (normal, 2.0 to 3.5 g/dL). A skin test of purified protein derivative from tuberculous bacilli was nonreactive. Serum lactic dehydrogenase was 399 IU (normal, 100 to 225 IU) and serum glutamic oxaloacetic transaminase 102 IU (normal, 7 to 40 IU). His chest x-ray film (Figure 1) initially showed evidence of bronchopneumonia. A lung scan was also compatible with pneumonia. Arterial blood gases revealed hypoxemia and hypocapnia with desaturation (pO_2 54.1 mmHg, pCO_2 31.4 mmHg, pH 7.48, oxygen saturation 90 percent). His calculated alveolar-arterial oxygen gradient was 56.65 mmHg. His sputum Gram stain revealed normal flora. F. R. did not respond to intravenous penicillin. Six days after admission, his chest x-ray film (Figure 2) revealed a pneumonia characterized by marked interstitial and intra-alveolar infiltrates.

A bronchoscopy and transbronchial biopsy were performed under direct fluoroscopy. Tissue and brushing specimens were sent for cultures and special stains. Grocott's silver methenamine staining revealed cysts of Pneumocystis carinii along with marked interstitial fibrosis, hyperplasia of alveolar walls, and focal multinucleated giant cells. Cultures for fungi and bacteria were negative. Stains for fungi and tuberculosis were negative. He was treated daily with intravenous trimethoprim, 20 mg/kg, and sulfamethoxazole, 100 mg/kg, (Bactrim), which he continued to take until the day of discharge. After discharge, the patient continued to take trimethoprim/sulfamethoxazole orally.

Within 24 hours after the patient started taking timethoprim/sulfamethoxazole, he became less dyspneic. By the fifth day, there was marked improvement in blood gas levels: pH 7.46, pCO_2 28.8 mmHg, and pO_2 84.4 mmHg. On repeat chest x-ray film, a worsening of the infiltrate in the left lung and the reappearance of the infiltrate in the right lung (Figure 3) were noted. Seven days after initiation of trimethoprim/sulfamethoxazole, the patient began to show improvement, as manifested by decreasing infiltrates seen on another chest x-ray film (Figure 4).

Eight days after the initiation of trimethoprim/sulfamethoxazole therapy the patient's condition was complicated by thrombosis of the right middle cerebral artery and cerebral cortical infarction. Two days later, he developed a Mallory-Weiss gastric tear and upper gastrointestinal bleeding.

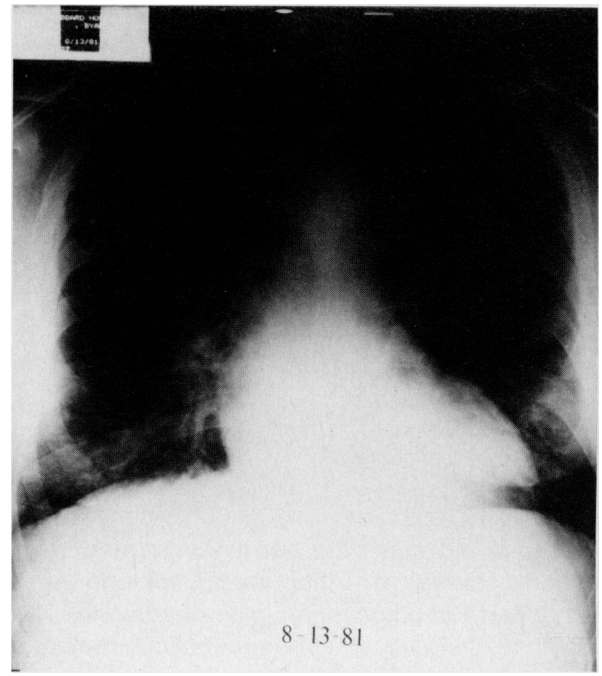

Figure 1. Chest x-ray (8-13-81) showing moderate cardiomegaly and mixed alveolar and interstitial infiltrates at both lung bases

After stabilization, 23 days after admission, F. R. was discharged and transported home to the care of his physician in Maryland.

Subsequent follow-up has revealed that F. R. has recovered significantly from his neurologic problems and has had no recurrent respiratory infections or dysfunction. He underwent a second segmental resection of the colon for locally recurrent cancer in November 1982. There was no gross evidence of the tumor remaining following resection. He did not receive additional 5-fluorouracil following his treatment for Pneumocystis carinii pneumonia.

Laboratory testing at that time revealed a total globulin level of 3.6 g/dL. The total white cell count ranged from 4.5 to 7.5 $\times$ $10^3/\mu L$ and was normal. The total lymphocyte count ranged from 564 to 1,750 cells/mm^3 (normal 1,920 to 4,320).

The delayed sensitivity to tuberculin was nonreactive. Lymphocyte subpopulations were carried out. Helper/suppressor cell populations, as measured by the presence of OKT_4 and OKT_8 antigens, were found

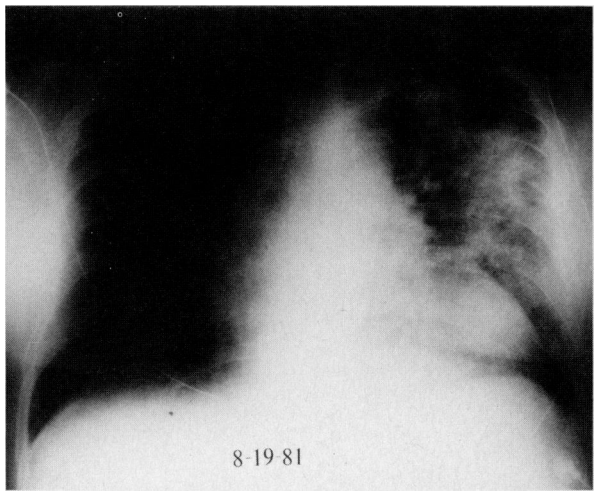

Figure 2. Chest x-ray (8-19-81) showing some clearing of the infiltrate in the right lung base, but infiltrate in left lung has increased

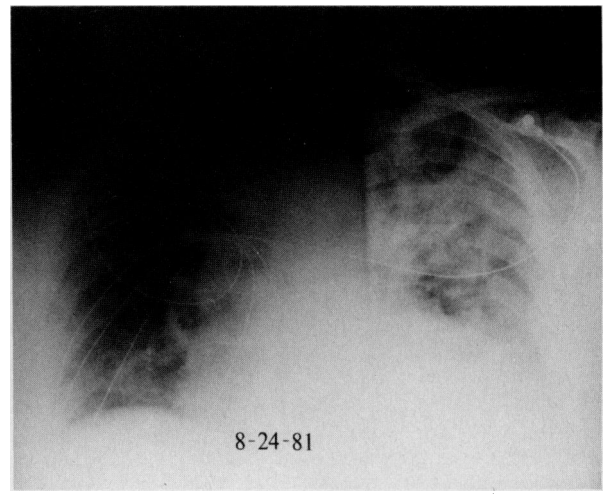

Figure 3. Chest x-ray (8-24-81) showing worsening of infiltrate in the left lung field. Infiltrate at right base has reappeared

to be within normal limits (Table 1). Assay for human T-cell lymphotropic virus type III (HTLV III) was not available at this time.

DISCUSSION

Pneumocystis carinii pneumonia is a widespread organism found in a number of species including mice, rats, rabbits, guinea pigs, dogs, and humans. The presence of clinical infections in humans has long been noted to occur sporadically in patients who are immunocompromised.[2] Burke and Good[4] reviewed 46 cases from the University of Minnesota Hospital and found that all except one had immunodeficiency disease or had been treated with corticosteroids and/or other cytoxic drugs. They also found in reviewing 302 of 350 other cases that these patients had either congenital immunologic deficiency or were receiving immunosuppressive therapy.

Walzer et al[7] reviewed 194 patients. These cases were reported to the Centers for Disease Control over a period of three years. The results showed that this disease occurred almost exclusively in the immunosuppressed host who had serious underlying disease. The vast majority of patients had leukemias (46.9 percent), lymphomas, immunodeficiency disease, or organ transplants. Solid tumors comprised only 3.6 percent of all cases.

Recently, and at the time of this patient's illness, Gottleib and associates[3] and Mursur et al[6] reported

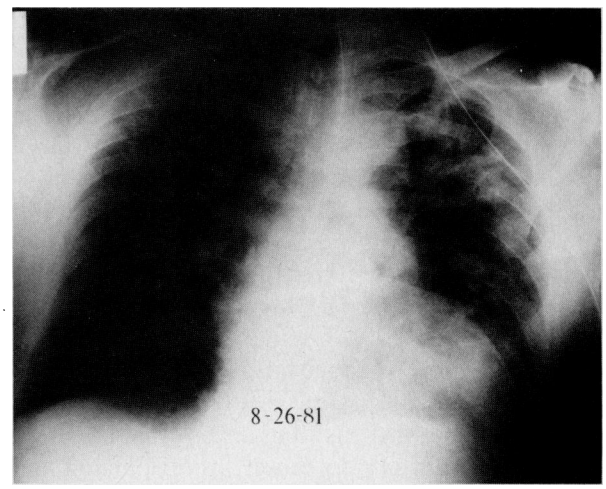

Figure 4. Chest x-ray (8-26-81) showing practically cleared infiltrate in right lung field. Marked clearing of infiltrate in left lung field, especially the mid-left lung

on the epidemic occurrence of Pneumocytis carinii pneumonia in young homosexual men. Many of these individuals had been healthy. Most were homosexual or bisexual, and many have had numerous sexual contacts. Other groups found to be at risk for this syndrome leading to recurrent opportunistic infections include drug abusers, Haitian immigrants, and hemophiliacs.[5]

This patient was not a member of any risk group. Neither did his illness fit the criteria for that syn-

TABLE 1. T-LYMPHOCYTE PROPORTIONS IN PATIENTS RECEIVING 5-FLUOROURACIL

Patient	T_3 (63–85)	T_{11} (75–89%)	T_4 (36–60%)	T_8 (17–43%)	T_4/T_8 (1.2–2.2)
F.R.* (Case report patient)	63	66	29	26	1.10
H.J.*	80	89	59	27	2.19
M.M.*	79	92	53	28	1.89
S.A.*	82	74	47	30	1.57

* H.J., M.M., S.A.—Colon cancer patients receiving weekly or monthly 5-fluorouracil over extended period (6 to 12 months)
T_3 and T_{11}—Pan T-cell marker
T_4—Helper T-cell percentage
T_8—Suppressor T-cell percentage
T_4/T_8—Helper/suppressor T-cell ratio

drome. He had been receiving monthly courses of 5-fluorouracil, a fluoropyrimidine used to treat gastrointestinal malignant neoplasms and other solid tumors. A number of drugs are known to be potent suppressors of the immune system,[1] and some classes of cancer chemotherapy are among these. Whether the immune system is affected and what components affect it depends upon the specific drug, the dosage schedule, and the duration of administration.

Prednisone is widely used because of its immunosuppressive properties and because of its cytotoxic effects on lymphocyte-derived and certain other neoplasms. Prednisone is known to suppress both the primary and secondary immune responses of delayed cellular immunity, thus accounting for its usefulness in the transplantation of organs. Prednisone has been particularly incriminated in this disease, and has been shown experimentally to cause clinical pneumonia in animals either treated alone or animals treated with prednisone with the administration of infected human pulmonary tissue.[8,9] Certain alkylating chemotherapeutic agents such as cyclophosphamide are especially immunosuppressive.[1] While antimetabolites vary in their effect upon the immune system, 5-fluorouracil has been characterized by less immunosuppression.[2] The primary toxic manifestation of this drug is leukopenia, which predisposes patients to infection, most commonly bacterial.

Some antimetabolites are used as immunosuppressive agents and most cancer agents have been considered to have this property.[10] However, 5-fluorouracil is much less immunosuppressive. Blomgren et al[2] found that patients treated with 5-fluorouracil either continued to express delayed cutaneous hypersensitivity or to convert from negative to positive. No cases of conversion from a positive reaction to a negative one occurred, as was the case of those treated with cyclophosphamide.[2] Possible causes of the occurrence of pneumocystic pneumonia in this patient are unclear. However, factors such as dosage, duration of treatment, and scheduling may be important in the impairment of the immune system.[10] An increased dosage in the presence of cancer may well have existed in this patient. The unique circumstances may have given rise to significant lymphopenia and monocytopenia, thus allowing Pneumocystis carinii colonizing this patient's lungs to proliferate.[10] Other possible explanations for the infection include immune suppression by virus, malnutrition, or a combination of such factors. The presence of cytomegalovirus is known to cause immunosuppression. There was, however, no histologic evidence of inclusion bodies of cells from the lung biopsy. Malnutrition, overwhelming cancer, radiation therapy, and the use of other immunosuppressive drugs likewise are unlikely and can be eliminated by the history and physical findings.

It is clear that there was no prolonged impairment of cellular immunity in this patient in the manner of the acquired immunodeficiency syndrome, as the pneumonia, which easily cleared with appropriate treatment, did not recur. Gross measures such as the total lymphocyte count, which was variable but ranged upward to normal levels, and normal T-cell populations after recuperation suggest at least a restoration of cellular immunity (Table 1).

CONCLUSIONS

This case represents the observation of an infection in an unusual setting, with an increasingly common opportunistic organism in a patient receiving an antineoplastic agent not usually thought to significantly depress cellular immunity. Awareness of this association should alert one to the possibility of immunosuppression and the occurrence of such opportunistic infections in the many patients with gastrointestinal neoplasms who are undergoing treatment with this drug.

Literature Cited

1. Aisenberg AC. Drugs employed for the suppression of immunological responsiveness. N Engl J Med 1965; 272:1114–1117.

2. Blomgren SE, Wolberg WH, Kisken WA. Effect of fluoropyrimidines on delayed cutaneous hypersensitivity. Cancer Res 1965; 25:977–979.

3. Gottleib MS, Schroff R, Schenker HM, et al. Pneumocystis carinii pneumonia and mucosal candidiasis in previously healthy homosexual men. N Engl J Med 1981; 305:1425–1431.

4. Burke BA, Good RA. Pneumocystis carinii infection. Medicine 1973; 52:23–51.

5. Fauci AS, Macher AM, Longo DL, et al. NIH Conference. Acquired immunodeficiency syndrome: Epidemiologic, clinical, immunologic and therapeutic considerations. Ann Intern Med 1984; 100:92–106.

6. Musur H, Michelis MA, Greene JB, et al. An outbreak of community-acquired Pneumocystis carinii pneumonia: Initial manifestation of cellular immune dysfunction. N Engl J Med 1981; 305:1431–1438.

7. Walzer PO, Perl DP, Krogstad DJ, et al. Pneumocystis carinii pneumonia in the United States: Epidemiologic, diagnostic, and clinical features. Ann Intern Med 1974; 80:83–93.

8. Barton EG, Campbell, WG. Pneumocystis carinii in lungs of rats treated with cortisone acetate. Am J Pathol 1969; 54: 209–236.

9. Sheldon WH. Experimental pulmonary pneumocystic carinii infection in rabbits. J Exp Med 1959; 110:147–160.

10. Hersh EM. Modification of host defense mechanisms. In: Hollard JF, Frei E, eds. Cancer Medicine. Philadelphia: Lea & Febiger, 1973, pp 681–698.