Pulmonary Nocardiosis Complicating Malignant Lymphoma Successfully Treated with Chemotherapy

Jack Pinkhas, M.D.;* Ishak Oliver, M.D.;* Andre de Vries, M.D.;* Shimon A. Spitzer, M.D., F.C.C.P.;** and Eliezer Henig, Ph.D.†

A case of pulmonary nocardiosis is reported in a patient with malignant lymphoma and hypogammaglobulinemia. The nocardiosis initially appeared as a dense infiltration in the right upper lobe, subsequently as bilateral lung infiltrations. Nocardia asteroides was found in infralaryngeal secretion obtained by transtracheal aspiration. Treatment with sulfadiazine, trimethoprim, and sulfamethoxazole (Septra) led to clinical recovery and disappearance of the x-ray findings. Following discontinuation of treatment there was a relapse of the lung nocardiosis roentgenologically in the initial location. The need for prolonged treatment is stressed.

Nocardiosis is a relatively rare infection mostly caused by Nocardia asteroides, a fungus-like soil pathogen.1,5 In two thirds of the cases the lungs are involved.4 The pathogen has a predilection for patients with depressed defense mechanisms as in dysproteinemia,5,8 malignancy and other debilitating diseases,1,3 and who are being treated by radiation, corticosteroids or chemotherapy.3 Out of 13 patients with neoplasms and nocardiosis described by Young et al3 ten had hematopoietic malignancies and all had been treated by radiation or chemotherapy. In the present report we describe a patient with malignant lymphoma who developed two episodes of pulmonary nocardiosis. In both episodes the diagnosis was made without operation and in both treatment with chemotherapy was successful.

Case Report

A 49-year-old male clerk was first seen in July, 1967, one month after he had become aware of multiple lumps in the neck and groin. On admission his temperature was 37.5°C (99.5°F) and generalized lymphadenopathy was found. The liver and spleen were not palpable and a chest x-ray film was normal. Abnormal laboratory findings were a relative lymphocytosis and a low serum gamma globulin, 240 mg/100 ml, and a bone marrow aspiration biopsy revealed a diffuse lymphocytic infiltration. Surgical biopsy of an axillary lymphnode showed lymphosarcoma. During the next two and a half years, under periodic treatment with vincristine, cyclophosphamide and chlorambucil, and with prednisone continuously, he was afebrile and felt well, but lymphadenopathy remained detectable. In January, 1970, he developed fever and a nonproductive cough, his lymphadenopathy became more marked, and hepatosplenomegaly and left pleural effusion were found. A pleural tap revealed atypical lymphoid cells. Smears, cultures and guinea pig inoculation were negative for bacteria and fungi. In spite of repeated intrapleural instillations of nitrogen mustard and atabrine the pleural effusion persisted until October, 1970. Subsequently, cyclic polychemotherapy was given with nitrogen mustard, vincristine, procarbazine (Natulan) and prednisone and resulted in marked subjective and objective improvement, with a decrease in lymphadenopathy, disappearance of hepatosplenomegaly and of pleural effusion.

The patient was readmitted in April, 1971, with a temperature of 38°C (100.4°F) and a productive cough. Lymphadenopathy was not marked and the liver and spleen were not palpable. Crepitant rales were heard over the right upper lung field. Abnormal laboratory findings were marked shift to the left of the white cell count with 59 percent bandforms on a total of 7,600/cu mm and hypogammaglobulinemia with IgG 380 mg/100 ml, IgA 38 mg/100 ml, and IgM 25 mg/100 ml. Numerous sputum smears did not reveal malignant cells, fungi or tubercle bacilli. Sputum cultures revealed Escherichia coli and Klebsiella. Results of guinea pig inoculation with sputum were negative. Repeated blood culture findings were sterile. A chest x-ray film (Fig 1) revealed a dense triangular infiltration in the upper lobe of the right lung.

From the Department of Medicine D,* the Cardiopulmonary Laboratory ** and the Microbiological Laboratory,† Tel-Aviv University Medical School, Beilinson Hospital, Petah Tikva, Israel.

Reprint requests: Prof. deVries, Beilinson Hospital, Petah Tikva, Israel

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FIGURE 1. Admission chest x-ray film, April, 1971, showing triangular infiltration in right upper lobe.

Figure 2. Treatment and temperature course.

Figure 3. Chest x-ray film, June, 1971, showing bilateral infiltrations.

Treatment (Fig 2), including various antibiotics and chemotherapeutic agents, prednisone, amphotericin B and gamma globulin, was of no avail. His fever became septic and supervening pancytopenia required repeated blood, leukocyte and platelet transfusions. In June, 1971, a chest x-ray film showed massive infiltrations in both lungs (Fig 3) and the patient's condition appeared critical.

Transtracheal aspiration, performed according to the method of Pecora, produced a whitish material. Microscopic examination of smears prepared from the aspirate revealed a gram-positive organism appearing as small bacilliform fragments as well as longer strand formations with branching. The fragments stained by a modified Ziehl Neelsen's method were moderately acid-fast. In culture, grown aerobically on blood agar and Sabouraud's dextrose agar and incubated at 37°C (98.6°F) for a few days, colonies grew raised, irregular, folded and finely furrowed (Fig 4). They were white to cream-colored. In the beginning their surfaces were somewhat moist, later becoming chalky. Microscopically, the colonies were composed of delicate, branching, intertwining filaments, which were Gram-positive. They broke up readily into small bacillary forms. The organism was partially acid-fast only if decolorization with acid alcohol was carried out carefully. On the basis of these characteristics, the organism was identified as *Nocardia asteroides*. The organism revealed a moderate sensitivity to gentamicin and a marked sensitivity to sulfadiazine, trimethoprim, combined with sulfamethoxazole (Septrin) and sulfisoxazole (Gantrisin).

Treatment with intravenously administered sulfadiazine and oral therapy with trimethoprim and sulfamethoxazole was started (Fig 2). After 48 hours the leukocyte count dropped to 1,3000/cu mm with 13 percent polymorphonuclear cells, and the platelet count dropped to 33,000/cu mm. The treatment with sulfa drugs was continued, with administration of whole blood, leukocyte and platelet transfusions. Dramatic improvement in the patient's condition was observed and his temperature became normal after six days. The patient was discharged on orally administered sulfadiazine 4 gm, trimethoprim 320 mg, and sulfamethoxazole 1.6 gm and prednisone 15 mg per day; the trimethoprim, sulfamethoxazole and sulfadiazine were discontinued after four months. The patient remained afebrile, his cough disappeared and repeated chest x-ray films showed gradual regression.
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Figure 4. Nocardia asteroides colonies on Sabouraud dextrose agar.

of the lung infiltrates. In September, 1971, a chest x-ray film (Fig 5) revealed no evidence of disease.

In March, 1972, eight months after discharge, he was readmitted because of sudden appearance of chills, rise in body temperature up to 40°C (104°F) and a productive cough. A chest x-ray film (Fig 6) revealed an infiltrative process in the upper lobe of the right lung, strikingly similar to the one found in April, 1971. Nocardia asteroides was found on sputum examination. Treatment with intravenously administered sulfadiazine 6 gm/day was followed by rapid improvement. The patient became afebrile after one week, the x-ray findings in his lung gradually subsided and he was discharged three weeks later in a good condition with a normal chest x-ray appearance while on trimethoprim and sulfamethoxazole 240 mg and 1.2 gm per day and prednisone 15 mg/day. Now, three months later, continuing this treatment, he feels well, works regularly and the only abnormal physical findings are slightly enlarged lymph nodes in the axillary and inguinal regions. His hematologic values are normal.

DISCUSSION

Pulmonary nocardiosis may mimic tuberculosis, actinomycosis, pneumonia, pulmonary abscess or tumor metastases.  The diagnosis is the more
difficult when pulmonary nocardiosis is simultaneously present with one of these conditions. When the roentgenologic findings are erroneously attributed to tumor metastases and the nocardial infection is not recognized and treated promptly, the latter may be the cause of death.

The laboratory diagnosis of nocardiosis is notoriously difficult and repeated sputum examinations may be necessary to prove a nocardial infection of the respiratory tract. Nocardia may be found in a sputum sample both on microscopic examination and in culture, but a positive finding is sometimes obtained by only one of them. In culture more rapidly growing bacteria may obscure small numbers of nocardial colonies. Plates should not be discarded too hastily in order to provide sufficient time for the growth of Nocardia. In the presently reported critically ill patient numerous microscopic examinations and cultures of the sputum failed to reveal N. asteroides during his first episode of pulmonary nocardiosis. The organism was detected only in the material obtained by the transtracheal aspiration method described by Pecora, providing infralaryngeal respiratory tract secretion. On the other hand, during his second episode of pulmonary nocardiosis the pathogen was found in the expectorated sputum.

Treatment of nocardiosis consists of sulfadiazine at a dosage of 4-6 gm/day. Lately, impressive results were achieved by the administration of sulfamethoxazole and trimethoprim (Septrin). The presently reported patient was treated with...
both sulfadiazine and trimethoprim and sulfamethoxazole, which brought a dramatic improvement in his condition. The marked granulocytopenia occurring early during this treatment raised the problem of whether it was due to the drug therapy or to the overwhelming infection. The latter possibility is favored by the normalization of the granulocyte count with the improvement in the patient's condition during continued drug administration. The treatment with human gamma globulin may have been contributory to recovery in this patient who had a marked immunoglobulin deficiency.

Following clinical and roentgenologic recovery and repeated negative sputum cultures the patient was maintained on sulfadiazine and trimethoprim and sulfamethoxazole therapy for four months in order to prevent a relapse of the nocardial infection. Brine, Young et al and Adams et al similarly gave preventive treatment for two to five months following recovery. In our patient, however, the pulmonary nocardiosis apparently had not been eradicated by this schedule, since two months after discontinuation of the treatment the process recurred. Since the pulmonary infiltrate detected in the second episode of nocardiosis was strikingly similar to the one found in the early stage of the first episode, it seems likely that the second episode was a relapse arising from a dormant focus in the original site. If this assumption is correct, treatment following clinical and roentgenologic recovery should be extended over a much longer period.

It is of interest that in this patient the nocardial lung infection occurred during a period of clinical quiescence of the lymphomatous process, bearing in this respect a close similarity to one of the patients reported by Young et al. In our patient the marked immunoglobulin deficiency and the continuous treatment with corticosteroids may have been contributory to the development of the nocardial infection.

REFERENCES