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Nocardiosis: a neglected chronic lung disease in Africa?

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ABSTRACT *Nocardia* organisms were cultured from the sputum of 11 patients at the central hospitals in Harare, Zimbabwe, over a 12 month period. Pulmonary nocardiosis was diagnosed in one further patient on the basis of direct microscopy. Among the nine patients available for follow up, pulmonary nocardiosis was considered to be the major clinical problem in six. The patients usually presented with a chronic pulmonary infection with fever and cough without evidence of dissemination of underlying systemic disease. The chest radiograph showed consolidation in any part of the lung, and this was seen to extend slowly over several months. Prolonged diagnostic delay was a frequent problem. Haemoptysis, alcohol abuse, and empirical treatment for tuberculosis commonly featured in the history. Treatment with sulphonamides was generally successful in those patients who complied. Nocardiosis is a treatable lung disease that may be more common in developing countries than is currently recognised.

Introduction

Nocardia is a filamentous, branching, partially acid fast aerobic bacterium belonging to the order Actinomycetales, which also includes the mycobacteria. Three species are recognised as being responsible for most human nocardial infections. *N asteroides* is the usual cause of pulmonary and disseminated infection.[1] The typical pattern with *N caviae* and *N brasiliensis* is of cutaneous and soft tissue infection with multiple discharging sinuses,[2] as seen with mycetoma of the foot.

Pulmonary nocardiosis is an uncommon but well recognised infection both in the immunosuppressed and in the apparently immunocompetent patient. Although readily treated if detected early, delay in diagnosis is common.[2] In developing countries, where other chronic lung diseases, particularly tuberculosis, are very prevalent, *Nocardia* is often missed or misidentified in laboratory specimens. A high level of suspicion on the part of the clinician and of experience on the part of laboratory personnel are essential for early detection.

We present our experience in the clinical and laboratory diagnosis of pulmonary nocardiosis in a tropical country.

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Methods

We reviewed all specimens received by the mycology laboratory from patients with pulmonary disease during 12 months. The specimens were mainly sputum but aspirates, washings, and biopsy specimens obtained at bronchoscopy were also received. All specimens were from patients admitted to the Harare central hospitals with a clinical diagnosis of pulmonary infection. The usual reason for requesting mycological examination was the failure of such an infection to respond to antibacterial or antituberculous treatment.

Smears from all specimens were Gram stained and some were also stained by a modified Kinyoun method.[3] All specimens were inoculated into Lowenstein-Jenson media (L-J) and Sabouraud dextrose agar containing 0·5 g/l cycloheximide (SAB + C) incubated aerobically at 37°C. They were also inoculated into blood agar incubated anaerobically at 37°C so that we could determine whether any *Actinomyces* species were present. Cultures were first examined after 10 days but continued for at least four weeks. *Nocardia* spp were identified from isolates on SAB + C and L-J on the basis of colony appearance, Gram staining, and acid fastness. For species identification isolates were tested for their ability to hydrolyse starch[4] and to grow in the presence of casein, tyrosine, and xanthine.[5]

Efforts were made to trace all patients from whom *Nocardia* species were isolated. Fibreoptic broncho-

Table 1 *Clinical features of the 12 patients at presentation*

Patient No	Age	Sex	Occupation	Residence	Cough	Chest pain	Dyspnoea	Haemoptysis	Weight loss	Empirical treatment for other chest infections
1	45	M	Vagrant	Urban	4 mo	–	2 w	–	–	Tuberculosis, lung abscess
2	19	F	Housewife	Rural	3 mo	3 mo	–	+	–	
3	67	M	Farmer	Rural	2 mo	6 y	2 w	+	–	
4	55	M	Teacher	Rural	6 mo	–	–	+	–	
5	45	M	Painter	Rural	5 mo	5 mo	3 mo	+	+	Tuberculosis, lung abscess
6	60	M	Farmer	Rural	2 mo	2 mo	–	+	+	
7	42	M	Teacher	Urban	3 mo	–	–	+	+	Tuberculosis
8	64	M	Retired miner	Rural	Many years	–	Many years	–	–	Tuberculosis
9*	25	F	Unemployed	Rural	2 mo	2 mo	1 w	–	–	
10	49	M	Postman	Urban	12 mo	1 w	–	–	–	
11	33	F	Teacher	Rural	2 mo	–	–	–	+	
12	56	M	Labourer	Urban	12 mo	–	–	–	+	

**N brasiliensis* was isolated from this patient.

scopy with aspiration or lavage of affected segments was performed where not contraindicated. Sputum was examined repeatedly for *Nocardia* as well as mycobacteria and pyogenic bacteria and patients' progress was followed for as long as they would continue to attend the central hospitals when they complied with treatment. Patients with nocardiosis were treated with high doses of sulphonamides[6] for at least six weeks afters the sputum had become free of *Nocardia*.

Results

One hundred and fifty six specimens were examined during the study. *Nocardia* was cultured from the sputum of 11 patients. All of these isolates were presumptively identified as *N asteroides*. They appeared as small, smooth, mid brown colonies on SAB + C and as long, irregularly stained Gram positive filaments with occasional branching on Gram stain; some were partially acid fast. In subculture they did not hydrolyse starch or grow in the presence of casein, tyrosine, or xanthine. In one further patient (No 9) *Nocardia* was cultured from an extrapulmonary site and, although detected in the sputum by microscopy, it failed to grow in culture. This isolate yielded dry, cerebriform, yellow-orange colonies on SAB + C. It was identified as *N brasiliensis* as it grew in the presence of casein and tyrosine but not xanthine and did not hydrolyse starch.

CLINICAL FEATURES

The presenting features in the 12 patients (nine of whom were male) are shown in table 1. Their ages ranged from 19 to 67 years with a mean of 47. Eight of the patients came from rural districts but there was no geographical clustering. Cigarette smoking was not a feature, seven being non-smokers and the remainder claiming to smoke less than 10 cigarettes a day. Five of the patients were heavy drinkers (getting drunk every day or weekend). All the patients had a history of chronic cough, six had haemoptysis, and most complained of chest pain or dyspnoea. Haemoptysis was sometimes profuse, requiring repeated transfusions in

Table 2 *Outcome in the 12 patients*

Patient No	Delay from presentation to diagnosis	Final diagnoses other than nocardiosis	Outcome
1	10 mo		Improved with sulphonamides but defaulted; suspected late central nervous system recurrence
2	6 w	Tuberculosis	Nocardiosis resolved with antituberculous therapy
3	5 w		Lost to follow up
4	8 mo		Improved with sulphonamides but subsequently defaulted
5	1 mo		Nocardiosis resolved with sulphonamides
6	10 w		Lost to follow up
7	10 mo		Improved with sulphonamides for 6 mo, then died after massive haemoptysis
8	5 w	Chronic bronchitis cor pulmonale respiratory failure	Died 2 d after starting sulphonamides
9	4 y		Improved with sulphonamides
10	3 w		Lost to follow up
11	2 w	Treated Cushing's disease	Improved with sulphonamides but changed to ampicillin because of rash; 6 mo of total treatment
12	2 w	Bronchiectasis chronic respiratory failure	Died in respiratory failure after 4 w of sulphonamides

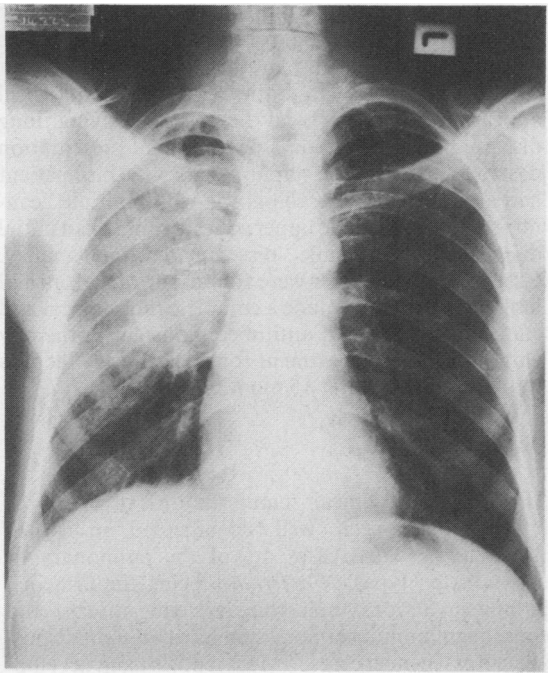

Fig 1 *Chest radiograph on patient 5 at presentation; in the tropics these appearances would normally be considered a sufficient basis for the empirical treatment of tuberculosis.*

one case and being the immediate cause of death in another.

Delay in diagnosis was a common problem, with a median time from presentation to isolation of *Nocardia* of six weeks (range two weeks to four years). Before the isolation of *Nocardia* four patients had been treated for "sputum negative" tuberculosis and two for suspected lung abscess, in all cases without improvement. Two patients had evidence of extrapulmonary disease. One (patient 1) developed hemiplegia with focal epilepsy after defaulting from sulphonamide treatment for a prolonged period, and this resolved when we restarted treatment with sulphadiazine 8 g daily. Nocardial brain abscess was considered the likely diagnosis. Another patient (No 9) presented with a four year history of discharging sinuses near the right knee and a two month history of productive cough and chest pain. Small, pale yellow granules were seen both in pus from the leg and in sputum. *N brasiliensis* was isolated from the pus but not the sputum. The patient had been having sulphonamide treatment for two weeks before a sputum specimen was examined. Only one patient, a 33 year old woman (case 11), had evidence of an underlying systemic disorder. She presented with diffuse consolidation of the left lung while receiving glucocorticoid replacement therapy after treatment for Cushing's disease and proved pulmonary tuberculosis the year before. *Nocardia* was isolated from the sputum on this occasion.

HAEMATOLOGY

Mild anaemia was common, eight patients having less than 12 (range 9·4–15·3) g/l haemoglobulin at presentation. Both normochromic normocytic and hypochromic microcytic anaemia occurred. The leucocyte count was normal in five cases, moderately raised (10–12 × 10^9/l) in four and above 15 × 10^9/l in three. There was neutrophilia in all cases where the total count was raised. Seven patients had a platelet count greater than 500 × 10^9/l and two had counts over 1000 × 10^9/l. The erythrocyte sedimentation rate (ESR) was measured in eight patients and was above 30 mm in the first hour in six and over 100 mm in two (Westergren).

RADIOLOGY

All the patients had radiological evidence of pulmonary consolidation, which was bilateral in four cases. Typically there was a diffuse, occasionally cavitating area of consolidation that tended to extend slowly over several months. All areas of the lung were affected, with upper zone shadowing in seven cases (figs 1–3).

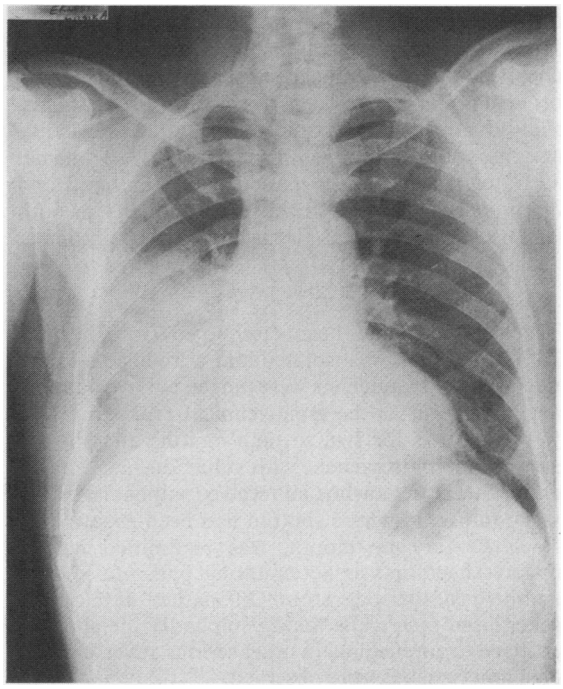

Fig 2 *Chest radiograph of patient 4 at presentation showing mid and lower zone consolidation.*

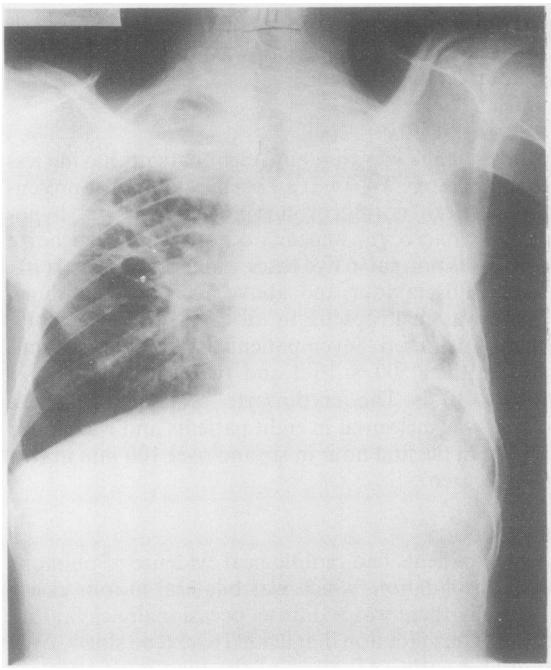

Fig 3 *Chest radiograph of patient 1 at presentation showing extensive bilateral consolidation with cavitation.*

BRONCHOSCOPY

In the seven patients who underwent fibreoptic bronchoscopy the gross appearances were normal. Transbronchial lung biopsy, performed in six patients, showed non-specific chronic inflammation only in five and caseating granulomas in one (patient 2). Bronchial aspirates from all seven patients were cultured and *Nocardia* was grown from two, though in both instances *Nocardia* was also isolated from sputum.

OUTCOME

Three patients had been discharged from hospital before *Nocardia* was isolated and were lost to follow up. Of the remainder, six were judged to have pulmonary nocardosis as the major clinical problem. These were followed for two to nine months and showed substantial improvement with sulphadiazine 4 or 8 g daily. One patient, who had received sulphadiazine for six months and whose sputum had been negative for *Nocardia* for one month, was readmitted with a massive haemoptysis necessitating pneumonectomy, and he died after operation. One patient developed a generalised rash while taking sulphadiazine and was changed to ampicillin. No other serious adverse effects of sulphonamides were observed.

In three patients other lung problems were thought to be the principal cause of their illness and the contribution of nocardiosis was uncertain. One patient (No 8) had chronic obstructive airways disease with cor pulmonale and another (No 12) had advanced bronchiectasis. In both cases the radiological appearances were typical of the underlying lung disease; both died within a few weeks of presentation despite treatment with sulphonamides. A third patient had an unusual chest radiograph with multiple "cannonball" lesions in the upper zones leading to an initial diagnosis of possible disseminated malignancy. Caseating granulomas were found on transbronchial lung biopsy and she made a complete radiological and clinical recovery with antituberculous chemotherapy without receiving treatment for nocardiosis. She was well at follow up after 15 months.

Discussion

The range of clinical manifestations of *Nocardia* infection has been well documented in North America.[1 2 6 7] Most cases are of the pulmonary or disseminated types, *N asteroides* being the principal pathogen. Serious underlying systemic disease and consequent immunosuppression have been predisposing factors in most cases.[2 6] Most reports from developing countries, in contrast, have been of chronic cutaneous and soft tissue disease in patients without any evident cause of immunosuppression.[8 9] There have been isolated reports of pulmonary nocardiosis from the tropics.[10 11] Rhandawa *et al*[12] found a prevalence of 4·6% among patients with suspected tuberculosis in Delhi in whom mycobacteria could not be found. Workers in Eastern Nigeria[13] have recently reported the isolation of *Nocardia* in sputum from five of 100 patients with a clinical diagnosis of respiratory infection, suggesting that nocardiosis may occur in a substantial proportion of such patients in Africa.

We detected *Nocardia* in the sputum of 12 patients during a 12 month period among inpatients at two big central hospitals. Nocardiosis was the most frequent diagnosis made by the mycology laboratory during this period. There is a large burden of chronic chest disease in our population but much of this is not investigated extensively and never reaches the central hospitals. Most of our patients had chronic pulmonary disease but were otherwise well. Underlying systemic disease was observed in only one patient and we did not see the overwhelming acute infection that has been described from North America.[7] Excessive alcohol consumption was common, however.

The typical presentation in our patients was with fever and cough, often with haemoptysis. There was radiological evidence of progressive pulmonary consolidation, which failed to respond to empirical treatment for suppurative or tuberculous infection. Anaemia of chronic disease was in some instances

worsened by substantial blood loss through haemoptysis. The ESR was often raised, considerably so in some patients. The frequent finding of thrombocytosis may represent a reaction to infection or blood loss.

None of our patients was tested for antibodies to the human immunodeficiency virus (HIV) as they presented before April 1986, when very few cases of HIV related illness had been seen in Zimbabwe. They were generally older than the known risk group for HIV infection in Africa; they showed no tendency to develop other infections, generalised lymphadenopathy, or Kaposi's sarcoma; and they responded well to treatment. We therefore have no evidence to suggest that HIV infection was a predisposing factor in these patients. Our findings illustrate again the well described delay in diagnosis in this condition. This is largely attributable to a lack of awareness of the diagnosis and inexperience in identifying the pleomorphic forms of *Nocardia* on microscopy. We found the modified Kinyoun stain to be unreliable and no longer use it. *Nocardia* is easily overlooked in the Gram smear, where the organisms often appear as long (10–20 μm), irregularly stained filaments, with only occasional branching, and can be dismissed as chains of streptococci by inexperienced personnel. *Nocardia* will grow readily under the conditions that are standard for the culture of *Mycobacterium tuberculosis* but successful recognition does depend on some familiarity with this unusual organism. L-J and Sabouraud's are the only media used routinely for sputum culture that support the growth of *Nocardia*.

Cycloheximide is added to culture media to isolate actinomycetes from the soil[14] and we found SAB + C to be as effective as L-J in the isolation of *Nocardia* from sputum. SAB + C has the advantage that it does not support the growth of *M tuberculosis*, reducing the risk of handling this organism where there are no suitable facilities. This is also true of brain heart infusion agar, which we have adopted since the completion of this study and which may be a better growth medium for *Nocardia*.

There has been debate about the clinical significance of *Nocardia* that are cultured from the sputum. Hosty *et al*[15] grew *Nocardia* on L-J media from 134 of more than 80 000 sputum specimens screened for tuberculosis (0·16%). Although they stated that none of the patients had pathological nocardiosis, it has been pointed out that several had unexplained pulmonary disease.[7] In subsequent North American studies *Nocardia* have been found less frequently.[16,17] Raich *et al* found only seven (0·016%) unexplained positives out of 44 071 sputum specimens examined in a tuberculosis laboratory and concluded that *Nocardia* was not a saprophyte of the respiratory tract and was a rare laboratory contaminant.[17] Most subsequent authors have upheld this view and have considered the isolation of *Nocardia* in the presence of disease to be highly indicative of pathological nocardiosis.[2,7] In our series there was one patient with pulmonary tuberculosis in whom the finding *Nocardia* appeared to be clinically irrelevant. In two others the responsible clinician did not think that nocardiosis was the dominant clinical problem; and three further cases were lost to follow up, so that no assessment could be made of the contribution of nocardiosis to their condition. There are no criteria that allow a clear judgment on the significance of *Nocardia* in individual cases, and no firm line can be drawn in this series between commensal and pathological infections; but our experience suggests that the former can occur. We are at present investigating the prevalence of *Nocardia* spp in patients with various respiratory diseases in Zimbabwe.

The treatment of nocardiosis has been reviewed by Curry.[6] High doses of sulphonamides remain the standard treatment. Co-trimoxazole has also been used extensively and may be superior in disseminated disease.[18] We usually started our patients on sulphadiazine 8 g daily with copious oral fluids and potassium citrate for alkalinisation of the urine. This was reduced to 4 g daily after four weeks. Treatment was continued for at least six weeks after the sputum had become free of *Nocardia* if the patient would comply. Minocycline is an alternative drug in the presence of sulphonamide hypersensitivity.

The diagnosis of pulmonary nocardiosis depends on the isolation of *Nocardia* in an appropriate clinical setting. Physicians in the tropics should consider this condition when there is progressive pulmonary consolidation in the mid or lower zones or when empirical antituberculosis chemotherapy for longstanding upper zone consolidation has failed. Nocardiosis is a treatable lung disease that has not previously been recognised in Zimbabwe and may occur more widely than has been realised in other tropical countries.

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