Psychosis Associated With Tacrolimus at Therapeutic Serum Levels

N. A. Uvais, MBBS, DPM[a,*]; Benil Hafeeq, DM[b]; Jyotish Chalil Gopinathan, DM[b]; and Feroz Azlz, DM[b]

The calcineurin inhibitor tacrolimus is a commonly used immunosuppressive agent to prevent rejection of allograft after renal transplantation. It is a drug with narrow therapeutic range and has been shown to induce various neuropsychiatric side effects such as headache, paresthesia, tremor, insomnia, photophobia, confusion, seizure, posterior reversible encephalopathy, akinetic mutism, and dysarthria.[1] Very rarely, it can also precipitate psychosis, intracranial hemorrhage, aphasia, and coma in up to 5.2% of drug users.[1] However, most of the cases of manic psychosis as well as paranoid psychosis are reported in the setting of an elevated blood concentration of the drug.[1–3] Here, we report the case of a 37-year-old man who developed acute paranoid psychosis 7 months after renal transplantation, possibly induced by tacrolimus in the setting of normal blood concentration of the drug.

Case Report

A 37-year-old married man had living donor kidney preemptive transplantation surgery. He was maintained well on tablet tacrolimus 5 mg/d and tablet prednisolone 20 mg/d. During the regular nephrology follow-ups, it was learned that the patient was not taking his medication as advised and was harboring suspicions regarding his wife. As a result, he was referred to the psychiatric outpatient department. According to his wife and mother, the patient had exhibited abnormal behaviors for the last month, characterized by suspicions that his wife was trying to harm him by changing his medication dose and misusing money collected by a local organization for his treatment, irritability, and reduced sleep. The patient's mental status examination showed a clear conscious state, anxious affect, delusion of persecution, and poor insight. He had no other significant history of mood, anxiety, psychotic, or substance use disorder. There was no family history of psychiatric illnesses. He was diagnosed with psychotic disorder due to a general medical condition and was started on tablet aripiprazole 5 mg/d on an outpatient basis and was asked to follow up after 1 week.

At the follow-up appointment, his blood investigations showed a gradual increase in serum creatinine from 2.1 to 3.1 mg/dL over a period of 1 week. He was admitted to the hospital's nephrology department for worsening graft function. The patient's tacrolimus level was 8.9 ng/mL. He was managed with intravenous pulse doses of methylprednisolone (250 mg/125 mg/125 mg) with improvement in graft function and creatinine to 2 mg/dL. No BK virus viremia was identified. Baseline immunosuppression was augmented by adding azathioprine. Glimepiride was also started given his high blood sugar levels. He was discharged after 3 days of hospitalization with improved graft function.

The patient returned for a follow-up appointment in the psychiatry outpatient department after 1 week. He was better with improved sleep, and his delusions were resolving. Considering the good tolerability and effectiveness, aripiprazole was increased to 10 mg/d. He presented for another follow-up appointment 1 week later and reported significant improvement. A formal mental status examination revealed cheerful affect and good insight.

Causality assessment using Naranjo's algorithm[4] resulted in a score of 6, denoting "probable" causality. The presence of documented reports of this reaction, the positive temporal association, the ruling out of possible alternative causes, and presence of objective evidence (physician confirmation) were considered while calculating the score.

Discussion

In this case, the patient developed acute paranoid psychosis while on tacrolimus and prednisolone. Considering the presence of immunosuppressive agents with a potential to precipitate psychosis and the absence of past or family history of psychiatric illness, a diagnosis of psychotic disorder due to a general medical condition was made. Both tacrolimus and prednisolone have been shown to induce psychosis. However, prednisolone usually causes mania and psychosis at higher doses, especially in the early periods of treatment initiation.[5,6] Furthermore, aggressive treatment with intravenous steroids for the current graft dysfunction did not aggravate his psychosis, indicating that the potential cause of psychosis in our patient was probably tacrolimus. Our patient showed no signs of delirium or encephalopathy. Hence, no brain imaging or electroencephalography was conducted.

[a]Department of Psychiatry, Iqraa International Hospital and Research Centre, Calicut, Kerala, India

[b]Department of Nephrology, Iqraa International Hospital and Research Centre, Kozhikode, Kerala, India

*Corresponding author: N. A. Uvais, MBBS, DPM, Iqraa International Hospital and Research Centre, Malaparamba, Calicut, Kerala, 673009, India (druvaisna@gmail.com).

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Previous literature described cases of tacrolimus-induced hallucinations, paranoid delusions, and manic psychosis in the setting of elevated tacrolimus blood concentration.[1–3] There is a single report[7] of manic psychosis associated with subtherapeutic tacrolimus levels. This is the first case, to our knowledge, of acute paranoid psychosis induced by tacrolimus in the therapeutic range. Our case indicates that the psychosis induced by tacrolimus may not necessarily be based on its blood levels.

The mechanism by which tacrolimus causes psychosis is thought to be due to its ability to inhibit the glutamate/γ-aminobutyric acid excitatory system and its actions on the central serotonergic systems.[2] The usual strategy in the management of tacrolimus-induced psychosis would be medication cessation or reduction of the dose or switching to another immunosuppressive agent such as cyclosporine. However, as our case indicates, adding an antipsychotic agent to the treatment regimen was also shown to be effective.[8]

In conclusion, clinicians should be aware of this rare adverse effect associated with tacrolimus use for early detection and effective management. Furthermore, our case is unique in that tacrolimus in a therapeutic range precipitated psychosis, and addition of an antipsychotic to the ongoing treatment regimen effectively resulted in remission.

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