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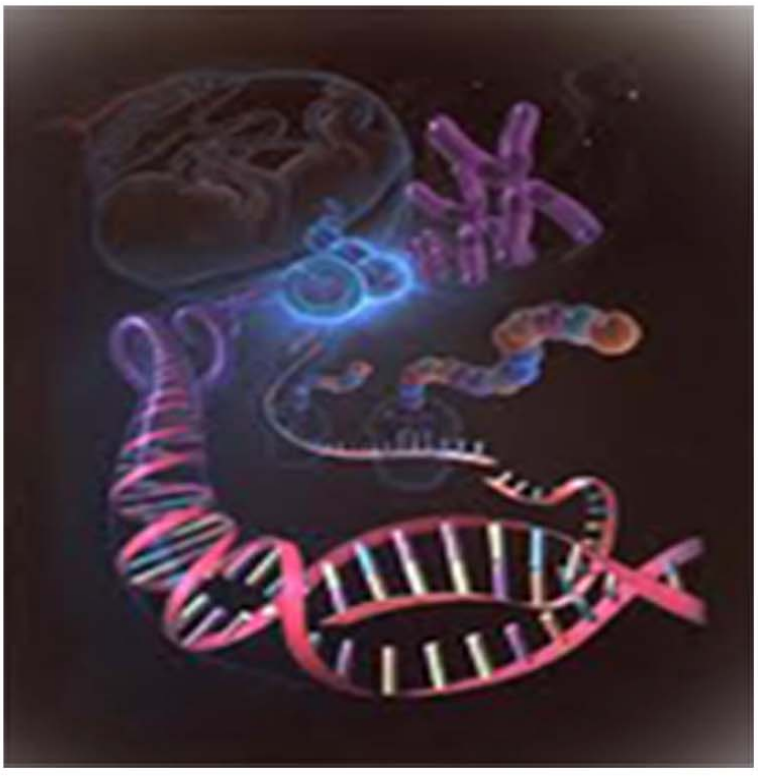

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Review Article

NOCARDIOSIS: A REVIEW OF CLINICO-MICROBIOLOGICAL FEATURES

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Nocardiae cause a variety of suppurative infections in humans and animals. The manifestations of nocardiosis can be solely pulmonary, but Nocardia species can also disseminate from a pulmonary or cutaneous focus to virtually any organ. In patients with suspected Nocardial infection and a compatible clinical picture, a definitive diagnosis usually depends on demonstration of the organisms in smears or sections examined microscopically prior to isolation and identification of the causal agent. The greatest clinical experience in the treatment of nocardiosis is with the sulphonamides, and these remain the drugs of choice.

Keywords: Nocardiosis, Clinical manifestations, Laboratory diagnosis, Management

INTRODUCTION

Nocardiosis is an infrequent but severe bacterial infection that commonly presents as a subacute or chronic, suppurative or less frequently granulomatous disease, caused by the soil-inhabiting aerobic actinomycetes belonging to the genus Nocardia (Singh *et al*., 2000). The disease occurs not only in compromised hosts but may occur in immunologically intact individuals (Malik *et al*., 1980).

Nocardiae are saprophytic, making an important component of the normal soil microflora and are often being associated with water. They may also be associated with decomposing plant material, dust and air. Nocardial infections are not thought to be transmitted from person to person and are not usually acquired nosocomially (Lerner, 1996; and Saubolle and Sussland, 2003). The disease has universal distribution (Corti and Villafañe-Fioti, 2003). Males suffer from Nocardiosis more frequently than females. Most workers found that males out numbered females by a ratio of 3:1 (Curry, 1980).

Trevisan named the genus Nocardia for Nocard who, in 1889, described an aerobic actinomycete from bovine farcy, a lymphatic disease of cattle caused by *Nocardia farcinia*. Eppinger (1890), first described nocardiosis in man in a report of a pulmonary disease with “pseudotuberculosis” of lungs and pleura, caseous peribronchial lymph nodes, meningitis and multiple abscesses in the brain. Branched hyphae were present in stained films of pus. Eppinger erroneuously assigned the

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organism to the genus name *Cladothrix* and Blanchard transferred it to *Nocardia* in 1895 (Emmons Chester *et al.*, 1977).

Nocardia species are ubiquitous soil organisms with more than 50 species that have been isolated from clinical infections. The genus Nocardia is rapidly expanding and at present consists of 22 species. The most frequently isolated species belong to the *N. asteroides* complex, which is a heterogeneous group that includes *N. asteroides* sensu strictu, *N. farcinica*, *N. nova* and *N. abscessus*. Other medically important species are *N. brasiliensis, N. otitidiscaviarum, N. africana, N. brevicatena* complex*, N. carnea, N. paucivorans, N. pseudobrasiliensis, N. transvalensis* and *N. veterana*. Identification of clinical isolates beyond the genus level is important since *Nocardia* species differ in the clinical spectrum of the disease they cause and their susceptibility to antibiotics. In particular, *N. farcinica* is much more resistant than other Nocardia species (Agterof, 2007).

Nocardia is not part of the normal human flora and any isolate must be carefully evaluated. The organisms are readily aerosolized with dust, especially in dry areas. Consequently, the respiratory tract is the main portal of entry, with 50 to 70% of cases presenting with pulmonary involvement, most commonly with organisms representing the former *N.asteroides* complex. Bronchiectasis and other structural lung abnormalities have been reported as an important risk factor for respiratory colonization by Nocardia species. Organisms can also be acquired by direct inoculation, resulting in primary infections of the skin and subcutaneous tissues, often presenting as a localized, nodular process. These infections can progress via lymphatic spread to regional nodes and, occasionally, by direct spread to contiguous joints and bones. Agricultural work represents an important risk factor, with *N. brasiliensis* being the most common infecting species (Ambrosioni, 2010).

Systemic immunosuppression and prior treatment with corticosteroids are regarded as important risk factors. Other clinical conditions that can also predispose to the development of nocardiosis include lymphoma, sarcoidosis, systemic lupus erythematosus, chronic granulomatous disease, chronic alcoholism, diabetes mellitus, HIV infection, trauma, surgery and post- transplantation. (Yu and Chua, 2001). Chronic Granulomatous Disease (CGD) predisposes to infections at an early age with *Nocardia* species. About 1.3% of the reported cases of nocardiosis involve patients with this underlying condition. A case has been reported in which a patient with chronic granulomatous disease had infection due to *N. farcinia* (Fijen *et al.*,1998).

A collation of epidemiologic information indicates a minimum of 500-1,000 human cases/ year in the USA alone, although recent clinical reports from many centres indicate that the incidence of infection is rising. This may be due in part to improvements in diagnosis, and to improved survival of patients in immuno suppressed state because of more aggressive therapy of rejection of transplants, and to improvements in therapy of other opportunistic infections (leaving the patient vulnerable to the possibility of later infection with Nocardiae). There seems no geographic predilection, with the exception that mycetomas due to Nocardia species occur predominantly in tropical areas. In Europe and North America, about 85% of the infections seen are pulmonary and/ or systemic,

with estimates that 75-79% of cases will have some pulmonary involvement and 45% systemic dissemination. (Stevens *et al.*,1983)

CLINICAL MANIFESTATIONS

The manifestations of nocardiosis can be solely pulmonary, but *Nocardia* species can also disseminate from a pulmonary or cutaneous focus to virtually any organ.

Nocardiae cause a variety of suppurative infections in man and animals. Primary pulmonary nocardiosis may be subclinical or pneumonic; it may be chronic or acute with possible secondary, often fatal, involvement of other systems. In non-tropical countries, most infections are caused by *Nocardia asteroides*, *N. farcinia* and *N. nova*, and relatively few by *N.brasiliensis* and *N. otitidiscaviarum.* Localized cutaneous and subcutaneous nocardiosis are encountered less frequently. Their aetiological agents include *N. asteroides*, *N. brasiliensis*, *N. farcinia*, *N. otitisdiscaviarum* and *N. transvalensis* (Goodfellow, 1996).

Pulmonary nocardiosis is an acute, subacute or chronic suppurative infection with a pronounced tendency for remissions and exacerbations. The clinical manifestations are acute or subacute pneumonia with abscess or cavity formation. Generally, the initial diagnosis is pneumonia, tuberculosis, and carcinoma or lung abscesses of other aetiologies. The most common symptoms are productive cough, high fever, chills, sweats and weight loss. 25% of cases present with pleural involvement, including pleural effusions and empyema. Histopathologically, pulmonary lesions show tissue necrosis with polymorphonuclear leukocyte, macrophage and lymphocyte infiltrates, but usually not the hallmark epitheloid cells seen in tuberculosis. Sometimes, tissue sections may reveal a granulomatous response with central necrosis that may mimic tuberculosis or histoplasmosis. Progressive fibrosis occurs in inadequately treated patients, with a chronic course similar to that of tuberculosis (Corti and Villafañe-Fioti, 2003).

Rarely, Nocardia species can invade pre-existing lung cavities, producing a 'fungus ball' appearance (Tilak *et al.*, 2008).

The remissions and exacerbations of pulmonary nocardiosis over periods of several weeks are frequent. It mimics pulmonary tuberculosis in both clinical symptoms and radiological characteristics. The chest radiographic manifestations are pleomorphic and non-specific. Consolidations and large irregular nodules, often cavitary, are most common; nodules, masses and interstitial patterns also occur. Upper lobes are more commonly involved. In countries like India where tuberculosis is very common, anti tuberculosis drugs are started on the basis of radiology and clinical symptoms. A classic radiographic picture of tuberculosis that is unresponsive to medication should raise the suspicion of Nocardia infection (Chopra *et al*., 2001). It is important to consider Nocardiosis in the differential diagnosis of pulmonary diseases which do not respond to antitubercular treatment and in which the sputum is negative for AFB (Dias *et al.*, 2009). Although, nocardiosis resembles tuberculosis, the first line anti tubercular drugs have no role to play in its treatment (Kumar *et al*., 2011).

The disease may be erroneously diagnosed as Wegener's granulomatosis, if cavitating pulmonary lesions and vasculitic skin lesions occur concurrently (Gibbs, 1986).

Nocardial lesions in the lungs or elsewhere in

the body frequently erode into blood vessels. Once blood borne, organisms can invade other anatomic locations. This process can also occur following traumatic inoculation from a contaminated source (e.g., a thorn, wood splinter, traumatic accident, bullet wound, insect bite or animal bite). Thus, when lesions are found at two or more locations within the body, the infection is defined as systemic or disseminated nocardiosis. Any anatomic location can be involved, but the most common site that become infected during dissemination include the CNS, cutaneous and subcutaneous tissues, eyes (especially the retina), kidneys, joints, bone, and heart. Unlike pulmonary infections, disseminated or systemic nocardiosis tend to become relentlessly progressive, and self-limited or subclinical disease is not recognized frequently. (Beaman and Beaman, 1994).

Cerebral nocardiosis is an uncommon clinical entity, representing only 2% of all cerebral abscesses. Most common presentation is with evidence of progressively expanding intracerebral mass lesion which can be multiple or single. Nocardial brain abscesses are often misdiagnosed as malignant brain tumours and a definitive diagnosis may not be possible without detecting bacteria from the lesion. Infection of the brain by nocardia is often insidious in onset, difficult to diagnose and treat successfully. Nocardial brain abscesses are frequently solitary (54%). The mortality rate in patients with multiple abcesses is twice of that among patients with solitary abscesses (66% vs.33 %) (Hymer *et al.,* 2011).

Peritonitis is a common problem in patients undergoing continuous ambulatory peritoneal dialysis. Nocardia peritonitis is not symptomatically different from other causes of peritonitis, and there have been few reported cases in the literature (Li *et al.*, 2008; Chu *et al.,* 2003; Dwyer *et al.,* 2001; Recule *et al.*, 1994). It appears there are no obvious predisposing factors to the development of *Nocardia peritonitis*. Abscess formation is rare, but once diagnosed, surgical treatment and prolonged antimicrobial therapy are indicated.

*Nocardia synovitis i*s rare. The majority of the previously reported cases have been in immunocompromised patients and have been an expression of disseminated Nocardiosis.

An unusual presentation of *Nocardia asiatica (N. asiatica)* in an Iraqi patient with myasthenia gravis suffering from a disseminated infection and presenting with an anterior mediastinal cystic mass has been described (El-Herte *et al.*, 2012).

A case of disseminated nocardiosis in a patient without any underlying immuno suppression has been reported (Dar *et al.*, 2009).

Ocular nocardiosis is an uncommonly reported clinical entity. Infection may develop after minor trauma to the eye in healthy individuals, following ocular surgery such as cataract extraction, or following hematogenous dissemination in immunocompromised patients. Ocular pathology of nocardiosis includes uveitis, exudative choroiditis, retinal abscess, retinal detachment, keratitis, and iritis. Nocardial endopathalmitis is associated with a high mortality, and survivors have invariably had total blindness in the involved eye (Brown-Elliott *et al.*, 2006).

The typical clinical picture in Nocardia keratitis is a well-defined epithelial defect with scalloped margins and a white granular appearance. The margins of the ulcer have discrete, yellowish-white, pinhead-sized infiltrates. The stromal infiltrate has feathery margins and a wreath pattern with satellite lesions (Rao *et al.*, 2000).

Isolated *Nocardia scleritis* is rare and usually occurs as an extension of corneal infection involving the limbus. The common predisposing factors are surgery and injury. A number of cases of scleritis due to *Nocardia* spp. have been reported (De Croos *et al*., 2011; Jain *et al.*, 2009; Das *et al*., 2007; Maruo *et al*., 2011; Sahu *et al.*, 2012).

LABORATORY DIAGNOSIS

In patients with suspected Nocardial infection and a compatible clinical picture, a definitive diagnosis usually depends on demonstration of the organisms in smears or sections examined microscopically prior to isolation and identification of the causal agent. Clinical materials, such as bronchial washings, sinus discharge and biopsy and autopsy specimens, need to be examined as soon as possible to prevent overgrowth by contaminants. Fluid material can be examined in wet mounts under the microscope without staining (Goodfellow, 1996).

Microscopy

Nocardia species have a Gram positive mycelium with branched hyphae which rarely exceed one micron in width. The partially acid fastness of the organism is a characteristic feature (Randhawa *et al.,* 1977). Acid-fastness, which is usually more pronounced in clinical than cultured material, is best seen using the modified Kinyoun acid-fast procedure. Even with this technique, Nocardiae may be only partially acid-fast; that is, they show both acid-fast and non-acid-fast bacilli and filaments (Goodfellow, 1996).

Silver methamine stain has been found to be equally effective and reliable as modified Ziehl-Nelson staining technique in demonstrating these bacteria in these samples (Mathur *et al.,* 2005).

Culture

Several general purpose media can be used to isolate Nocardiae from clinical material. They include brain-heart infusion, sabouraud dextrose and yeast extract- malt extract agars. Nevertheless, selective media are needed to isolate Nocardiae from clinical specimens that harbour large number of contaminating bacteria. Several media have been recommended for the selective isolation of Nocardiae, notably chemically defined formulations supplemented with paraffin, Czapek's agar amended with yeast extract, Diagnostic sensitivity Test agar supplemented with tetracyclines, Nocardia selective agar, buffered charcoal yeast extract agar supplemented with anisomycin, polymyxin and vancomycin and Sabouraud dextrose agar supplemented with chloramphenicol. Nocardiae usually form well sized colonies on most standard laboratory media, including modified Bennett's, brain-heart infusion, Sabouraud dextrose, modified Sauton's, Yeast extract-glucose and yeast extract-malt extract agars, within 14 days at 37 °C (Goodfellow M., 1996). Other media which may be useful include- Modified Thayer Martin's medium (Murray *et al*., 1988), Paraffin agar, Gelatin agar (Shawar *et al.*, 1990).

Nocardia species can be recovered on isolation media for bacteria, fungi or mycobacteria, but growth is slow and incubation should be continued for at least two weeks. They can grow at high temperatures (37 to 45 °C) and growth is accelerated by CO_2. Premature discontinuation of culture will decrease the sensitivity of recovery and may contribute to underestimation of the true incidence of nocardiosis. Typically, colonies are chalky white,

but they can also be yellow, pink or orange. A characteristic smell is produced, vividly described as a musty basement odour or earthy smell (Agterof *et al.*, 2007).

Recognition of the Nocardiae can be optimized by seeing the filamentous, white to yellow to orange colonies with aerial mycelia and delicate, dichotomously branched substrate mycelia with a dissecting microscope (Saubolle and Sussland, 2003).

Identification

Accurate identification of Nocardia to the species level is important, in that differences among species have emerged in terms of virulence, antibiotic susceptibility, and epidemiology. However, identification of the pathogenic Nocardia to the species level can be problematic because no single method can identify all Nocardia isolates and because the methods employed are time consuming, often requiring 2 weeks. Useful phenotypic tests include the use of casein, xanthine, and tyrosine hydrolysis; growth at 45 °C; acid production from rhamnose; gelatin hydrolysis; opacification of Middlebrook agar and antimicrobial susceptibility patterns (Forbes Betty *et al*., 2007).

Molecular Diagnosis

A number of molecular approaches such as Polymerase Chain Reaction (PCR)-restriction fragment length polymorphism analysis and PCR of a sequence of 16S rRNA gene with subsequent sequencing have been used to rapidly and accurately identify these organisms. Of note, using the MicroSeq system for identification, almost 15% of isolates were identified as Nocardia but no definitive species was given. Therefore, identification approaches employing phenotypic and molecular methods will continue to evolve and be refined for the aerobic actinomycetes (Forbes Betty *et al*., 2007).

Wellinghausen *et al.* reported three new species of Nocardia (i.e., *N. paucivorans, N. abscessus* and *N. veterana*) while investigating seven patients of nocardiosis with clinical infection by conventional biochemical methods and 16S rRNA sequencing. (Wellinghausen *et al*., 2002)

Serology

Currently, no serologic test is available for rapid diagnosis of active nocardiosis. Attempts to develop serologic tests such as hemagglutination, immunodiffusion for precipitins and complement fixation met with only partial success because of cross- reactivity among heterogeneous Nocardia species, *Mycobacterium tuberculosis*, Mycobacterium leprae and other actinomycetes (Mc Neil and Brown *et al*., 1994).

However, a 55/54 kD culture filtrate antigen has also been under investigation as a strong candidate for a specific antibody marker of active nocardiosis (Kjelstrom and Beaman *et al*., 1993).

Management

The greatest clinical experience in the treatment of nocardiosis is with the sulphonamides, and these remain the drugs of choice. Trimethoprim-sulphamethoxazole is the most commonly available sulfa-containing drug, and although there is some uncertainty regarding the proportion of the two components of the drug with optimal synergy against the organism. Trimethoprim-Sulphamethoxazole is found to be effective in the treatment of the majority of isolates of all Nocardia species. The excellent oral bioavailability of the drug and its good tissue and cerebrospinal fluid penetration are advantages. Dosages used with success vary from 25 to 75 mg/kg d of SMX. If

there is prompt clinical response, the dose may be lowered after the first 6-8 weeks of therapy. At times, a sulfa drug cannot be used because of allergy, intolerance or toxicity. Non sulfa drugs found most often to be effective *in vivo* for *N. asteroides* are amikacin (7.5 mg/kg q12 h), minocycline (200 mg bid.), imipenem-cilastatin (500mg q6h), ceftriaxone (1-2 mg q12h) and cefotaxime (2g q8h). General recommendations are for a treatment duration of 3 months for the immunocompetent host with isolated cutaneous or pulmonary disease, 6 months for the immunocompromised host with cutaneous or pulmonary disease, 6 months for immuno-competent host with central nervous system or disseminated disease, and 12 months for the immunocompromised host with central nervous system or disseminated disease. Possibility of relapse may be lower and survival may be improved when treatment is given for longer than 6 months (Burgert, 1999).

Linezolid can be effective alternative to trimethoprim/sulfamethoxazole for the treatment of nocardiosis. Unfortunately, the high cost and potentially long term serious toxicities of linezolid appear to limit its use and relegate it to salvage therapy alone or in combination with other antimicrobials (Jodlowski, 2007).

In a recent study, the antimicrobial susceptibilities of 186 clinical isolates of *Nocardia* spp. isolated was determined in Gipuzkoa, northern Spain, between 1998 and 2009. Most isolates were recovered from respiratory samples, *Nocardia nova*, *N. farcinica*, *N. cyriacigeorgica*, *N. abscessus*, and *N. carnea* being the species most frequently isolated. Linezolid and amikacin were the only two antimicrobials to which all isolates were susceptible. The majority of *N. flavorosea*, *N. carnea*, and *N. farcinica* isolates were trimethoprim-sulfamethoxazole resistant (Larruskain, 2011).

CONCLUSION

Infections caused by *Nocardia* species are infrequent but challenging to the clinicians. Alertness to the possibility of nocardiosis can expedite the diagnostic work-up, especially in patients with predisposing factors.

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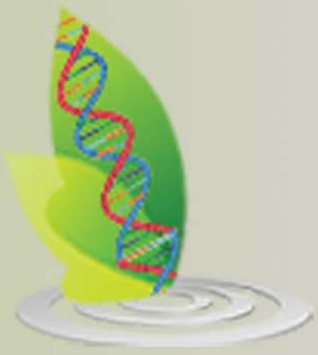

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