

Pulmonary Nocardiosis in a Renal Transplant Patient

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Nocardia is a significant opportunistic pathogen in patients with compromised immunity. The authors isolated *N. asteroides* from an abscess of the axilla and from respiratory specimens of a renal allograft patient with pneumonia. Direct smear of the sputum and bronchial washing specimens showed many branching, filamentous forms which were gram-positive and acid fast. Culture yielded slow growing small white colonies which became orange on further incubation. Aerial hyphae were produced. Identification of the species was based on typical cultural and biochemical tests. The isolate was susceptible to amikacin, minocycline and rifampicin. The patient became afebrile after 8 weeks of treatment with cotrimoxazole and brief treatment with other antimicrobial agents.

Key Words: Pulmonary nocardiosis, *N. asteroides*, renal transplantation.

Nocardia is a significant opportunistic pathogen in patients whose immunity is compromised by neoplasm, immunosuppression, corticosteroid therapy and pulmonary alveolar proteinosis (Saltzman *et al.* 1962; Goodman and Koenig 1970; Idriss *et al.* 1975; Krick *et al.* 1975; Von Graevenitz 1977; Avram *et al.* 1978). In Korea a few cases of *Nocardia* abscess have been reported (Suk *et al.* 1974; Ahn *et al.* 1979; Lee *et al.* 1986). Several strains of *Nocardia* were also isolated from sputum specimens of tuberculosis patients, but the significance was never ascertained (Koh *et al.* 1974). Isolation of *Nocardia* from pulmonary infections among transplant patients has not been reported in Korea. The authors isolated *N. asteroides* from a renal allograft patient, first from an abscess of the axilla, then from respiratory specimens. The bacteriological characteristics of the isolate and the clinical features of the patient are presented.

CASE REPORT

A 29-year-old man (unit no. 1181375) was admitted to Severance Hospital on July 12, 1982. His past history included hypertension and renal failure. He had

successfully received a kidney allograft in July 1981. Since the surgery, he had been treated with daily doses of immuran 75 mg and prednisone 20 mg. In January 1982, he was hospitalized with a fever and cough of 10 days duration. He was diagnosed as having pulmonary tuberculosis, and a pleural fluid culture yielded *Mycobacterium tuberculosis*. Antituberculosis medication, consisting of isonicotinic acid hydrazide, p-aminosalicylic acid and ethambutol was initiated. On May 8, he was readmitted with a chief complaint of fever for 2 days. Chest X-ray showed a soft, hazy lesion in the right lung field. Sputum examination was negative for acid fast-bacilli, but antituberculosis treatment was continued. He visited Outpatient Department on June 28, because of an abscess on the axilla. As the pus specimen, obtained by an incision and drainage, yielded a heavy growth of *N. asteroides*, he was again admitted (Fig. 1).

Laboratory findings at the time of the present admission included a WBC count of 4,200/ μ l with 86% segmented neutrophils, 4% bands, and 10% lymphocytes. Blood chemistries were normal including creatinine 0.9 mg/dl and blood urea nitrogen 14 mg/dl. Urinalysis was also normal. sputum examination showed a large number of WBCs and branched, filamentous, gram-positive bacilli. A heavy growth of *N. asteroides* was obtained. Bronchoscopy revealed an injected right bronchus, but the severity of the injection was more pronounced in the upper left bronchi where mucosal destruction was also noted. A specimen of bronchial washing also showed filamen-

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Fig. 1. Course of nocardiosis. +: light growth, +++: heavy growth, -: no growth, INH: isonicotinic acid hydrazide, PAS: p-aminosalicylic acid, KM: kanamycin, AMP: ampicillin, AMK: amikacin, MIN: minocycline. Dosage of cotrimoxazole was 0.5 g bid, amikacin 250 mg bid and minocycline 100 mg bid.

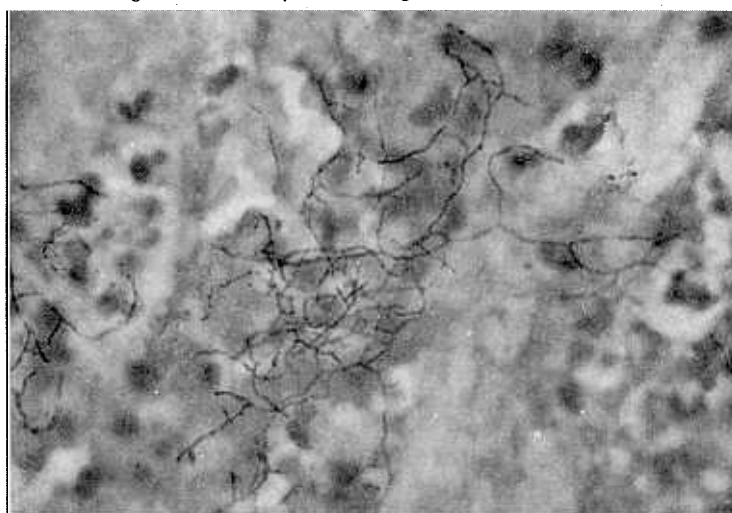


Fig. 2. A gram stained smear of a bronchial washing specimen, showing gram-positive, branched, long, filamentous forms together with polymorphonuclear

tous forms (Fig. 2) and yielded a heavy growth of *N. asteroides*.

Cotrimoxazole therapy, 0.5g, P.O. qid, was begun on July 12, 1982 together with ampicillin and kanamycin. The latter two were later dropped. However, fever persisted and a sputum specimen taken on August 18 yielded a light growth of *N. asteroides*. A chest X-ray at this time showed an aggravated parenchymal consolidation. From August 21 to 29, the WBC count dropped to 600 to 1,900/ μ l and sepsis was suspected, however, blood cultures did not yield any growth. Amikacin, 250 mg I.M. bid, was added on August 25 and minocycline, 100 mg I.V. bid, on September 2. On September 10 he became afebrile. His oral intake and general condition began to improve. The chest X-ray taken on September 20 showed that the consolidation had been resolved. He was discharged on September 25. Immunosuppression therapy was continued, but nocardiosis did not recur up to 1986.

Bacteriological cultures were performed according to our routine procedure, i.e., pus, sputum and bronchial washing specimens were inoculated onto blood agar and MacConkey agar plates. A pus specimen was also inoculated into a thioglycollate broth tube. Agar plates were incubated in a CO₂ incubator. The identification of *Nocardia* isolate was done according to the method of Gordon *et al.* (1974). Casein medium was prepared by combining previously autoclaved skim milk with previously autoclaved agar to obtain a final concentration of 5% and 1% respectively. Tyrosine or xanthine were incorporated into nutrient agar to produce a 1% concentration. Utilization of benzoate, citrate, lactate and succinate was tested using Koser's citrate agar base, and esculin hydrolysis using esculin broth. Acid production from carbohydrates was tested using Gordon's basal medium. Growth temperature was determined by inoculating yeast extract agar slants and incubating them either in a 45°C water bath or in a refrigerator at 10°C. With the exception of temperature determination for growth, all tests were carried out at room temperature, and depending on the test incubation continued for up to 2 weeks. Antimicrobial susceptibility was tested with the standardized disk diffusion test (NCCLS, 1979), but the result was read after a 48-hour incubation.

Direct smear of the sputum specimen showed many branching, filamentous forms, which were gram-positive (Fig. 2) and weakly acid fast. Dense colonies 0.5 mm in diameter developed on blood agar plates after a 48 hour incubation. The initial color was white, but became orange on further incubation. Aerial

Table 1. Characteristics of *N. asteroides* isolate

Test	<i>N. asteroides</i> *	Isolate
Acid fastness	+	+
Aerial mycelium	+	+
Colony color		Orange
Decomposition of		
casein	-	-
tyrosine	-	-
urea	+	+
xanthine	-	-
Utilization of		
benzoate	-	-
citrate	v	-
lactate	v	+
oxalate		-
succinate	+	+
Hydrolysis of		
esculine	+	+
starch	v	-
Acid from		
adonitol	-	-
arabinose	-	-
dulcitol	-	-
erythritol	-	-
galactose	v	-
glucose	+	+
inositol	-	-
lactose	-	-
maltose	-	-
mannitol	-	-
mannose	v	-
melibiose	-	-
raffinose	-	-
rhamnose	v	-
sorbitol	-	-
xylose	-	-
glycerol	+	+
Nitrate reduction	+	+

* From Gordon *et al.* 1974, and Wilson, 1984.

+: positive, -: negative, v: variable.

hyphae were observed after several days incubation. It grew at 10°C and 45°C. Other characteristics are shown in table 2. The isolate was susceptible to amikacin, minocycline and rifampicin, but resistant to ampicillin, penicillin G, chloramphenicol, clindamycin, erythromycin, tetracycline, cotrimoxazole, cephalothin, cefazolin, cefamandole, cefoxitin, dibekacin, gentamicin, kanamycin and tobramycin.

DISCUSSION

Organisms of *Nocardia* are aerobic, filamentous, branching, gram-positive and partially acid-fast bacilli normally found in the soil. Currently 16 species are recognized (Goodfellow and Lechevalier 1986). Among the species, *N. asteroides*, *N. brasiliensis* and *N. caviae* can cause infections in humans (Gordon 1985). Infection was rare prior to 1957 (Avram et al. 1978) and a clinical and laboratory curiosity (Murray et al. 1961), but with the increase in the number of compromised patients, it has now become a well known infection. The estimated annual incidence of 1,000 in America (Beaman et al. 1976) was considered to be an underestimation (Curry 1980). In Japan, about 50 pulmonary nocardiosis (Noto et al. 1985) and 45 cutaneous forms (Nishimoto and Ohno 1985) were reported. In Korea, one case of *N. brasiliensis* abscess (Suk et al. 1974) and 3 cases of *N. asteroides* abscess (Ahn et al. 1979; Lee et al. 1986) were reported. The authors isolated another strain of *N. asteroides* from a pus specimen which was received from a local clinic in Seoul. The dearth of reports from Korea might be due to either the lack of proper laboratory support or of a keen awareness of the infection.

Although *Nocardia* can cause a variety of infections, including those of the central nervous system, eye, and even osteomyelitis and bacteremia (Idriss et al. 1975; Sher et al. 1977; Avram et al. 1978; Masters and Lentino 1984), the most common are cutaneous and pulmonary infections (Curry 1980). In Korea, *Nocardia* was isolated from the sputum specimens of several tuberculosis patients, but its significance was not known (Koh et al. 1974). *N. asteroides* may cause severe pulmonary infections which are suppurative and cavitary in nature. This pulmonary infection is often mistaken for tuberculosis or mycosis (Murray et al. 1961). In the present case, the patient had been receiving antituberculosis therapy for several months, and if the culture from the abscessed axilla had been negative for *N. asteroides*, the diagnosis of pulmonary nocardiosis might have been delayed.

Pulmonary infection is caused by the inhalation of *Nocardia* (Beaman et al. 1976), although one case in a drug abuser who injected himself with contaminated drug was reported to be the cause of pulmonary infection (Vanderstigel et al. 1986). In Our case, although the organism was first isolated from the pus of the axilla, the patient might have been infected by inhalation. The chest X-ray taken in May already suggested

a fungal infection. The ability of pulmonary infections to disseminate is well known; they can produce secondary cutaneous, ocular or central nervous system infections among others.

Early diagnosis and prompt treatment are necessary to improve survival rates (Krick et al. 1975), but diagnosis is often made only after surgical biopsy or at postmortem (Anderson et al. 1979). Isolation of *Nocardia* may be almost impossible unless the infection is suspected. As it grows slowly, several days of incubation are required before colonies appear. Unless *Nocardia* infection is specifically suspected, the culture medium is often discarded before the colonies develop (Murray et al. 1981; Taylor and Turner 1985). In this case, the pus culture developed colonies after 48 hour of incubation.

While examination of the sputum remains the primary method of diagnosis of pulmonary nocardiosis, specimens of bronchial washings are considered useful in some cases (George et al. 1978). The bronchial washing specimen of this patient yielded a heavy growth of *N. asteroides* without normal throat flora.

Identification of *Nocardia* may be difficult. It is known that colonies of *Nocardia* are similar to rapidly growing *Mycobacterium* (Staneck 1981). Formation of aerial mycelium is a characteristic of *Nocardia*, but not of *Mycobacterium*. Although presumptive identification can be made on the basis of acid fastness, *Actinomyces* in tissue section may also appear as acid fast, necessitating the culture of the organism (Robby and Vickery 1970). The identification may be delayed due to both the need for specially prepared media and a lengthy incubation.

The antimicrobial susceptibility of *Nocardia* is known to be difficult to determine by means of the disk diffusion test, therefore the dilution test is recommended (Bach et al. 1973). The authors used the disk diffusion method, because of its simplicity. Only amikacin, minocycline and rifampicin disks produced inhibition zones. However, our patient was treated with cotrimoxazole as this drug has been well documented for its efficacy. He became afebrile only after receiving cotrimoxazole for 8 weeks, amikacin for 13 days, and minocycline for 3 days. Other antimicrobial agents, reported to be effective, are sulfonamides, ampicillin, erythromycin, amikacin and minocycline (Bace et al. 1973; Curry 1980; Meier et al. 1986). Recently, N-F-thienamycin was reported to have high anti-nocardial activity (Gombert 1982). The susceptibility of the isolates differed, and this indicates the necessity of accurate susceptibility testing prior

to the selection of antimicrobial agents.

Nocardia infection requires a prolonged treatment. When the treatment time was less than 3 months, the relapse rate was very high (Geisler and Anderson 1979). A recurring pneumonia after two and a half years of therapy has been reported (Josson *et al.* 1986). *Nocardia* was still found in the sputum of our patient 5 weeks after the commencement of therapy, however, nocardiosis did not recur as of 1986.

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