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Nocardial infection of the skin

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SUMMARY

This paper describes the relationship between different forms of nocardia infection involving the skin. The best recognized of these conditions are systemic nocardiosis and actinomycetoma due to *Nocardia* spp. in which the organisms are present in either filamentous or grain form respectively. Attention is drawn to evidence for the existence of a primary cutaneous form of nocardiosis which follows inoculation and in which the organisms grow in filamentous phase. It is not clear whether such cases can progress to mycetoma formation if left untreated, or whether other factors are involved. The clinical and laboratory features of these different clinical varieties of nocardia infection are discussed.

INTRODUCTION

Infections of the skin caused by *Nocardia* species are not common, but they include two distinct clinical forms, characteristic of systemic nocardiosis and actinomycetoma respectively. In systemic nocardiosis the organisms grow as slender branching filaments and give rise to single or multiple abscesses (Frazier, Rosenow & Roberts, 1975). The lung and the brain are most frequently affected but the skin or subcutaneous tissue may also be involved. The primary site of infection is usually the lung. Actinomycetoma differs from this pattern in a number of respects. Although the tissue reaction is broadly similar the organisms are grouped into tight aggregates of filaments known as grains which range from 40 to 100 μm, in diameter. The subcutaneous tissue is the primary site of infection but spread to skin or bone by direct invasion may occur. Wider dissemination by blood-stream or lymphatic spread is extremely rare.

Originally these two main types of nocardia infection were thought to be caused by separate groups of organisms, *Nocardia asteroides* in nocardiosis (systemic) and *N. brasiliensis* or *N. caviae* in actinomycetoma. However, it is now clear that such a rigid classification is not valid (Berd, 1973; Causey, Arnell & Brinker, 1974). For instance in a survey of cases of nocardiosis in the U.S.A. between 1972 and 1974 (Beaman *et al.* 1976) it was reported that *N. asteroides* was isolated from 81·2 % of 197 cases of systemic nocardiosis but *N. brasiliensis* and *N. caviae* were the causative organisms in 5·6 and 3·0 % of cases respectively. In the remaining 10·2 % the organisms were not fully identified. Conversely *N. asteroides* has been shown to cause actinomycetoma (e.g. Sanyal, Thammayya & Basu, 1978).

While nocardiosis is generally regarded as a respiratory infection which may disseminate from the primary focus, a significant number of patients present with solitary extrapulmonary or extraneural lesions; 39 % in the survey mentioned

previously (Beaman *et al.* 1976). The usual sites of these focal lesions are the skin, subcutaneous tissue or joints. In many cases abscesses in these organs follow metastic spread from a pulmonary focus which may subsequently heal. Less commonly, similar lesions appear to result from direct inoculation of organisms into the skin (Vasarinsh, 1968).

PRIMARY NOCARDIA INFECTIONS OF THE SKIN

Primary nocardia infection of the skin may cause one of two distinctive patterns, depending on whether the organism is present in the form of branching filaments or grains.

Primary cutaneous nocardiosis was originally believed to be a rare form of the infection (Vasarinsh, 1968). However in a recent study from the U.S.A. six cases were reported from Texas over a 2 year period (Satterwhite & Wallace, 1979); these were due either to *N. asteroides* or *N. brasiliensis*. In four cases the infection arose at the site of a recent injury or laceration; two patients had received systemic corticosteroids following the injury. In two patients the lesions resolved after surgical drainage without specific antibiotic therapy. The lesions produced included pyoderma, cellulitis, and abscesses. All the other patients received sulphonamide drugs for periods ranging from 2 weeks to 4 months and there was no evidence of spread of infection or subsequent relapse. Another form of cutaneous nocardiosis following presumed inoculation is the lymphangitic or sporotrichoid form, where the initial site of infection becomes acutely inflamed and secondary lesions develop along the course of draining lymphatics. This type of nocardia infection has been reported for both *N. brasiliensis* (Moore & Conrad, 1967) and *N. asteroides* (Haim & Merzbach, 1979). It is not clear whether *N. caviae* can produce nocardiosis following inoculation, although localized skin abscesses not associated with internal involvement have been reported (Causey, 1974). Nocardia have also been isolated from other cutaneous or mucocutaneous sites such as a pilonidal sinus or ischio-rectal abscess (Hickey & Berglund, 1953). However, it is not clear whether these cases followed direct implantation or secondary dissemination of organisms.

The reasons for suspecting that cutaneous nocardiosis may sometimes be a result of implantation of organisms include the development of solitary lesions or lymphatic spread shortly after a history of tissue injury, the occurrence of spontaneous improvement and the absence of systemic spread. These findings are broadly similar to those of the cutaneous chancriform syndrome which may be caused by other pathogenic bacteria or fungi (Wilson, 1963). However, it is important to recognize that solitary skin lesions may also result from focal metastatic spread from the lung and this point should be borne in mind when considering management and investigations.

The second form of primary nocardia infection of the skin is a more chronic process, actinomycetoma. Here the infectious process is characterised by the formation of nocardia grains which are small structures containing aggregates of filaments. The morphology of nocardia grains stained with haematoxylin/eosin is very distinctive. *N. brasiliensis* is the commonest member of the genus which may cause mycetoma although both *N. asteroides* (Sanyal, Thammayya & Basu, 1978) and *N. caviae* (Alteras, Feuerman & Dayan, 1980) may also cause this pattern of

infection. Mycetomas caused by these organisms are morphologically similar. The lesions commonly develop on the foot or arm but the back may also be involved. In the latter instance secondary invasion of the lung may follow direct extension of the primary lesion. The bone may also be affected following extension from the initial site of infection. In early cases the main sign of infection is the development of a firm subcutaneous swelling, but later draining sinus tracts form. These discharge serosanguinous material and grains onto the skin surface.

In histological sections the grains of *Nocardia* species are small, ranging from 40 to 100 μm in diameter (Mahgoub & Murray, 1973). They may not be visible to the naked eye. Grains are a pale blue colour with a refractile pink fringe in haematoxylin/eosin stained sections. In contrast to eumycetoma (true fungal mycetoma), experimental models of nocardia actinomycetoma have been established in animals. For instance Mackinnon & Artagaveytia-Allende (1956) produced an experimental infection in mice three weeks after intraperitoneal injection. More recently it has been found that, in experimental *N. caviae* infections in normal and T lymphocyte deficient mice, grains develop slowly after intravenous inoculation in normal but not immunodeficient animals and that cell wall deficient organisms, L-forms, are associated with grain formation (Beaman & Scates, 1981).

SECONDARY INVOLVEMENT OF THE SKIN IN SYSTEMIC NOCARDIOSIS

The principle route of infection in systemic nocardia infections is respiratory. Organisms can be isolated from soil and on rare occasions, on 'settle' plates indicating airborne spread. For instance Houang *et al.* (1980) recorded an outbreak of systemic nocardiosis caused by *N. asteroides* in a renal unit associated with contamination of the ventilation system. Although the view has been expressed that nocardia may colonize the respiratory tract particularly in those with chronic obstructive airways disease (Peabody & Seabury, 1960), this is not a common finding (Raich, Casey & Hall, 1961). By contrast, invasive pulmonary infection is the commonest clinical manifestation of systemic nocardiosis and can be caused by all three pathogenic *Nocardia* species (Beaman *et al.* 1976). Although it is usually an acute or subacute respiratory disease, on rare occasions lesions may persist for many years (Kirby & McNaught, 1946).

The central nervous system is the commonest site for disseminated nocardia infections but the skin may also be involved. Here the lesions are usually single or multiple abscesses, subcutaneous nodules, cellulitis or draining sinus tracts (Pizzolato, 1971). Most appear to arise following bloodstream spread but others may result from direct extension from a pulmonary focus through the chest wall. In many cases there is evidence of an underlying deep focus of infection or a metastatic lesion in other sites.

DISCUSSION

There are sufficient grounds for believing that *Nocardia* species cause disease in man following entry via one of two main routes, the skin or lung. Although alternative sites of entry, such as the gastrointestinal tract, have been proposed there has seldom been conclusive data to support this view. Inhalation via the

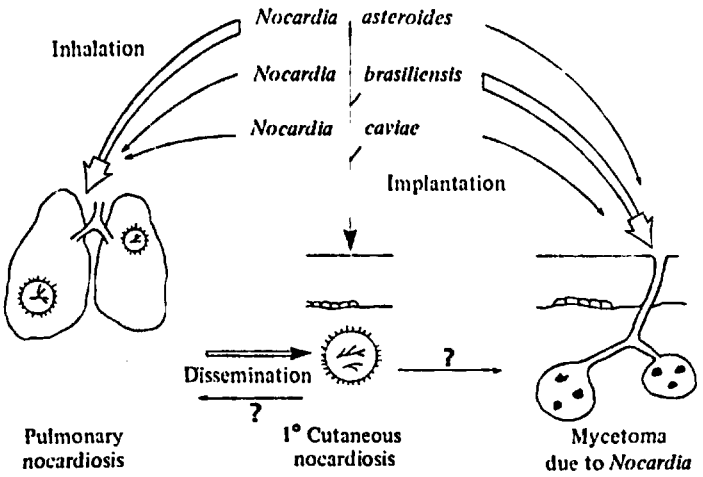

Fig. 1. Pathogenesis of Nocardia infections of the skin.

respiratory route gives rise to a localized pulmonary process which may spread via the bloodstream to cause disseminated disease. Inoculation via the skin will produce a local acute suppurative reaction centred on organisms in a filamentous phase or alternatively, a more chronic infection associated with the formation of aggregates of filaments, grains (Fig. 1). While both primary cutaneous (including lymphocutaneous) nocardiosis and nocardia actinomycetoma follow inoculation of organisms into the skin, it is not clear whether mycetoma formation is simply a chronic manifestation of the former or whether other factors are involved. Until the pathogenesis of both clinical forms or nocardiosis is better understood it seems reasonable, and simpler, to treat them separately rather than to refer to them as acute or chronic primary cutaneous nocardiosis respectively.

It is not clear whether exposure to *Nocardia* is widespread and, as a consequence, whether sub-clinical sensitization is a common occurrence. However, if this is the case, the host's immunological competence as well as other factors may determine whether inhaled organisms are eliminated or whether they cause a progressive infection. In man systemic nocardiosis is frequently associated with factors affecting the hosts immune response. In one report (Beaman *et al.* 1976) the organism was considered to be an opportunistic pathogen in 53% of 253 cases reported. Immunosuppressive therapy, organ transplants or neoplasia were the commonest underlying factors. However, in some cases localised lung disease was present, tuberculosis and alveolar proteinosis being the best recognized of these conditions. In a study of mycetoma formation in immunodeficient mice Beaman & Scates (1981) showed that T lymphocyte deficient animals were more susceptible to *N. caviae* infections, but tended to develop systemic nocardiosis rather than the more localized mycetoma. Nude athymic mice surviving longer than 3 months sometimes developed mycetomas. This work supports the view that the hosts immune response and in particular T lymphocytes may affect both the rate of evolution as well as the clinical appearance of nocardia infections. Other factors such as the infecting dose may also play an important role in determining the type

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Table 1. *Distinguishing features of systemic and primary (cutaneous) forms of nocardia infections affecting the skin*

	Disseminated (systemic) nocardiosis	Primary cutaneous nocardiosis	*Nocardia* actinomycetoma
Geographic Distribution	Worldwide	Worldwide	Tropics or Sub-tropics
Presence of predisposing diseases	Common	Rare	Rare
History of trauma	Rare	Common	Common
Other organs involved (besides skin)	Lung, brain bone	Lymphatics	Bone
Sites on skin	Anywhere	Exposed areas	Exposed areas, back
Draining sinuses	Absent	Absent	Present
Number of skin lesions	Single or multiple	Usually single	Usually single
Nocardia species (commonest)	*N. asteroides*	*N. asteroides* *N. brasiliensis*	*N. brasiliensis*
Growth pattern *in vivo*	Filamentous	Filamentous	Grains

of illness seen in man. In reported cases of primary cutaneous nocardiosis following inoculation, there is seldom evidence that the hosts immune responses are impaired and a vigorous reaction, such as the development of local lymphadenopathy, may develop. However, it is possible that where this mechanism fails to eliminate all organisms while confining them to the initial site of infection, an actinomycetoma may develop. The factors affecting this change of phase, filament to grain, are also unclear; but the host's immune response, mentioned previously, as well as the ability of organisms to lose cell wall structure (Beaman & Scates, 1981) may affect this transformation. It is also possible that under the right circumstances cutaneous ioculation may lead to systemic disease similar to that which more commonly follows inhalation.

It is also not clear why *N. asteroides* and *N. brasiliensis* are predominantly associated with systemic and pulmonary disease or actinomycetoma respectively. However, climatic and geographic considerations may affect this pattern of disease; For instance in temperate areas of the U.S.A. where systemic nocardiosis is more common than mycetoma, *N. asteroides* is the predominant *Nocardia* species found in soil; but the position is reversed in Mexico where mycetoma is more common and *N. brasiliensis* is the predominant soil organism (Rippon, 1977). Other factors which might affect the distribution of disease would include the ease of dispersal via aerosols and the pathogenic capabilities of each organism following cutaneous inoculation *N. asteroides* has been shown to undergo L-form transformation in host macrophages (Bourgeois & Beaman, 1974). This transformation may well favour mycetoma development and it would be interesting to see if *N. brasiliensis* showed a greater facility for this cell wall change. At present it is difficult to compare the pathogenicity of the different organisms. Some workers using experimental infections in mice (Gonzales-Ochoa & Sandoval-Cuellar, 1976), have shown that *N. brasiliensis* is the more pathogenic of these organisms. However, the 'virulence' of different *Nocardia's* depends not only on species but also route

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of inoculation (Beaman *et al.* 1980) and hence the effect of interspecific variations on mycetoma formation is difficult to judge. These considerations are not simply of academic interest, as the behaviour of *Nocardia* species following cutaneous inoculation is important in explaining the factors affecting host response to subcutaneous mycoses.

Partial separation of the various forms of cutaneous nocardiosis is possible on clinical and microbiological grounds (Table 1). However, the distinction between primary cutaneous nocardiosis associated with abscess formation and a limited form of disseminated nocardia infection is seldom possible to make with a high degree of accuracy. Until more precise criteria for separating these conditions are available it is prudent to investigate all such cases for evidence of systemic involvement.

REFERENCES

ALTERAS, I., FEUERMAN, E. J. & DAYAN, I. (1980). Mycetoma due to *Nocardia caviae*. *International Journal of Tropical Dermatology* **19**, 260–262.

BEAMAN, B. L., BURNSIDE, J., EDWARDS, B. & CAUSEY, W. (1976). Nocardial Infections in the United States, 1972–1974. *Journal of Infectious Diseases* **134**, 286–289.

BEAMAN, B. L., MASLAN, S., SCATES, S. & ROSEN, J. (1980). Effect of route of inoculation on host resistance to Nocardia. *Infection and Immunity* **28**, 185–189.

BEAMAN, B. L. & SCATES, S. M. (1981). Role of L-forms of *Nocardia caviae* in the development of chronic mycetomas in normal and immunodeficient murine models. *Infection and Immunity* **33**, 893–907.

BERD, D. (1973). *Nocardia brasiliensis* infection in the United States. *American Journal of Clinical Pathology* **60**, 254–258.

BOURGEOIS, L. & BEAMAN, B. L. (1974). Probable L-forms of *Nocardia asteroides* induced in cultured mouse peritoneal macrophages. *Infection and Immunity* **9**, 576–590.

CAUSEY, W. A. (1974). *Nocardia caviae*: a report of 13 new isolations with clinical correlation. *Applied Microbiology* **28**, 193–198.

CAUSEY, W. A., ARNELL, P. & BRINKER, J. (1974). Systemic *Nocardia caviae* infection. *Chest* **65**, 360–362.

FRAZIER, A. R., ROSENOW, E. C. & ROBERTS, G. D. (1975). Nocardiosis. A review of 25 cases occurring during 24 months. *Mayo Clinic Proceedings* **50**, 657–663.

GONZALES-OCHOA, A. & SANDOVAL-CUELLAR, A. (1976). Different degrees of morbidity in white mice induced by *Nocardia brasiliensis*, *N. asteroides* & *N. caviae*. *Sabouraudia* **14**, 255–259.

HAIM, S. & MERZBACH, D. (1979). Primary cutaneous chancriform syndrome caused by *Nocardia asteroides*. *Mykosen* **22**, 360–363.

HICKEY, R. C. & BERGLUND, E. M. (1953). Nocardiosis: Aerobic actinomycosis with emphasis on the alimentary tract as a portal of entry. *Archives of Surgery* **67**, 381–385.

HOUANG, E. T., LOVETT, I. S., THOMPSON, F. D., HARRISON, A. R., JOEKES, A. M. & GOODFELLOW, M. (1980). *Nocardia asteroides* infection – a transmissible disease. *Journal of Hospital Infection* **1**, 31–40.

KIRBY, W. M. M. & MCNAUGHT, J. B. (1946). Actinomycosis due to *Nocardia asteroides*: Report of two cases. *Archives of Internal Medicine* **78**, 578–591.

MACKINNON, J. E. & ARTAGAVEYTIA-ALLENDE, R. C. (1956). The main species of pathogenic actinomycetes causing mycetomas. *Transactions of the Royal Society for Tropical Medicine and Hygiene* **50**, 31–40.

MAHGOUB, E. S., MURRAY, I. G. (1973). *Mycetoma*, pp. 30–46. William Heinemann Medical Books.

MOORE, M. & CONRAD, A. D. (1967). Sporotrichoid nocardiosis caused by *Nocardia brasiliensis*. *Archives of Dermatology* **95**, 390–393.

PEABODY, J. W. & SEABURY, J. H. (1960). Actinomycosis and nocardiosis: A review of basic differences in therapy. *American Journal of Medicine* **28**, 99–105.

PIZZOLATO, P. (1971). Nocardiosis. In *The Pathologic Anatomy of Mycoses*, pp. 1059–1080. Berlin: Springer-Verlag.

RAICH, R. A., CASEY, F. & HALL, W. H. (1961). Pulmonary and cutaneous nocardiosis. The significance of the laboratory isolation of Nocardia. *American Review of Respiratory Diseases* **83**, 505–509.

RIPPON, J. W. (1977). Nocardia: A geographic prevalence. *Archives of Dermatology* **113**, 237.

SANYAL, M., THAMMAYYA, A. & BASU, N. (1978). Actinomycetoma caused by organisms of the *Nocardia asteroides* complex and closely related strains. *Mykosen* **21**, 109–121.

SATTERWHITE, T. K. & WALLACE, R. J. (1979). Primary cutaneous nocardiosis. *Journal of the American Medical Association* **242**, 333–336.

VASARINSH, P. (1968). Primary cutaneous nocardiosis. *Archives of Dermatology* **98**, 489–493.

WILSON, J. W. (1963). Cutaneous (chancriform) syndrome in deep mycosis. *Archives of Dermatology* **87**, 81–85.