CASE REPORT

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Rare Case of Acute Psychotic Disorder Associated with Immunosuppressant Medications Use After Kidney Transplantation

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ABSTRACT

Renal transplantation is the treatment of choice for patients with end-stage renal failure as it provides patients with the best quality of life because of its survival benefits, either short or long-term. However, despite the benefits of renal transplantation over dialysis, the life-long immunosuppressant treatment needed after kidney transplantation has several drawbacks. The present case developed a psychotic disorder after 8 years of regular intake of immunosuppressant medications tacrolimus and prednisone. He was switched to cyclosporine, and the dose of prednisone was decreased, but he only showed partial improvement in his behavior. The patient was started on the antipsychotic drug risperidone, and the delusions subsided within 12 weeks of starting the medication. This case highlights the importance of clinical awareness of rare but severe psychiatric effects due to immunosuppressant use. In conclusion, early recognition of psychiatric side effects of immunosuppressants and systemic corticosteroids and starting appropriate treatment is essential to prevent more serious psychiatric side effects.

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INTRODUCTION

End-stage renal disease (ESRD) is defined as "renal failure severe enough to require maintenance dialysis or renal transplantation to save the patient's life."[1] End-stage renal disease incidence, as well as prevalence, has been increasing all over the world.[2] In the Kingdom of Saudi Arabia (KSA), end-stage renal disease is considered a serious medical issue because of its high prevalence and incidence, impact on life, and costly treatment.[3] Two main lines of treatment for the treatment of ESRD exist: dialysis and renal transplantation. The main management options for such cases are home-based dialysis and hospi tal-based/in-center hemodialysis. Renal transplantation is the treatment of choice for these patients as it provides the best quality of life due to its survival benefits, either short or long term.[2] In KSA, there are currently over twenty thousand patients on renal dialysis and over 9000 patients receiving immunosuppressant treatments after renal transplantation. The prevalence of renal transplantation in KSA is estimated at 294/million population.[4]

Despite the benefits of renal transplantation over dialysis, the life-long immunosuppressant treatment needed after kidney transplantation has several drawbacks.[5] The postoperative follow-up period of renal transplantation patients is associated with numerous mental health problems such as depression, bipolar disorder, anxiety disorders, adjustment impairment, cognitive disorders, as well as psychotic disorders.[6,7] About 20% of patients receiving tacrolimus treatment experience mild neuropsychiatric side effects like tremors, sleep disturbances, headaches, vertigo, abnormal sensations, and mood disturbances. About 5% of patients experience significant neuropsychiatric side effects like seizures, psychotic features, encephalopathy, focal deficits, and movement disorders.[8] Although psychotic symptoms are uncommon side effects of tacrolimus compared to mood or cognitive side effects, they may occur in some patients and lead to severe complications, including behavioral disturbances and noncompliance with immunosuppressant treatments.[8] Tacrolimus is a calcineurin inhibitor, an immunosuppressive agent prescribed to solid organ transplantation recipients to prevent allograft rejections. It has regulatory effects on the *N*-methyl-D-aspartate receptor and has a role in dopamine signal transduction. These neurotransmitters are well known to be implicated in the pathophysiology of psychosis.[9] Development of psychosis due to immunosuppressants can occur after many years of treatment and can also occur at average

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serum levels. Psychotic manifestations can improve with antipsychotic medications, but the primary management option should include cross-titration to alternative immunosuppressants.[9] Psychiatric treatment of this side effect is necessary because it can affect compliance with immunosuppressants, which is essential in the post-transplantation period, and indirectly may lead to organ rejection.[10]

CASE PRESENTATION

A 33-year-old male had a history of hypertension and end-stage renal disease treated with a kidney transplant 8 years ago. He is regular on immunosuppressant medications tacrolimus 4 mg/day and prednisone 5 mg/day. Six months ago, he started to have psychotic symptoms in the form of persecutory delusion and delusion of infidelity associated with abnormal and aggressive behavior toward his wife and family members, which led to divorce. He was referred to the psychiatric clinic for assessment. On the first presentation in the clinic, the patient was conscious, alert, oriented to time, place, and person, and irritable. He accused family members of conspiring to hurt him. He was not cooperative during the interview. Collateral history from the patient's family revealed that he had persecutory thoughts about the conspiracy of his colleagues against him. The patient also claimed that he had a special mission given by God. He had isolation most of the day in his room with a complaint of sleep disturbance. His work colleagues noticed a decrease in work performance. No history of mood or cognitive symptoms was observed. He had no personal or family history of psychiatric illness. He had no history of other medical conditions, no history of seizures, or head trauma. A full neurological examination was normal. Computed tomography (CT) of the brain and electroencephalography were insignificant. Tacrolimus serum level was within normal limits. The urine drug screening was negative, and routine laboratory tests were unremarkable. After the initial assessment, the diagnosis of immunosuppressant-induced psychotic disorder was suspected. The kidney transplant team was contacted and agreed to switch the immunosuppressant to cyclosporin 300 mg/day and decrease the dose of prednisone to 2.5 mg/day. Cyclosporin serum level C0 was 188 ng/mL. However, the patient showed partial improvement in his behavior and negative symptoms and became more cooperative. The patient was started on risperidone 2 mg and increased gradually to 6 mg. Atypical antipsychotic medications may be the most appropriate treatment to avoid extrapyramidal side effects. Risperidone was selected because of its effectiveness and relatively few metabolic side effects. After the antipsychotic treatment, the patient showed good improvement and showed good insight into his clinical condition. The delusions subsided within 12 weeks of starting antipsychotic medications. The psychotic features were assessed by the positive and negative syndrome scale for Schizophrenia (PANSS) on the first presentation, 6-week post-immunosuppressant switch, 6-week post-antipsychotic treatment, and 12-week post-antipsychotic treatment consecutively (Table 1).[11] His family also confirmed remission, and his colleagues reported good functionality at his job. During a later follow-up visit, the patient was asymptomatic, and risperidone was suspended. He has remained asymptomatic for a 3-month follow-up period. The Naranjo Adverse Drug Reaction probability scale was applied to assess this association, and its score was "probable" (score 5); this further supports the diagnosis of immunosuppressant-in duced psychotic disorder (Table 2).[12] The patient has signed a written consent for the publication of this case report.

DISCUSSION

The present case is reported mainly because of 3 main reasons: the rare side effect of immunosuppressants, the development of psychosis after a long time (8 years) of using immunosuppressants, and no complete remission of psychosis after the replacement of immunosuppressant therapy. Most clinical reports describe the onset of psychiatric symptoms days to weeks after starting with tacrolimus. Psychiatric manifestations have been reported in patients with or without histories of mental illnesses. A similar case was published by Gok and Eroglu in 2017, which developed psychosis after 4 years of immunosuppressive agents following renal transplantation.[10] Other case reports were either psychosis occurs within weeks to months of using immunosuppressant medications, associated with higher doses of immunosuppressants, or the patient completely recovered after switching to an alternative immunosuppressant.[9,13-15] In the present case,

Table 1. Improvement of Psychotic Features After Intervention [(11)]

Score	Assessment on 1st Presentation	6-Week Post Immunosuppressant Switch	6-Week Post Antipsychotic Treatment	12-Week Post Antipsychotic Treatment
Total PANSS score	104	87	60	41
Positive subscale score	25	21	15	9
Negative subscale score	25	21	14	10
General psychopathology subscale score	54	45	31	22
Interpretation	Markedly ill	Moderately ill	ildly ill	Not ill

Table 2. Assessment Using the Naranjo Adverse Drug Reaction Probability Scale [12]

Question	Score
1. Are there previous conclusive reports on this reaction?	+1
2. Did adverse event appear after the suspected drug was given?	+2
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?	+1
4. Did the adverse reaction appear when the drug was readministered?	0
5. Are there alternative causes that could have caused the reaction?	0
6. Did the reaction reappear when a placebo was given?	0
7. Was the drug detected in any body fluid in toxic concentrations?	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	0
10. Was the adverse event confirmed by any objective evidence?	+1
Total score	5

the sudden onset of psychosis, middle-age presentation, normal premorbid psychosocial adjustment, and absence of a previous history of dysfunction or prodromal phase raise the suspicion of possible secondary causes. The patient was on regular immunosuppressant medications, tacrolimus and prednisone, following renal transplantation. Prednisone, a systemic corticosteroid, is mainly used to treat inflammatory and autoimmune diseases. Long-term use of corticosteroids has been associated with the development of psychiatric side effects in almost sixty percent of patients. It has been documented that these psychiatric side effects are more likely to exist during the first week of systemic corticosteroids.[6] The incidence of severe psychiatric side effects following systemic corticosteroid therapy is relatively low, ranging between 5 and 6%, and includes various affective, cognitive, psychotic, and behavioral symptoms.[16] Furthermore, it has been observed that the dosage of systemic corticosteroids was a determinant factor for the development of psychiatric side effects as nearly one-fifth of patients taking a dosage over 40 mg prednisone or equivalent were more likely to develop psychiatric problems, including psychosis, mania, and severe depression. Many factors were found to influence the development of such psychiatric side effects, including age, gender, comorbidity, and previous psychiatric history.[13] In the present case, decreasing the prednisone dose slightly improved the patient's behavior. We can conclude that, although the dosage of systemic corticosteroids was minimal, long-term use could be considered a risk factor for the development of psychosis. The same has been observed by others.[14]

Tacrolimus is a widely used immunosuppressive agent in solid organ transplants to prevent and treat allograft rejection. However, it has been reported to cause psychosis, sometimes after years of tolerability.[13] It has been reported that the psychiatric side effects can be reduced by lowering the dosage of tacrolimus or replacing it with another immunosuppressant medication.[7,17] Another case reported that discontinuing tacrolimus and switching to an alternative immunosuppressant significantly improved Psychosis.[17] In the current case, we prefer replacing tacrolimus with another immunosuppressant (Cyclosporin) rather than lowering the tacrolimus dosage as the tacrolimus trough level was within normal limits. The patient was on a higher dose during the 1-year post-transplant period and he did not experience any psychotic symptoms during that time. In agreement with others,[9,17] not only reducing the dosage of immunosuppressant medication or switching to another immunosuppressant agent improved the psychotic symptoms but antipsychotic treatments could be considered to improve the situation. Complete remission of psychotic symptoms was achieved after 12 weeks of starting risperidone treatment, as the patient got a total score of 41 on the positive and negative syndrome scale for schizophrenia (PANSS).[11] In the present case, the partial improvement of psychosis after switching to a different immunosuppressant, full remission after antipsychotic treatment, and remaining asymptomatic after discontinuation of the antipsychotic may confirm the diagnosis of immunosuppressant-induced psychotic disorder. Some of the reported cases showed full remission within a few days after discontinuing tacrolimus. Still, others needed to continue on antipsychotics for weeks to months to show full remission.[10-13,15] It has been reported that the dosage of most antipsychotic medications is not affected by renal function as the liver metabolizes them, and they showed no significant interactions with either calcineurin inhibitors or systemic corticosteroids.[18] Neuropsychiatric side effects due to tacrolimus treatment cannot be verified by biomarkers or brain imaging, and they can occur after many years of starting treatment.[19]

CONCLUSION

The life-long use of immunosuppressants for patients with ESRF after kidney transplantation could produce neuropsychiatric manifestations and rarely psychotic symptoms. Cessation, reducing the dosage of immunosuppressant medications, or switching to another immunosuppressant is not always enough to improve

the condition, and antipsychotic medication could be considered in such cases. In addition, early recognition of psychotic side effects of immunosuppressants and systemic corticosteroids is essential in preventing the occurrence of more severe complications. Further and more extensive research is needed to study the side effects, their impact, and appropriate management options.

Data Availability Statement: The data used in this study are available from the corresponding author upon reasonable request.

Informed Consent: Written informed consent was obtained from the patient who agreed to take part in the study.

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