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HUMAN NOCARDIA INFECTIONS: A REVIEW OF CLINICO - MICROBIOLOGICAL FEATURES

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ABSTRACT

Nocardia, a gram-positive bacillus with the microscopic appearance of branching hyphae, can produce considerable risk in the host. It is a localized or disseminated infection caused by an aerobic actinomycete that usually affects immune compromised patients. This review will address the microbiology of Nocardia, risk factors for infection, clinical presentations and pharmacotherapy.[1]

KEYWORDS: Nocardiosis, Risk factors, Pathology, Diagnosis, Pharmacotherapy.

INTRODUCTION

The genus Nocardia was named after Nocard who first isolated the causative bacteria of granulomatous bovine disease [bovine farcy] in 1888 on Guadeloupe island. It was latter named Nocardia farcinica. The most important member of the genus is Nocardia asteroids, which was isolated from a human case shortly after Nocard's original isolate.

Nocardia Species

Nocardia are strictly aerobic. The important species most commonly associated with human disease include: N.asteroides [so named because of its star shaped colonies in culture medium], N.brasiliensis, N.otitidiscaviarum [formerly N.caviae], N.farcinia, N.nova, N.abscessus, Nocardia transvalensis.

Nocardia asteroides is taxonomically diverse and is often described as N.asteroides complex. Several named members of the complex – N.farcinia, N.nova, N.abscessus have been separated from the group; they are sometimes referred as sub groups of N.asteroides. At least 11 additional species are associated with human disease. N.asteroides which is most commonly associated with human infection and causes invasive disease – is actually a species complex.[2]

Morphology

Morphologically, Nocardia species are gram-positive filaments and resembles actinomyces, but N.asteroides and N.brasiliensis species are weakly acid-fast when decolorized with 1% sulphuric acid. It forms partially acid-fast beaded branching filaments [acting as fungi, but being truly bacteria].[2]

Epidemiology

Nocardiosis has a universal distribution, and affects people between 20 and 60 years of age. Cross and Bindford noticed that the high frequency with which Nocardiosis complicates other pathologic conditions that act as predisposing causes, such as Lymphoproliferative syndromes, solid neoplasiasis, AIDS, liver cirrhosis, immunodepression treatments like corticosteroids and cytotoxics.[3]

Recently, episodes of Nocardiosis in AIDS patients and in recipients of solid organ transplants have been reported.[4-6] Risk factors for the development of Nocardiosis in the above type of patients include early rejection of graft and intense immunosuppressive therapy.[7] And also there is a another group of illness that increase the risk of development of Nocardiosis; these are the chronic granulomatous diseases and hematologic malignancies. In these cases most frequently caused species is the N.farcinia.[8]

The incidence of Nocardiosis in AIDS patients shows geographic variations. It occurs in rural areas than urban. In general, AIDS patients with $CD4^+$ T-cell counts < 100 cell/Micro liter are more likely to develop pulmonary and extra pulmonary disease. The incidence rate is low and the frequency of Nocardia infections in HIV patients increased from 0.3 to 1.8% in the year 1985-89. The main reason for the low incidence is the extensive use of co-trimoxazole for Pneumocystis carinii pneumonia prophylaxis.[9]

There is a tendency to think that Nocardia infection affects only imunosuppressed patients, but it is partially true. In 1980, Curry WA.[10] 455 cases of Nocardia infections in that 39% of them did not receive immunosuppressive therapy. Palacios et al[11] found an incidence of 82% in intravenous abusers. The use of systemic corticosteroids remains as an important independent risk factor for Nocardia infections.

Etiology

Nocardia species are ubiquitous soil organisms that often infect patients who are immunosupressed, have pulmonary disease, or have a history of surgery or trauma.[12] The aerosol route is the main portal of entry, and the lungs are the most frequently affected organs. As Nocardia species are not the part of the human flora, any isolate from the tissue or normally sterile site must be carefully evaluated.[13]

Nocardiosis is due to micro-organisms of the genus Nocardia, which includes gram positive acid fast bacilli, with > 50 species identified. Pulmonary Nocardiosis and disseminated Nocardiosis can be considered to be opportunistic diseases, because both occur mainly in patients with deficient cell-mediated immunity, such as solid organ transplant and hematopoietic stem cell transplant recipients, HIV- infected patients, patients taking steroids and other malignancies. Patients with structural lung diseases, such as cystic fibrosis or bronchiectasis, are more susceptible to Nocardia infection, especially if they are receiving corticosteroids. In patients with disseminated Nocardiosis all the causes of immunocompromise need to be ruled out.[14]

In patients with primary cutaneous Nocardiosis, infection occurs after direct inoculation of skin. It evolves as a superficial infection or progress in depth and affects the sub cutaneous tissues. Lymphatic involvement of both nodes and lymphatic vessels can develop, as well as a nodular-lumphangitic form. Infection can spread into deeper skin tissues and emerge over months or years as a MYCETOMA. There is no definitive evidence of person-to-person transmission of Nocardia infection.[15,16]

Risk Factors

Nocardia is usually an opportunistic pathogen but can cause disease even in healthy hosts. Persons with depressed immunity are at high risk of developing the infection. The risk factors include individuals on treatment for lymphoma and other malignancies, recipients of solid organ transplants especially lung followed by heart, small bowel, kidney and liver and

allogenic HSCT, patients receiving long-term treatment with steroids or other immunosuppressive agents, alcoholism and retroviral infection.[17] Use of Azathioprine and prednisone has a high risk than cyclosporine and prednisone.[18] In autoimmune diseases and rheumatic heart disorders, long term and high dose use of corticosteroids and concomitant use of immunosuppressant's along with pre-existing pulmonary diseases and diabetes mellitus are reported to be most common risk factors.[19]

Associated Co-Morbidities

The infection can also occur as a co-infection with tuberculosis or CMV infection in patients with HIV infection. Association with co-morbidities like Diabetes mellitus, chronic alcoholism, pulmonary obstructive disease, structural lung abnormalities, Pneumoconiosis and bronchiectasis are reported.[20]

Pathogenesis

Nocardia asteroides is the species of Nocardia most frequently infecting humans and most cases occur as an opportunistic infection in the immunocompromised patients. The infection caused is known as NOCARDIOSIS. The exact mechanism is unknown; the main route of acquisition of pulmonary Nocardiosis is probably through direct inhalation of contaminated particles. Most of the cases start as minor respiratory syndromes that self-limit spontaneously. In some patients, the infection spreads starting from lung with a particular predilection for the brain, skin, and sub cutaneous tissues. Infection with Nocardia may also occur by direct inoculation through the skin, producing cellulitis, lymphagnitis or both.[21]

Intravenous drug abuse may provide alternative route of entry, i.e. direct inoculation through the skin, leading to the abscesses, especially in recent venopuncture sites. Surgical wound infections due to N.farcinia have also been reported.[22]

Types of Nocardia Infections

A. Nocardiosis of Lung: Pulmonary Nocardiosis is the most common manifestation of nocardial infection. Involvement of Lung occurs in 70% of all cases.[23] Nocardia asteroides are the most common organism though 9 species have been associated with human disease. Pulmonary Nocardiosis can rarely occur through gastrointestinal tract especially through appendix. Pulmonary infection rarely follows dental procedures, periodontal infection. Symptoms include cough, fever, dyspnea, chest pain, weight loss, and hemoptysis. It can present as acute, sub-acute and chronic with reemission and exacerbations. There is usually

delay in diagnosis due to lack of clinical suspicion and non specific features. Lung involvement may be part of disseminated Nocardiosis. Radiologically, pulmonary Nocardiosis presents mainly as multiple pulmonary nodules, consolidations, cavity bilateral in immunocompetent and immunocompromised patients[24] other clinical findings include broncheictasis, pleural thickening, mass like consolidation, ground glass opacity, reticular infiltration, pericardial effusion.[25] CT-scan is more sensitive and shows lesions than chest radiograph.

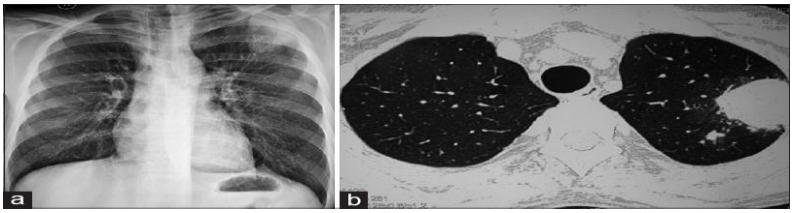

Figure 1: (a) a chest radiograph of a renal allograft recipient infected with Nocardia spp. showing left upper lobe mass lesion. (b) Corresponding computerized tomography revealing mass-like consolidation.[26]

B. Nocardiosis of CNS: The most common extra pulmonary site of Nocardia species is the CNS. It is uncommon but it is clinically important as it is associated with high mortality. It accounts for 2% brain abscess.[27] It can affect the brain and spinal cord. The presentation usually includes headache, seizures, cord compression, vomiting, and focal neurological deficit. Radiological features include brain or spinal cord as parenchymal lesions. Multi focal ring enhancing lesions are more dominant of brain. The risk factors for the CNS infection include Meningitis and granuloma.[28]

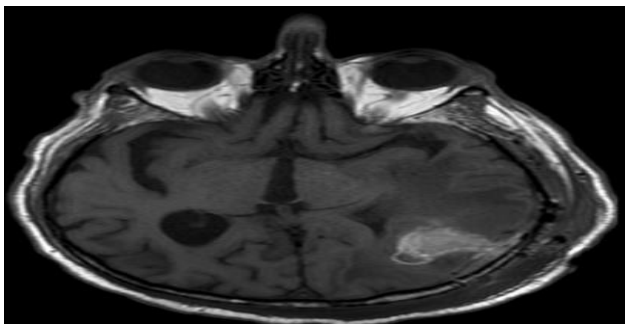

Figure 2: Brain MRI with abscess due to Nocardia in a diabetic patient.[29]

C. Nocardia of Skin: Cutaneous infection follows traumatic introduction of Nocardia into sub cutaneous tissues. A cutaneous infection takes one of the three forms:

A. Cellulitis: It is a slowly developing sub acute cellulitis. It is firm and may involve underlying muscles, bones or joints.[30] It generally begins 1-3 after a recognized breach of the skin, often with soil contamination. Dissemination is very rare. N.brasiliensis is the most common isolate, but N.asteroides is often isolated from people living cold climates.[31]

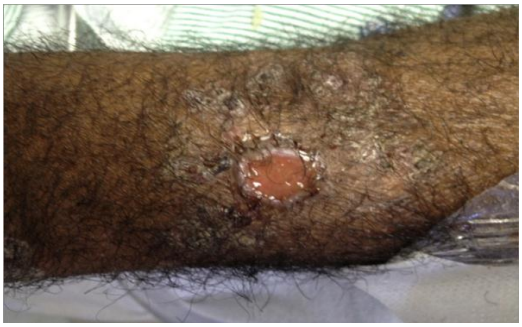

Figure 3: Ulcerated lesion around the brown-violaceous papules in the left upper extremity.[32]

B. Lymphocutaneous Disease: It is usually begins as a pyodermatous lesion at the site of inoculation, with central ulceration. Subcutaneous nodules often seen along the lymphatics draining the primary lesion. Most cases are due to N.brasiliensis.

C. Actinomycetoma: Cutaneous infections may result in fungating tumor like masses called Mycetoma. The exudate infrequently contains white granules. The suppurative swelling has got multiple sinus tracts and the draining sinuses usually open on the surface.[30] Lesions typically develop on the feet or hands but may involve the posterior part of the neck, the upper back, the head and other sites. The discharge is serous or purulent may be bloody and often contains 0.1-0.2 mm while granules consists of masses of mycelia.[31]

D. Nocardia of Eye: Nocardia species usually N.asteroides are uncommon causes of sub acute keratitis, usually after eye trauma. Nocardial endopthalmitis can develop after eye surgery. In one series, nocardiae accounted for more than half of culture-proved cases of endopthalmitis after cataract surgery. It can also occur during disseminated disease. Nocardial infection of lachrymal glands has also been reported.

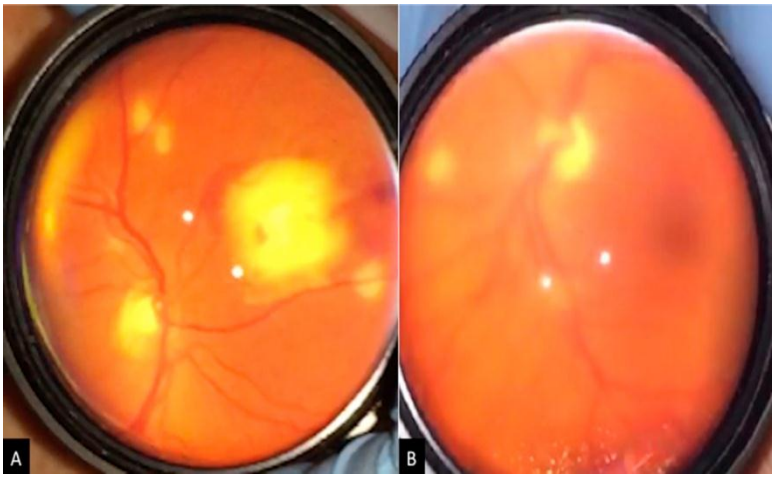

Figure 4: Dilated fundus of Left and Right Eye revealing multiple cream colored sub retinal lesions and large 2 disc diameter elevated sub retinal lesion with surrounding hemorrhages.[32]

Diagnosis: Nocardiosis is difficult to diagnose clinically, radiologically and histo-pathologically. Routine laboratory investigations reveal leukocytosis with neutrophilia. There will be an increase in inflammatory markers. Radiological findings depend on the site of infection. A definitive diagnosis usually depends on the demonstration of organisms in smears or sections examined microscopically together with isolation and identification by culture.[33] The specimens for the laboratory evaluation include sputum, BAL fluid, exudates, CSF or material obtained by FNAC and biopsy.[34]

Direct Microscopy

It is the most important method for identification of Nocardia species. The material received is spread on the glass slide and examined microscopically. Granules or clumps of organisms are crushed between glass slides and morphology is observed. Nocardia species are gram positive and the filaments are so long [beaded], thin and branch at right angles.

These are weakly acid fast. So, Gram's stain and modified Kinyoun acid-fast stain are to be done when Nocardia infection is suspected clinically.[35]

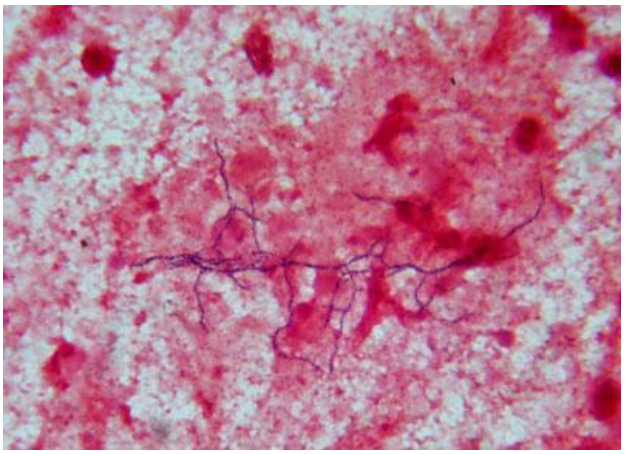

Figure 5: Bronchial Wash Direct Gram Stain (Showing filamentous, branching gram positive bacilli).

Nocardial growth is so different from that of more common pathogens that the laboratory should be altered when Nocardiosis is identified in order to maximize the isolation of Nocardia.

In nocardial pneumonia, sputum smears are often negative. Unless the diagnosis can be made in smear negative cases by sampling in more accessible sites, bronchoscopy or lung aspiration is necessary. Tracheal aspiration should be avoided, as it frequently leads to nocardial cellulitis in tissues around the puncture wound.[35]

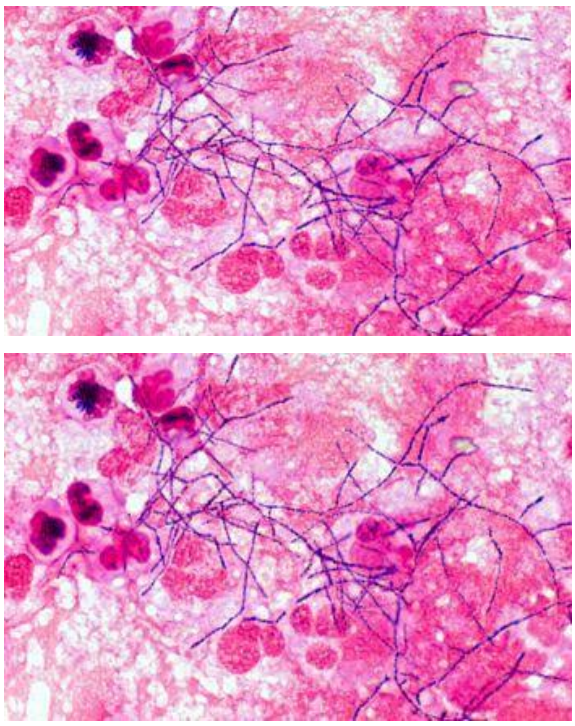

Figure 6: Modified Kinyoun acid-fast stain of Nocardia asteroides.

Modified Kinyoun Stain: It is a method of staining the acid fast micro organisms, specifically mycobacterium and Nocardia. The procedure for Kinyoun stain is similar to the ziehl-neelson method, but does not involve the heating the slides being stained as it contains greater concentration of phenol and basic fuchsin. It uses the carbol fuchsin as a primary stain followed by decolorization with an acid-alcohol solution and methylene blue as counter stain. When viewed under microscope the stain shows acid fast organisms as red colored and non acid fast organisms as blue.

Modifications: A solution of 1% sulphuric acid can be substituted in place of 3% HCL solution. This sulphuric acid does not decolorize as strongly as hydrochloric acid.

Culture Studies: Nocardia species are aerobic and grow on blood agar or saborauds agar. However, growth on blood agar may be slow and incubation of 48 hours is necessary. The culture shows dry granular wrinkled yellowish white colonies of Nocardia asteroides.

Figure 7: Saborauds dextrose agar plate showing dry, pale yellowish orange colonies of Nocardia asteroides after two days of incubation of pleural fluid at 37^0C.

Molecular Methods: The Nocardia species can also be identified by PCR and 16SrDNA sequencing which are very accurate methods of diagnosis.[36]

Treatment

Sulfonamides are the Drug of choice for Nocardiosis. The combination of sulfamethoxazole and Trimethoprim is probably equivalent to sulfonamides. The combination is most effective but has a greater risk of hematologic toxicity. Dose of SMX 50-100 mg per kg and 10-20 mg of TMP per kg should be given each day in two divided doses. Later, the daily doses can be decreased to as little as 5mg per kg and 25 mg per kg respectively.

Minocycline is the best established alternative oral drug and should be given in doses of 100-200 mg twice a day. Linezolid appears to be active in vitro and has been effective in some cases at a dose of 1200 mg. N.nova infections can be treated with erythromycin at 500-750 mg per kg 4 times a day and ampicillin 1gm 4 times a day.

Amikacin, the best established parenteral drug is given at a dose of 5-7.5 mg/kg every 12 hours. Serum levels should be monitored during prolonged therapy in patients with diminished renal function and in the elderly. Newer, beta-lactams like cefotaxime- 6gm, ceftizoxime-6gm, ceftriaxone-1-2gm, imepenam-2gm per day are usually effective. These agents may be less effective in some cases caused by N.farcinia.[37]

Surgery may be particularly important for patients with brain abscesses, pericardial disease, Mycetoma, emphysemas, mediastinal collections and some ocular infections. In patients with thick-walled multiloculated abscesses, including patients with mycetomas, therapeutic aspiration may not be sufficient and more aggressive surgical debridement may be necessary. CNS disease that fails to respond to therapy may require aspiration or craniotomy; both were found to be equally effective in one series.

Surgery should be considered when patients have not improved or have clinically deteriorated within the first 2 weeks of therapy, when lesions have not decreased in size on brain imaging within one month of therapy, and when abscesses are generally large or very accessible.[38]

CONCLUSION

Increases in the number of patients receiving immunosuppressive therapies for solid organ or hematopoietic stem cell transplants, hematologic and solid tissue cancers, and auto inflammatory conditions, ensure that Nocardia will remain a formidable pathogen.

Clinicians, chest disease specialists, and clinical microbiologists should consider carefully the possibility of human Nocardiosis.

Clinical microbiology laboratories must follow standard protocols when performing sputum cultures and consider isolation and identification of Nocardia species from various clinical specimens for better patient management in case of chest infections.

Although this organism is capable of producing serious and metastatic disease in the appropriate host, early recognition and initiation of appropriate treatment can lead to successful outcomes.

ABBREVIATIONS

CD^{4+}- Cluster of differentiation, AIDS-Acquired immune deficiency syndrome, HIV-Human immunodeficiency virus, CMV-Cytomegalo virus, SMX-Sulfamethoxazole, TMP-Trimethoprim.

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