Bipolar affective disorder type I imparts significant morbidity and disease burden in the population. It is characterized by occurrence of one or more manic episodes which may be preceded or followed by a depressive or hypomanic phase. About half of these manic episodes are characterized by the presence of psychotic features. The condition is further complicated when the patient has multiple comorbid conditions. We report here the case of a Caucasian woman, aged 66 years, previously diagnosed with Bipolar disorder who developed treatment refractory mania with psychotic feature after being on the immunosuppressive agent, tacrolimus, after kidney transplantation.

Keywords: Tacrolimus, Bipolar affective disorder, Psychosis, Treatment resistance, Renal transplant

Caucasian woman, aged 66 years, with a past psychiatric history of bipolar type 1 disorder and a medical history significant for cadaveric renal transplant, aortic stenosis, end-stage renal disease, hypertension, diabetes mellitus type 2, thyroid dysfunction and right adrenal adenoma presented with acute mental status change and was referred to the psychiatric facility for disorganized thought process, pressured speech, and delusion 1.5-years post-transplant. The patient was a poor historian and collateral information was obtained from the family who informed us that she was not sleeping well for last few weeks. She would call them over the phone at night, was very talkative and reported to have pressured speech. She would talk about the male violinist “Joshua Bell”, stating that "she was Joshua" or that "Joshua is a family member". They reported that her symptoms gradually got worse in the previous few days where she became disoriented and confused and so, the family brought her to the hospital. Family also mentioned that she has a history of end-stage renal disease and had renal transplant in 1.5 years prior. She was placed on maintenance immunosuppression with tacrolimus 3 mg b.i.d., mycophenolic acid 360 mg b.i.d., and prednisone 5 mg daily after the transplant. She had post-transplant mania with psychosis one month after the transplant. She was stabilized at that time, but then had this sudden deterioration. She was recently switched from divalproex sodium to quetiapine in outpatient care because of thrombocytopenia. During the hospitalization, quetiapine was optimized to 800 mg, and a complete work up was done. However, she continued to be severely manic and her delusions appeared to be worse, now believing she was in a World War II scenario and the staff was Nazi’s. Her thought flow continued to show loose associations with recent onset of intermittent agitation. Since she was not responding to quetiapine, she was tapered off after 2 weeks and restarted divalproex sodium and risperidone with close monitoring of blood count. The divalproex sodium was increased up to 1500 mg in divided doses and optimized risperidone to 6 mg over the next 2 weeks. When her psychosis did not improve, she was switched to olanzapine oral at 5 mg in divided doses with a plan to increase up to 20 mg for the psychosis. At the same time, other causes of psychosis were explored including immunosuppressant medications and her concurrent adrenal adenoma. In a multidisciplinary approach, the psychiatry service and nephrology service discussed about the likelihood of tacrolimus-associated psychosis. The patient’s most recent tacrolimus level was 5.8 one month prior to admission, 2.3 during admission; however, 5 days after admission, it had increased to about 8.4. At that time, she was on prednisone 5 mg daily, tacrolimus 1 mg b.i.d., myfortic 360 mg oral daily. Though the most recent tacrolimus level was within therapeutic
range, it was still higher than her baseline levels. There had been only a couple case reports of psychosis associated with tacrolimus, and keeping that in mind during discussion with nephrology service, we planned cross taper of tacrolimus and initiation of cyclosporine. Tacrolimus was decreased to 1 mg daily and cyclosporine was started at 100 mg b.i.d. As cyclosporine peak and trough levels were obtained and were adequate, tacrolimus was finally tapered off completely. Finally, based on blood levels, cyclosporine was dosed at 125 mg in morning and 100 mg in evening.

Significant improvement was observed in the patient’s mental status as soon as the tacrolimus taper was started. By the time of discharge, she had better insight to her delusions and did not demonstrate bizarre behavior. She was ultimately discharged on olanzapine 20 mg at night, divalproex sodium 1500 mg at night, lorazepam 0.5 mg at night, propranolol 30 mg t.i.d. for tremors and hypertension, cyclosporine 125 mg in morning and 100 mg at night, myfortic 360 mg daily, prednisone 5 mg daily. She was continued on her home medications of amloidine 10 mg daily, alendronate 35 mg weekly, rosvuvastatin 5 mg daily, eplerenone 50 mg daily, cinacalcet 30 mg and 60 mg every other day, levothryroxine 175 µg daily. Patient was discharged with the recommendation for close follow up with psychiatry and nephrology.

**Discussion**

Bipolar affective disorder type I imparts significant morbidity and disease burden in the population. It is characterized by occurrence of one or more manic episodes which may be preceded or followed by a depressive or hypomanic phase. About half of these manic episodes are characterized by the presence of psychotic features. The condition is further complicated when the patient has multiple comorbid conditions as was observed in the case presented here.

Our patient had a very complicated presentation. At the age of 33 years, she was diagnosed with bipolar disorder type I and had one known manic episode 3 years prior to renal transplant. The first episode of mania was a month post-transplant. This particular episode started almost a year after being on maintenance immunosuppression therapy with tacrolimus, and in spite of getting treatment with mood stabilizers and antipsychotics, only after tapering off tacrolimus and switching to cyclosporine did the patient improve. Though, there have been neurologic symptoms like seizures and tremors reported, we have seen only a couple case reports that have reported psychosis as a consequence of tacrolimus maintenance therapy. However, per our knowledge, this is the first case report on treatment resistant mania in a previously diagnosed case of bipolar disorder.

Management of mental health issues in the post-transplant setting can be difficult given the potential for medication related neurotoxicity and the lack of established guidelines related to it. The majority of available literature focuses on assessment of depression pre- and post-transplantation; however, no specific guidelines exist for the management of patients with bipolar affective disorder. Our patient was stable on divalproex sodium 500 mg b.i.d. for about 2 years but that was discontinued 4 months prior to the episode due to thrombocytopenia, and patient was started on quetiapine 200 mg. It is probable the emergence of the mania with psychosis was precipitated by discontinuation of divalproex sodium. However, we believe the treatment resistant mania was due to the tacrolimus therapy. Psychosis and delirium are listed as possible adverse effects in the manufacturer's package insert.

Severe neurotoxic symptoms are reported to affect up to 5% of patients on calcineurin inhibitors and include psychoses, hallucinations, blindness, seizures, cerebellar ataxia, motor weakness, or leukoencephalopathy. Tacrolimus is associated with similar neurotoxic adverse events. Factors that may promote the development of serious complications include advanced liver failure, hypertension, hypocholesterolemia, elevated cyclosporine or tacrolimus blood levels, hypomagnesemia, and methylprednisolone. Our patient had underlying hypertension, diabetes mellitus type 2, thyroid dysfunction and a right adrenal adenoma. Interestingly, her tacrolimus levels were at therapeutic levels, but severe neurotoxicity seemed to not be related to tacrolimus levels, similarly as seen in the study by Veroux et al. Based on the FK506 consensus reports by Jusko et al and Wong, tacrolimus therapeutic ranges in kidney transplanted patients should be 10–15 µg/L in the first 6 months of treatment; 12–15 µg/L in the following semester; and 5–10 µg/L as maintenance therapy after one year. Bottiger et al reported neurotoxicity in 10% of patients with drug levels between 10 g/ml and 30 g/mL, while this incidence rises up to more than 20% in patients with a level >30 g/ml. This molecule can cross the intact blood brain barrier and probably attaches to myelin, which is rich in lipids, permitting tacrolimus to exert a direct toxic effect through nitrous oxide production. Tacrolimus has downstream regulatory effects on both dopaminergic and N-Methyl-D-aspartate receptor systems which may be another factor. Another postulated hypothesis relates to hypertensive encephalopathy, which corresponds to white matter changes observed in the parietal and occipital lobes.

There is relatively no literature on treatment of tacrolimus-induced psychosis. Future areas of study should question whether the type of donor, cadaveric vs live, has any contribution to the tacrolimus-induced psychosis. There also seems to be no consensus as to the time required to be on tacrolimus therapy for psychosis to develop. It is also contradictory that on one hand, medications that reduce inflammation are beneficial in acute psychotic episodes but tacrolimus, which is an immunosuppression agent which inhibits the T-cell receptor activation of interleukins, seems to have precipitated the psychotic episode.

This case illustrates the challenges and complexity in treating patients with multiple medical comorbidities and major psychiatric disorder. It reinforces the importance of collecting
detailed information and communication with other specialties. Our patient needed close follow up from nephrology and detailed work up and literature search by the psychiatrist for possible causes of her psychosis and further treatment. After a long course, detailed chart review, collateral information and multiple trials, we made the conclusion that the clinical manifestation and sudden determination in patient condition is possibly secondary to tacrolimus.

The challenges faced in the diagnosis, stabilization and management of this patient indicate that we need additional research in this topic. Further investigation should be directed towards the psychopharmacology and pathology of tacrolimus and other immunosuppressive agents and their role in psychiatric disorder.

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