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Case Report

Successful treatment of disseminated nocardiosis in a renal transplant recipient

Brig A.K. Hooda^{a,*}, Ashish Nandwani^b, Col Jasmeet Kaur^c,
Col J.S. Bishnoi^d, Col R.K. Nair^d

^a Consultant (Medicine & Nephrology), Army Hosp (R&R), Delhi Cantt-10, India

^b Fellow in Nephrology, The Ottawa Hospital, Canada

^c Senior Advisor (Pathology & Transplant Immunology), CH (CC), Lucknow, India

^d Senior Advisor (Medicine & Nephrology), Command Hospital (WC), Chandimandir, India

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Introduction

Nocardiosis, a suppurative disease caused by aerobic actinomycetes is an opportunistic infection with unfavorable prognosis in renal transplant recipients and high mortality. The disease manifests as cutaneous, subcutaneous, pulmonary and systemic infection. We present a case of disseminated nocardiosis in a deceased donor renal transplant recipient who presented with pulmonary and cerebral manifestations at 3 month post-transplant period and responded to treatment with co-trimoxazole and meropenem.

Case report

A 16 years old female patient, a case of chronic glomerulonephritis underwent a deceased donor renal transplant on 7th September, 2008. Her immunosuppression consisted of triple drug immunosuppression with tacrolimus in a dose of 0.12 mg/kg, mycophenolate mofetil 750 mg BD and steroids. She also received induction with anti-thymocyte globulin. Her immediate post-transplant course was uneventful and creatinine settled to 1.2 mg/dl on day 5 post-transplant. She had rise in creatinine from 0.8 mg% to 1.4 mg% on day 15 and graft biopsy showed borderline cellular rejection. She was treated with pulse methylprednisolone therapy (250 mg daily for 3 days) and creatinine decreased to 1.0 mg/dl. Her graft functions remained stable thereafter.

In December 2008, she developed low grade intermittent fever, cough with mucopurulent sputum and pleuritic chest pain. There was no history of breathlessness or any urinary complaints. Clinical examination revealed ill looking, febrile patient with pulse 116/min and BP 120/70 mmHg. There were discrete papular lesions on back and thighs. Chest examination revealed left infrascapular crackles and pleural rub. Examination of other systems was unremarkable.

Investigations revealed hemoglobin of 11.5 gm/dl, total white cell count of 8500/mm³, platelet count 136,000/cm,

* Corresponding author. Tel.: +91 9874361110.

E-mail address: ashokhooda@hotmail.com (A.K. Hooda).

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serum creatinine 2.3 mg/dl, serum bilirubin 0.4 mg/dl, AST 39 U/L, ALT 28 U/L and normal lipid profile. Her urine examination was unremarkable. Tacrolimus blood level was 8.62 ng/ml. Chest radiograph showed multiple non-homogenous opacities in right middle and left middle and lower zones. She was started on broad spectrum antibiotic cover with Cefoperazone–Sulbactam and Levofloxacin. Sputum examination showed gram positive cocci and budding yeast forms. Zeihl Neelson stain was negative for acid-fast bacilli. CT scan of chest showed bilateral areas of consolidation with halo sign in upper lobes suggestive of aspergillosis [Fig. 1]. Fiber-optic bronchoscopy was normal and broncho-alveolar lavage and transbronchial lung biopsy were not contributory. Liposomal amphotericin was added and she received a total dose of 2.8 gm over a 2-week period. She continued to be febrile and repeat chest x-ray showed bilateral cavitating lesions. CT guided fine needle aspiration cytology (FNAC) from lung lesion was done which yielded gram positive branching, delicate beaded filamentous rods on Gram's stain and Grocott's silver methenamine stain morphologically characteristic of *Nocardia* species [Fig. 2a and b]. Biopsy from skin lesion was suggestive of seborrheic keratosis.

She was started on co-trimoxazole in a dose of 2 double strength tablets thrice a day. While she had been on co-trimoxazole therapy for 8 days, she developed altered behavior. There was no focal neurological deficit or signs of meningeal irritation and fundus examination was normal. MRI brain was suggestive of inflammatory granuloma in left caudate nucleus and posterior frontal lobe and an incidental finding of arachnoid cyst in right middle cranial fossa [Fig. 3]. She was continued on co-trimoxazole and parenteral meropenem was added. She made gradual recovery and became afebrile 4 days after starting meropenem. She was continued on meropenem for 3 weeks and thereafter was continued on co-trimoxazole for 6 months. After 6 months of treatment, the pulmonary lesions resolved completely and repeat MRI brain also revealed resolving lesions. Her

Fig. 1 – CT scan of chest showing bilateral areas of consolidation.

Fig. 2 – (a) Photomicrograph showing gram positive branching, filamentous rods on Gram's stain (magnification 400X) and (b) Grocott's stain (magnification 400X).

graft function has remained normal with creatinine at last follow-up of 0.9 mg%.

Discussion

Nocardiosis is an opportunistic infection caused by Gram positive, weakly acid-fast filamentous aerobic organisms. Previously thought to be an uncommon infection, it is now believed that the disease incidence is on the rise and it

Fig. 3 – MRI brain showing inflammatory granuloma in left caudate nucleus and arachnoid cyst in right middle cranial fossa.

primarily occurs in patients with deficient cell mediated immunity especially those associated with prolonged steroid therapy, lymphoproliferative disorder, post-transplant immunosuppression and AIDS patients with CD4 count < 250/ μ L.¹ Many species are known to be pathogenic in humans of which *Nocardia asteroides* is responsible for causing the disseminated form of disease, usually in immunocompromised patients. The overall mortality associated with nocardiosis in kidney transplant recipients is 25%, but this figure increases by more than 2 fold in patients who have CNS involvement.² Despite the alarmingly high rates in mortality, medical literature on renal transplant patients with systemic nocardiosis is limited to case reports and reviews. The reported incidence in various renal transplant units worldwide ranges from 0 to 20% but in majority of the centers, the incidence is 2–4%.³ In India, an incidence of 1.37% in post-renal transplant patients has been reported in a large study spread over 30 years from south India.⁴ Pulmonary involvement was the predominant feature in this study and the main isolate was *N. asteroides*. Devi et al reported the first case from eastern India of nocardiosis in a renal transplant patient presenting as subcutaneous abscess.⁵ The lack of clinical data and consequent underreporting of nocardiosis is believed to be due to various factors. These include difficulty in disease diagnosis due to unfamiliarity with the disease, non-specific or lack of pathognomonic clinical presentation, presence of common and easily diagnosed co-infections that preclude further work-up for nocardiosis.⁶

In our case the diagnosis could be established only after 3 weeks of presentation. The routine evaluation procedures in a case of pneumonia viz. chest X-ray, CT scan, fiber-optic bronchoscopy and broncho-alveolar lavage were all non-contributory. The diagnosis was finally established by CT

guided fine needle aspiration cytology (FNAC) from the lung lesion which showed the characteristic gram positive branching, filamentous rods. Staining with modified acid-fast stain, and especially Gram stain, is particularly important to provide a rapid presumptive diagnosis of Nocardiosis while awaiting the results of the culture. Most *Nocardia* strains are acid-fast in direct smears if a weak acid is used for discoloration, but a classic Gram stain detects *Nocardia* morphotypes with equal sensitivity. Due to paucity of the specimen on FNAC, we could not culture and type the species and ascertain sensitivity pattern.

Pulmonary involvement is by far the most common nocardial disease. Pulmonary involvement includes alveolar or interstitial infiltrates, single or multiple nodules, with or without cavitation. Skin and brain are the most frequent non-pulmonary sites in nocardiosis. In immunocompromised patients infection spreads by hematogenous route and causes disseminated disease. The criteria for disseminated disease include involvement of two or more non-contiguous organs and/or central nervous system (CNS) involvement. Our case also presented with pulmonary involvement and while on therapy had dissemination of the disease to the brain. Reddy and Holly reported the first case of nocardiosis in a renal transplant recipient maintained on tacrolimus, mycophenolate mofetil (MMF) and prednisolone.⁷ They suggested that the introduction of new immunosuppressive agents may increase the incidence of nocardiosis in renal transplant recipients. Our patient was also on triple immunosuppression with tacrolimus, MMF and prednisolone. In addition, she had also received ATG for induction and subsequently methylprednisolone for treatment of an episode of acute rejection. Patients on intense immunosuppression, as was our case, are at a very high risk of developing opportunistic infections.

The treatment of choice for nocardiosis in solid organ transplantation is long-term sulfonamide therapy, frequently used as co-trimoxazole. It can be used alone or in combination with one or more of the following antimicrobial drugs – imipenem, meropenem, amikacin, ampicillin, 3rd generation cephalosporins, fluoroquinolones or minocycline.^{8,9} Ideally, therapy should be guided by culture sensitivity, and combination therapy should be considered in acutely ill patients and disseminated disease. The recommended duration of therapy ranges from 6 to 12 months. Clarithromycin can be an alternative treatment in cases of sulfonamide resistance, intolerance, or allergy.¹⁰ Our patient was initiated on treatment with co-trimoxazole, but in view of dissemination while on treatment, meropenem was added. She received co-trimoxazole for 6 months without any untoward effects of therapy and responded well.

Conclusion

CT guided FNAC from the lung lesion is a safe procedure and should be performed if other investigative procedures do not yield the diagnosis in renal transplant patients presenting with pneumonia. Even though disseminated nocardiosis in renal transplant patients carries a poor prognosis, if treated early and effectively, it can result in successful outcome.

Conflicts of interest

All authors have none to declare.

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