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Case Report

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Disseminated Nocardiosis caused by Nocardia concava in a post-renal transplant patient: A Case Report

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ABSTRACT

Disseminated nocardiosis is rare and often late presenting infection with a mortality rate of 85% in immunocompromised individuals. **Case**- A 50 year old male, post-renal transplant 6 months back, on maintenance immunosuppression with tacrolimus and prednisolone, following renal transplant he had multiple episodes of urinary tract infection with multidrug resistant *Klebsiella pneumoniae*. The patient presented with continuous fever with chills and rigor and cough for 7 days. Computed Tomography of Thorax revealed focal patchy areas, ground glass opacity and centrilobular nodules with tree in bud pattern, calcified subpleural nodules in right upper lobe and calcified mediastinal lymph nodes. On admission blood culture was sent, it flagged on day 2 of incubation. Gram stain revealed the presence of gram positive bacteria, modified acid fast bacilli smear was positive for weakly acid fast branching, filamentous bacilli. The growth on blood culture was confirmed to be *Nocardia concava*, by 16srRNA sequencing. **Conclusion**- Radiological evidence of nodular lesions in the lungs in a post-renal transplant recipient especially within 6 months should arise a high suspicion of pulmonary nocardiosis. Nocardia must be identified upto species level by 16srRNA sequencing, as treatment varies based on the species and some of the species can be resistant to cotrimoxazole. Infection with *Nocardia concava* must be treated with a combination of trimethoprim-sulfamethoxazole and linezolid.

Key Words: *Nocardia Concava, Disseminated Nocardiosis, renal transplant recipient, immune compromised patients, pulmonary nodules*

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INTRODUCTION

Nocardia are obligate aerobic, gram positive, beaded, partially acid fast, branching bacilli, present in soil and decaying matter.They are transmitted by inhalation or direct inoculation into the skin, resulting in cutaneous, pulmonary and disseminated infections[1].The most commonly isolated species is *Nocardia asteroides, Nocardia brasilensis, Nocardia caviae*. Infections with Nocardia species is rare, however in immunocompromised host such as organ transplant recipients, patients with malignancy, patients on dialysis, HIV, chronic lung disease, diabetes, patients on prolonged corticosteroid therapy etc, it can cause acute, sub-acute or chronic disease[1].Clinical symptoms include fever, fatigue, productive or non-productive cough, dyspnea and weightloss. Clinical symptoms of Nocardia and Actinomycetes are almost similar, however Nocardia has a greater propensity of hematogenous dissemination than the latter. Microbiological identification of Nocardia include growth on culture, gram staining and modified acid fast staining. Antibiotic therapy for Nocardia is highly variable among each species, as there are no specific guidelines for antibiotic susceptibility testing, it is essential to select antibiotics based on the molecular taxonomy. Molecular methods like 16S rRNA sequencing plays a key role in rapid identification of species which aid in initiation of appropriate antibiotics.

Although hsp65 was widely used in the past for identification of Nocardia species as they contain more microheterogeneity regions than 16S rRNA and is a better discriminatory, there are only fewer sequences of hsp65 gene of Nocardia species in public databases for comparisons, which limits its use for identification. On comparing these two gene sequences, the mean percentage dissimilarity in identification was found to be higher with hsp65 gene sequences. For these reasons, 16S rRNA sequencing is considered as a better method for identification of Nocardia upto species level[2]. Here we present a rare case of Disseminated Nocardiosis caused by *Nocardia concava* in a post-renal transplant recipient.

CASE PRESENTATION

A man in his 50's with renal failure secondary to focal segmental glomerulosclerosis underwent living related renal transplant 6 months prior. He underwent induction immunosuppression with Basliximab, and was on maintanence immunosuppression on Tacrolimus (3mg twice daily), Prednisolone (10mg once a day).

He was a known case of systemic hypertension for past 10 years and was diagnosed with new onset diabetes mellitus.Post-renal transplant, patient had multiple episodes of urinary tract infection with multidrug resistant *Klebsiella pneumoniae* for which he was treated with piperacillin-tazobactam, meropenem, ceftazidime-avibactam-aztreonam combination.

Patient presented to the nephrology clinic with high grade fever with chills and rigor,cough and decreased urine output for the previous 3 days.Baseline investigations were done, CBC- TC-6530, Hb-10.2, BUN-35, Creatinine-2.2. Computed Tomography of kidneys, ureters, and bladder revealed graft pyelonephritis with infrarenal fluid collection. Ultrasound guided aspiration of the fluid sent for culture was negative. However, ceftazidime-avibactam was started in view of graft pyelonephiritis. Computed Tomography of Thorax revealed focal patchy areas, ground glass opacity and centrilobular nodules with tree in bud pattern, calcified subpleural nodules in right upper lobe and calcified mediastinal lymph nodes. Bronchoalveolar lavage was done and sample was sent for culture, acid fast smear, fungal smear and GeneXpert, all of which turned to be negative. Serum galactomannan was positive with an index of 1.7. Respiratory fungal infection was suspected and patient was started on intravenous voriconazole, however patient developed symptoms of tacrolimus toxicity hence was switched over to intravenous caspofungin for 3 days, but was terminated as he developed hot flushes. The patient continued to have fever spikes; hence blood culture was sent. Patient had respiratory distress and decrease in saturation ensued, leading to intubation. He had oliguria, severe metabolic acidosis and hyperkalemia, and was started on continuous renal replacement therapy but it was terminated in view of hypotension eventually requiring triple inotropic support. Patient had cardiac arrest and despite maximum resuscitative measures he could not be revived.

MICROBIOLOGICAL DIAGNOSIS

Blood culture flagged on day 2 of incubation. Gram stain revealed the presence of gram positive, branching, beaded bacilli . It was subcultured on blood agar and chocolate agar which grew cream colored, dry, chalky powdery colonies after 48hours of incubation at room temperature. Eubacterial PCR was done using the colonies, it identified the presence of *Nocardia concava*, which was confirmed by 16srRNA gene sequencing. Blast search of the sequence was done using the taxonomy browser of the National Center for Biotechnology Information (NCBI). The 614 bp of the sequence revealed a 100% match with *Nocardia Concava*. The sequence has been submitted to Gen-Bank with accession number OR259036.

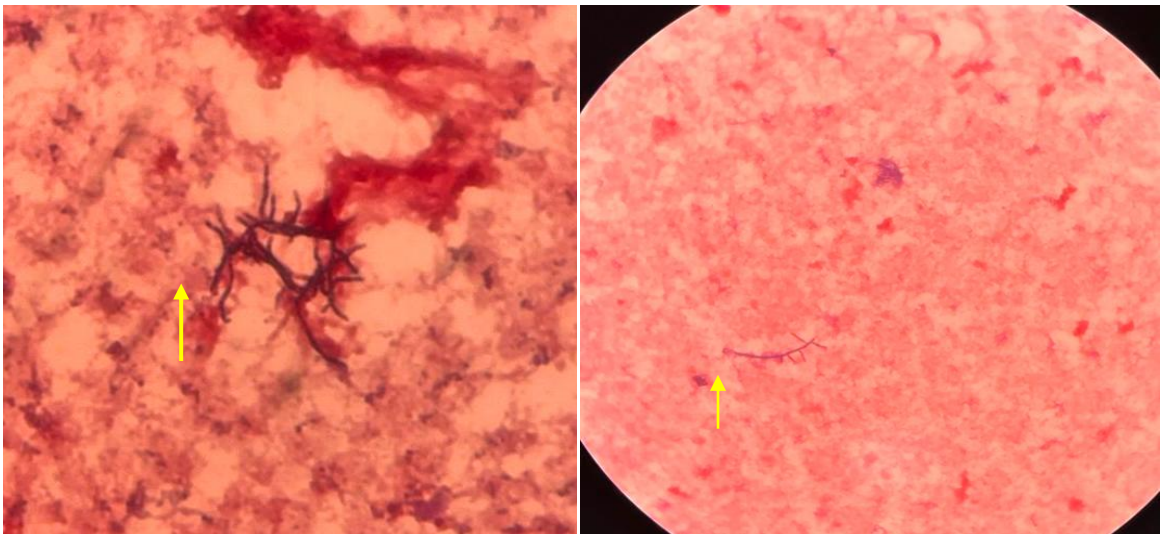

FIGURE-1: Gram stain showing gram positive, branching, beaded bacilli seen in microscopy

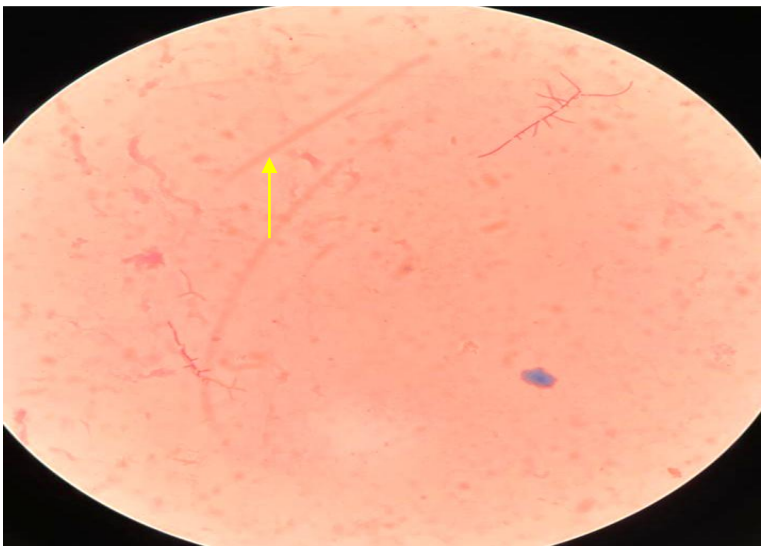

FIGURE-2: Modified Acid Fast Bacilli smear showing weakly acid fast branching, filamentous bacilli/ Nocardia

FIGURE-3: Dry, chalky, powdery colony colonies on blood agar and chocolate agar.

DISCUSSION

Nocardia are ubiquitous saprophyte.Some of the rarely occurring species include *Nocardia concave*, *Nocardia blacklockiae, Nocardia pseudobrasilliensis, Nocardia africana*.[9] *Nocardia concava* causes primary cutaneous infections in immunocompetent host, however in immunocompromised individuals with deficiency of cell mediated immunity, the cutaneous lesions disseminate to the lungs and the central nervous system. Involvement of skin, lungs and brain are highly suggestive of disseminated nocardiosis, although it can also manifest as thyroid abscess, endophthalmitis, hepatic and renal abscesses. Disseminated nocardiosis is defined as the involvement of atleast two non-contiguous organs and/or demonstration of bloodstream infection[8].The mortality rate of disseminated infection hovers around 85% due to its late presentation with no specific indicative signs in early stages.Species identification in Nocardia is important as the antibiotic susceptibility is highly variable among each species. Identification of species cannot be done using biochemicals as they lack sensitivity and specificity[8]. Therefore, molecular diagnostic methodusing 16S rRNA sequencing is essential for aiding in accurate diagnosis. Most Nocardia species are susceptible to linezolid, amikacin (exception some strains of *Nocardia wallacei*), trimethoprim-sulfamethoxazole (TMP-SMX) (exception some strains of *Nocardia farcinia*)[9]. Carbapenams can be used in disseminated nocardia infection, but some of the Nocardia species such as *Nocardia concava, Nocardia brasiliensis, Nocardia otitidiscaviarum* are known to be resistant to Imipenam[7].Empirical therapy with TMP-SMX alone may not be sufficient to control the infection as some species of Nocardia can have reduced susceptibility or exhibit intrinsic resistance to the drug. In this case patient had infection with *Nocardia concava* and primary site of infection was possibly the lung, which later disseminated through bloodstream. Nodular lesions on CT-Thorax in a renal transplant recipient especially 6 months following the transplant should raise a high suspicion of pulmonary nocardiosis, so as to aid in prompt diagnosis and early treatment[3,4].

Patients suspected to have invasive respiratory fungal infection, can give false positive galactomannan index, if on treatment with betalactam antibiotics[5],as it is evident in the present case.This patient was on trimethoprim-sulfamethoxazole as a part of post-transplant prophylaxis, however the infection persisted.

In a report from Japan a 73-year-old patient with disseminated *Nocardia concava* infection was successfully treated with a combination therapy of trimethoprim-sulfamethoxazole, linezolid, minocycline[6]. In another, a 42 years old patient in China with disseminated *Nocardia concava* presented with an auricular swelling and blood stream infection was also successfully treated with sulphadiazine sodium, ciprofloxacin and amikacin sulphate[7]. Early identification of the causative species aided in initiation of targeted combination therapy in both the above-mentioned patients. It has been proposed that in transplant recipient where the degree of immunosuppression is high, a higher dose of TMP-SMX is warranted to obtain complete eradication and prevent complications[8]. In the present case the treatment was delayed due to the misinterpretation of CT-Thorax findings and the false positive galactomannan assay titres leading to mortality. Hence a high index of suspicion is warranted in transplant recipients presenting with clinical signs and symptoms and CT-Thorax findings as was present in the above case.

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