



Letter to the Editor

Acute psychosis associated with immunosuppressive agent use years after liver transplantation



Sir,

Calcineurin inhibitors (Tacrolimus and cyclosporine (CsA)) are immunosuppressive agents given to solid organ transplant recipients. Calcineurin inhibitors have regulatory effects on both dopaminergic and N-methyl-D-aspartate receptor systems (Rushlow et al., 2009). 10–28% of patients who receive CsA experience neurotoxic side effects, and up to 5% experience severe symptoms including psychosis, hallucinations, blindness, seizures, ataxia or weakness. Tacrolimus is associated with an increased risk of psychosis, while azathioprine and cyclosporine are associated with relatively lower risk (Abbott et al., 2003). Most cases of cyclosporine toxicity occur within days of liver transplant and are associated with high intravenous doses (Wijdicks et al., 1995). However, late manifestation of psychosis years after transplantation has been reported (Gok and Eroglu, 2017). In this report, we present a case of psychosis occurring ten years after liver transplantation and discuss its management with low dose Risperidone.

A 68-year-old Caucasian female underwent liver transplantation in 2006 due to fulminant hepatic failure following treatment with the antibiotic telithromycin, which is associated with severe hepatotoxicity (Brinker et al., 2009). The patient was on the following immunosuppressants: Mycophenolate 500 mg Qday, Cyclosporine 50 mg QAM and 25 mg QPM, Prednisone 5 mg Qday. Doses had not been changed for the past ten years. Family history was negative for affective or psychotic disorders and the patient denied history of alcohol or substance use. The patient had no reported psychiatric history until January 2015, when following a 2-week period of depression and psychosis, she cut her wrists and was brought to an emergency department. The patient was admitted to the inpatient psychiatric unit and discharged on Paroxetine 30 mg Qday and Risperidone 2 mg Qday with good response and resolution of symptoms. The patient continued Paroxetine as an outpatient, but self-discontinued Risperidone within two months of discharge without reemergence of psychotic symptoms.

In December 2017, the patient began to exhibit increasing paranoia and persecutory delusions, accusing family members of trying to kill her, and asking her husband to choke her without provocation. Per the patient's family, the patient was not taking Paroxetine, but was taking other medications, including immunosuppressants, as prescribed. On psychiatric evaluation, the patient was selectively mute, internally preoccupied, and poorly related. The patient was alert, but was not responding to verbal commands or making eye contact. The patient was involuntarily admitted to the inpatient psychiatric unit and Paroxetine 30 mg Qday was restarted.

On admission, medical workup was within normal limits. Neuroimaging was not accomplished as the patient was agitated, but she had recently been seen by her outpatient neurologist with a negative clinical neurological workup. Head CT from June 2016 showed no structural neurological abnormalities. On the inpatient unit, the patient remained selectively mute, refusing food and oral medications.

However, the patient was reactive to her environment, making verbal comments when irritated, and using the bathroom without assistance. The patient did not demonstrate posturing, stereotypy, waxy flexibility, or echophenomena. The patient was minimally cooperative with psychiatric evaluations, but sporadically expressed feelings of guilt, worthlessness, and passive death wishes. The patient's neurological exam was non-focal without signs and symptoms of delirium. The outpatient hepatologist and the hospital hepatology service were consulted, and recommended against decreasing or stopping immunosuppressants due to high risk of transplant rejection. On the second day of admission, the patient resumed oral medications with encouragement from the inpatient psychiatry team. There was no change in psychotic symptoms while the patient was not taking immunosuppressants. Although the patient's mutism and depressive symptoms improved within the first week of admission, she remained paranoid with persecutory delusions. Risperidone was started and titrated up to 1.5 mg Qday. The patient's psychosis gradually resolved and she was discharged after 23 days of hospitalization on Paroxetine 40 mg Qday and Risperidone 1.5 mg Qday without recurrence of psychotic or depressive symptoms one year later.

We present an interesting case of psychosis in a patient with a stable immunosuppressant regimen and without neurological abnormalities several years after liver transplantation. In this case, the patient's psychosis led to non-adherence with her immunosuppressive regimen, potentially risking transplant rejection. Although late-onset psychotic episodes are described in the literature, the patient's medical history and presentation guide our diagnosis to a substance induced psychotic disorder rather than an endogenous psychosis. The neuropsychiatric side effects of calcineurin inhibitors can have life-threatening consequences and should be promptly managed by decreasing the dose, switching to another immunosuppressant, or adding a low dose antipsychotic (Krishna et al., 2013). Atypical antipsychotics may cause fewer dystonic reactions and extrapyramidal symptoms than typical antipsychotics, and are increasingly recommended as first-line treatment for corticosteroid-related psychiatric side effects (Ross and Cetas, 2012).

Although psychosis is a rare side effect of immunosuppressive agents, it can reduce treatment adherence, risking tissue rejection and worsening the prognosis for transplant recipients. It is important to identify mental status changes in patients on immunosuppressive treatment and collaboratively manage their care with psychiatry and the transplant team.

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References

- Abbott, K.C., Agodoa, L.Y., O'Malley, P.G., 2003. Hospitalized psychoses after renal transplantation in the United States: incidence, risk factors, and prognosis. *J. Am. Soc. Nephrol.* 14, 1628–1635.
- Brinker, A.D., Wassel, R.T., Lyndly, J., Serrano, J., Avigan, M., Lee, W.M., Seeff, L.B., 2009. Telithromycin-associated hepatotoxicity: clinical spectrum and causality assessment of 42 cases. *Hepatology* 49 (January (1)), 250–257. <https://doi.org/10.1002/hep.22620>. PubMed PMID: 19085949.
- Gok, F., Eroglu, M.E., 2017. Acute psychotic disorder associated with immunosuppressive agent use after renal transplantation: a case report. *Psychiatry Clin. Psychopharmacol.* 27 (3), 320–322. <https://doi.org/10.1080/24750573.2017.1356062>.
- Krishna, N., Chiappelli, J., Fischer, B.A., et al., 2013. Tacrolimus-induced paranoid delusions and fugue-like state. *Gen. Hosp. Psychiatr.* 35, 327.e5–327.e6.
- Ross, D.A., Cetas, J.S., 2012. Steroid psychosis: a review for neurosurgeons. *J. Neurooncol.* 109 (September (3)), 439–447. <https://doi.org/10.1007/s11060-012-0919-z>. Epub 2012 Jul 5. Review. PubMed PMID: 22763760.
- Rushlow, W.J., Seah, C., Sutton, L.P., Bjelica, A., Rajakumar, N., 2009. Antipsychotics affect multiple calcium calmodulin dependent proteins. *Neuroscience* 161 (3), 877–886 ISSN 0306-4522.
- Wijdicks, E.F., Wiesner, R.H., Krom, R.A., 1995. Neurotoxicity in liver transplant recipients with cyclosporine immunosuppression. *Neurology* 45 (November (11)), 1962–1964 PubMed PMID: 7501141.

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