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Disseminated Nocardiosis in a Patient with Lepromatous Leprosy

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Abstract Disseminated nocardiosis is a serious opportunistic infection with very high mortality, especially in individuals with defective cell mediated immunity. The use of immunosuppressant therapy is associated with increased risk of opportunistic infections and in south-east Asian countries where tuberculosis is widely prevalent, Nocardia is an often overlooked and under diagnosed pathogen, with clinically very similar presentations. Here we report a case of disseminated nocardiosis presenting as multifocal brain, in a patient with Lepromatous Leprosy, who was on immunosuppressive therapy for Type 2 Lepra reactions. An early diagnosis requires high index of suspicion and interventions like stereotactic brain surgery and is a determinant for positive clinical outcome.

Keywords: *brain abscess, disseminated nocardiosis, immunesuppresant therapy, opportunistic infections, leprosy, nocardia*

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1. Introduction

Nocardiosis is a rare opportunistic disease that affects patients with impaired cell mediated immunity, which includes solid organ and hematopoietic stem cell transplants, lymphoproliferative malignancies, Human Immunodeficiency Virus (HIV), diabetes mellitus, long term use of steroids or other immunosuppressants and autoimmune diseases. It commonly presents as pulmonary disease with features almost clinically indistinguishable from tuberculosis or fungal diseases, in the form of consolidation, pleural effusion, nodules or cavitary lesions. Nocardiosis often follows hematogenous dissemination or contiguous spread from lung. Abscess formation is characteristic and central nervous system (CNS) is the most common extra-pulmonary location for nocardiosis, it can also manifest as lymphocutaneous nocardiosis, pericarditis, synovitis, soft tissue infections, keratitis and abscesses in other organ tissues.

Here we report the case of a 30 year old manual labourer who was previously diagnosed to have Lepromatous Leprosy in Type 2 Lepra reaction, who developed disseminated nocardiosis while on treatment with oral steroids and immunosuppressants.

2. Case Report

A thirty seven year old gentleman, painter by profession; with no history of diabetes mellitus, no history of smoking, or alcoholism, but history of occasional use of tobacco for chewing, initially presented to a general practitioner with complaints of numbness of both upper and lower limbs for two months and associated anesthetic maculopapular lesions over the trunk. A split skin smear from ear-lobe was taken for acid-fast staining and it showed mycobacterium leprae. He was started on anti lepromatous leprosy regimen, Dapsone, Clofazamine and Rifampicin as per the National Anti-Leprosy Treatment Protocol (India); Multibacillary - Multi Drug Therapy (MB-MDT) from government hospital. Meanwhile, the patient developed weakness of left upper-limb with ulnar claw-hand, and physiotherapy with rehabilitation therapy was started. Patient was apparently well and adhered to the treatment for next one month, but he noticed multiple painful nodular eruptions over bony prominences of both arms and legs which appeared in crops and resolved spontaneously, and lower motor neuron weakness of left side of the face. Further evaluation by the dermatologist showed features of lepra reaction (Erythema Nodosum Leprosum), and the patient was started on Prednisolone with Azathioprine due to initial non-response and he continued the medications with regular follow up.

Patient developed cough and low grade fever, two months into the immunosuppressive therapy. No history of breathlessness or chest pain. Clinical examination showed small discrete lymph-node in the neck. No hepatoslpenomegaly. Radiological evaluation showed left sided consolidation with synpneumonic effusion. A pleural fluid study was done which showed exudative type of effusion and the Mantoux test was negative. Sputum for acid fast bacilli (AFB) staining was negative and cultures did not yield any organisms. Pleural fluid Adenosine deaminase level was estimated and was found to be low.

Patient was treated with antibiotics but due to non-response he was empirically started on Anti-Tuberculosis Therapy

(ATT) after which he showed symptomatic improvement and was discharged on anti-tuberculosis drugs.

After two weeks of ATT the patient presented with fever, left sided knee joint pain and antalgic gait. Clinical evaluation showed popliteal abscess and the pus culture was suggestive of nocardia species. The patient was started on antibiotics, and was discharged following clinical improvement.

The patient then presented after 1 month with history of tonic-clonic movements of left side of the body, followed by left hemiparesis. Physical examination showed weakness of the left upper and lower limb, with sparing of cranial nerves. Patient developed persistent head ache, vomiting and features of raised intracranial tension which progressed during in-patient stay.

The CT Brain showed cerebral edema and multiple ring-enhancing lesions and subsequently an MRI scan with MR spectroscopy was performed which showed conglomerate ring enhancing lesions in right temporal lobe measuring 1.6 x 1.5 cm and two ring enhancing lesions in right paracentral parietal region, the largest measuring 2.4 x 1.9 cm. Both lesions showed central diffusion restriction indicating possibility of abscesses, with T2 hypo-intense rim favouring granulomatous infection and MR spectroscopy showed elevated lipid and lactate peaks, suggestive of granulomatous disease with abscess.

In view of worsening symptoms, a decompression craniotomy with excision of the lesions was done. The gross specimen was a thick walled abscess with granuloma formation and contained copious amounts of pus. Histopathological examination showed neutrophilic abscesses surrounded by fibrous tissue with epithelioid granulomas and Langerhans giant cells along with mixed type of inflammatory infiltrates. Gomoris Methenamine Silver staining and Gram staining revealed thin (1 micron) filamentous organisms with right angled branching and beaded appearance in areas, consistent with an abscess due to Nocardia species.

Table 1. Laboratory investigations

Hemogram	**Immunology, Serology**	**Biochemistry**
Hb 13.1	HIV – negative	FBS – 99
TC 13400	HBsAg – negative	HbA1C -5.4%
Neutrophils 68%	HCV – negative	Blood Urea - 24
Lymphocytes 21%	VDRL – non reactive	S.Creatinine 0.9
Eosinophils 8%		
Monocytes 2%	Mantoux Test – non reactive	SGOT -24
Basophils 1%		SGPT – 30
Platelet Count 2.34 lacs		
ESR 95		Pleural fluid ADA – 11 (significant if > 30)

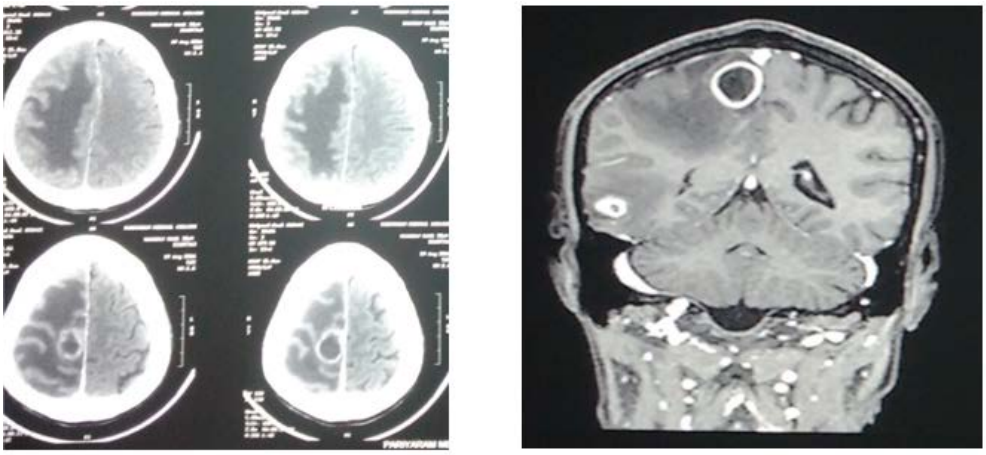

Figure 1. CT Brain and MRI Brain showing ring enhancing lesions

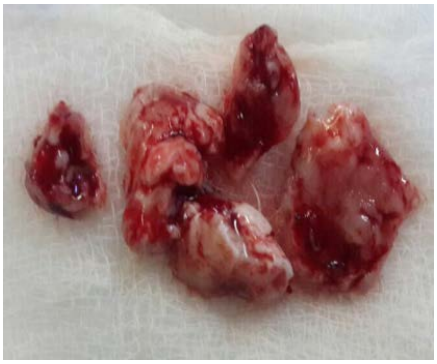

Figure 2. Granulomatous lesion excised from right parietal lobe of brain

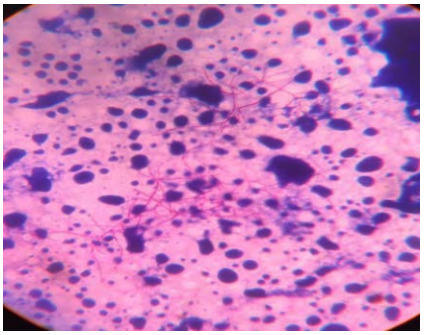

Figure 3. Gram positive bacilli in chains with right angled branching, suggestive of Nocardia species

Cultures reported Nocardia species sensitive to cotrimoxazole and linezolid. Subsequently, he was treated according to culture and sensitivity reports and his clinical condition improved.

The patient is on regular follow up and has shown steady improvement in his general condition and neurological status.

3. Discussion

Nocardia species are Gram positive, aerobic, branching filamentous bacteria belonging to the actinomycetes group which can be seen in soil and dust everywhere [1]. The main species causing human infection are *N.asteroids*, *N.brasiliensis*, and *N.caviae*. Nocardia is encountered as a rare opportunistic infection in immunocompromised states like organ transplants, leukaemia, HIV, chemotherapy, immunosuppressant therapy, diabetes mellitus, and autoimmune diseases [1,2]. The concomitant use of other immunosuppressants along with steroids pose higher risk as is seen in our case [1,2]. The pathogen most commonly involves pulmonary system with varying presentations-consolidation, lung nodules, pleural effusion, and necrotising lesions resulting in cavities. Dissemination involves primarily haematogenous spread-most commonly into brain and also contiguous spread to adjacent organs [1]. Clinically, these lesions are indistinguishable from that of tuberculosis or filamentous fungal infections. Cutaneous nocardiosis can resemble soft tissue infections produced by staphylococcus or streptococci, however this form is usually more indolent [3]. The infection can involve lymph nodes singly or in chains, lymphocutaneous form of the disease is also called sporotrichoid nocardiosis, given its similarity to presentation of sporotrichosis [2]. Hematogenous spread can involve eyes, heart valves, liver, spleen, adrenal glands, thyroid gland, intestine and other organ tissues [1,2,3]. Nocardia brain abscesses is a very severe infection which carries the highest mortality rate among all bacterial cerebral abscesses [4]. According to certain studies, the mortality rate in immunocompromised patients was 55% and in immunocompetent patients was 20%; with multiple abscesses the mortality remains as high as 66% [5,6]. The clinical presentation of nocardial brain abscess is indistinguishable from other bacterial brain abscesses or metastatic malignancies. Seizures and focal neurological deficits are the commonest manifestations. Brain imaging mostly shows ring enhancing lesions. In this case MRI brain with spectroscopy helped to clinch the diagnosis of the ring enhancing lesion as brain abscess-homogenous hyper intense lesions with central diffusion restriction and T2 hypointense rim around the lesions, with spectroscopy showing lipids and lactate peaks. [7] Diagnosis is confirmed by culture of aspirates from the site of infection. In our case, early surgical intervention helped to prove Nocardia species infection in brain. Complete excision of lesions with prolonged antibiotic therapy is needed to prevent relapses. Optimal antibiotic treatments have not been established for disseminated nocardiosis due to variable susceptibility patterns. Sulfonamides have been the antimicrobial of choice. [1,5,6,8] Trimethoprim-sulfamethoxazole (TMP-SMX) is the most commonly used sulfonamide preparation in India. Divided doses of 5-10 mg/kg per day of trimethoprim (or 25-50 mg/kg per day of sulfamethoxazole) are recommended. Alternative antimicrobials include amikacin, imipenem, linezolid, and minocycline. Combination therapy with TMP-SMX and one of the primary agents has been recommended for serious systemic disease [9]. In this case we used linezolid in combination with TMP-SMX. The duration of therapy is uncertain but should be prolonged considering the numbers of relapses after short course therapies, so therapy could continue until clinical recovery occurs.

Open Access case reports of abscess in the thigh in a lepromatous patient with corticosteroid was reported by de Nardo [3]. Cerebral abscess is the most common type of nervous system involvement but cerebellar abscess, paraplegia are also reported. [10] Primary cutaneous nocardiosis associated with lepromatous leprosy was reported by Savithri M Nueune, et all from Department of Pathology, from Karnataka [11].

Our case had some rare clinical associations. The patient was suffering from lepromatous leprosy and was debilitated by the disease related complications. Subsequently, patient developed a Type 2 Lepra reaction- Erythema Nodosum Leprosum (ENL) and was on immunosuppressive therapy.

Minero et all in their study observed that nearly 62% cases of disseminated nocardia had steroid as predisposing factor [12]. Simultaneous infections with acid fast bacilli like mycobacterium leprae and nocardia is uncommon, hence is a challenge to diagnosis.

4. Conclusion

Disseminated nocardiosis is a rare opportunistic infection among immunocompromised patients with very high mortality rates. A high index of suspicion is needed, along with early surgical intervention to make a diagnosis of cerebral nocardiosis due to its similarity to mycobacterial and fungal infections. Prolonged sequential targeted antimicrobial therapy can improve prognosis although continuous follow up is mandatory. From literature review, this is the first case report of disseminated nocardiosis presenting as cerebral abscess reported in a patient treated with immunosuppressants for leprosy and lepra reactions. Proactive surgical intervention with concurrent prolonged antibiotic therapy appear most likely to give positive outcome.

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