Paradoxical Response in Cerebral Nocardiosis in a Renal Transplant Recipient

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Abstract
Paradoxical response (PR) in patients on anti-tuberculosis drugs and immune reconstitution inflammatory syndrome (IRIS) in patients started on antiretroviral therapy are well known phenomenon. We encountered a case of a paradoxical response in cerebral nocardiosis in a renal transplant recipient. To our knowledge this phenomenon in cerebral nocardiosis has not been reported earlier in literature.

Introduction
Paradoxical response is worsening of an existing infection or disease process or appearance of a new infection/disease process after starting effective therapy and preceded by initial improvement. The immunopathogenesis of this syndrome is unclear and seems to be the result of unbalanced reconstitution of effector and regulatory T-cells, leading to exuberant immunological response in patients. PR is associated with infections like Mycobacterium tuberculosis, especially Tuberculous lymphadenopathy and meningitis, Mycobacterium avium complex infection, PCP infection and Cryptococcal meningitis.¹²³

Case Report
A 55 year old lady underwent live related kidney transplant surgery (LRKTR) in September 2011. Induction immunosuppression was with Methylprednisolone. Maintenance immunosuppression was with Tacrolimus, Mycophenolate mofetil and Deflazacort. She received TMP-SMX and VGCV prophylaxis till 6 months after transplant. She maintained stable renal function with creatinine clearance around 30%. In September 2015, she presented with a subacute onset of dry cough for 3 weeks followed by intermittent high grade fever. There was an erythematous, non tender skin nodule in the right axillary region. The cough then turned productive and headache developed. Xray chest (Figure 3) and CT chest showed consolidative lesions with signs of early breakdown. Patient’s sputum examination with modified acid fast stain confirmed the diagnosis of nocardiosis. MRI brain (Figure 1) revealed multiple small cerebral abscesses with perilesional edema located in cerebral parenchyma, posterior right basal ganglia and cerebellum. The initial treatment regimen included, TMP-SMX, Ceftriaxone, and Linezolid. This was later modified as per DST reports to TMP-SMX, Linezolid and Moxifloxacin. TMP-SMX was given in modified dose as per creatinine clearance.

One month later, she presented with two episodes of generalized tonic clonic convulsions, drowsiness and right sided monoparesis. MRI (Figure 2) brain confirmed increase in size of old lesions with increase in perilesional edema, and there were no new lesions. Chest X-ray (Figure 4) showed marked resolution of previous right upper zone lesion.

The treatment of nocardiosis in this patient was as per DST and drugs chosen had a good CNS (central nervous system) penetration, drug doses were optimized and the pulmonary lesion had shown clear improvement. Thus the clinical and radiological worsening could not be explained by failure of treatment and therefore a likelihood of paradoxical response of cerebral nocardiosis was considered. Review of doses of immunosuppression showed that an eight fold reduction of the dose of tacrolimus was done as the measured levels were too high. This change in dosage had been done three weeks prior to clinical and radiological deterioration thus showing temporal association with the neurologic manifestation.

20/9/2015: Diagnosed as disseminated nocardiosis and initiated on treatment. Tac dose – 2 mg/day, MMF – 1 gm/day Deflazacort 6 mg/day

10/10/2015: Tac levels – 40 ng/ml, hence dose reduced to 0.25 mg/day (1/8th of previous dose) Same doses of MMF and Deflazacort continued.

17/10/15: Tac levels - 4.83, tacrolimus dose kept at 0.25 mg/day. Same doses of MMF and Deflazacort continued.

8/11/15: Patient presented with seizures and altered sensorium, the Tac level was 0.27 ng/ml (A 18 fold decrease in level of immunosuppression). Treatment was as per DST, drugs used had good CNS penetration and were dosed as per creatinine clearance. The lung lesion showed resolution. Thus this can be a paradoxical response in CNS.

The patient was treated with tapering doses of dexamethasone (12 mg to 1mg and then continued on 6 mg of deflazacort). She responded well to the treatment. At 6 month follow up she is doing well, and follow up MRI brain (Figure 5) and CXR shows good resolution of all previous lesions.

Discussion
The exact pathophysiology of the PR phenomenon is not known. It has...
Hence an inflammatory response. It is not activation leading to an enhanced reduction in tacrolimus levels, which of tacrolimus dosage, caused 18 fold cell walls which are implicated in the development of an immunosuppressive microenvironment. Hence an effective treatment by itself could result in a heightened pro-inflammatory response.

Tacrolimus (Tac) is a calcineurin inhibitor (CNI) which leads to inhibition of cytokine genes concerned with T cell activation and proliferation. In our patient the eight fold reduction of tacrolimus dosage, caused 18 fold reduction in tacrolimus levels, which could have led to a rebound in T-cell activation leading to an enhanced inflammatory response. It is not common in clinical practice to have such a drastic (18 fold) reduction in the level of Tac and the consequent rebound in the inflammatory response. This may be the possible reason why PR in cerebral nocardiosis has not been reported before. A PR is well described with cryptococcal brain lesions in transplant recipients. A case of paradoxical response in a case of Nocardia transvalensis osteomyelitis and cerebral abscess is described. In this case, however the brain lesions had by PR in cerebral nocardiosis should be suspected if drastic reductions in immunosuppressive levels have occurred. Since a paradoxical response is a diagnosis of exclusion, it is very essential to rule out drug resistance before considering PR as a cause of worsening CNS manifestations.

**References**