



Graft Loss Following Onset of Schizophrenia Long After Liver Transplantation

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Abstract: Information regarding new-onset posttransplant psychotic disorders and their effect on nonadherence and posttransplant outcome is quite limited. We report a case of new-onset posttransplant schizophrenia that led to death. The patient, a woman with Wilson disease but no history of psychiatric problems or a substance use disorder had undergone liver transplantation at age 21. She married subsequently and bore children, being well able to handle her housework, child care, and full-time employment. She continued her medications as prescribed, and good graft function was maintained. At age 41, she experienced an episode of schizophrenia, then graft loss associated with nonadherence to immunosuppressive agents. Death ensued, occurring 6 months after the onset of schizophrenia. This case highlights the possibility that schizophrenia manifesting long after liver transplantation can result in graft loss and death due to medication nonadherence. Thus, awareness of the possibility of this rare clinical scenario is critical.

Keywords: schizophrenia, liver transplantation, graft loss

Introduction

Pretransplant psychotic disorders, schizophrenia and bipolar disorders, for example, have been considered potential contraindications to organ transplantation because of concerns about medication nonadherence and poor posttransplant outcome, although no longitudinal data supporting these concerns exist.¹ Recent studies on kidney transplantation have suggested that patients with a history of psychotic disorders can do well after transplantation.²⁻⁴

In contrast, information regarding new-onset psychotic disorders after organ transplantation is quite limited. Some cases have been reported mainly in the context of secondary causes, such as immunosuppressant-induced adverse effects,⁵ which usually manifest postoperatively, or steroid psychosis,⁶ which often occurs after steroid pulse therapy administered during episodes of rejection. In one reported case series,² psychotic symptoms newly appeared in four patients after organ transplantation (two liver, one kidney, and one kidney-pancreas transplant), and they were considered to be substance-related — cannabis in two cases, steroid-interferon combination in one, and benzodiazepines in one. Nonadherence occurred only in one of the cases of cannabis-induced psychosis, but graft rejection was not diagnosed.

To our knowledge, no case of schizophrenia newly occurring after liver transplantation and unrelated to secondary organic causes has been reported. Herein, we present the case of a woman who experienced a first episode of schizophrenia over

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20 years after liver transplantation, leading to graft loss associated with nonadherence to immunosuppressive agents and, in turn, to death of the patient.

Case Report

The patient was a 41-year-old Japanese woman who, according to family members and clinical records, had no history of psychiatric problems or substance use disorder. In 1994, at age 17, she had been diagnosed with Wilson disease, and she had undergone liver transplantation abroad at age 21. Subsequently, she graduated from university and, after two changes in employment, worked at an insurance company. She married at age 28, bore two daughters over time, and was able to handle her housework, child care, and full-time company employment. She was followed up at our hospital's transplant center and showed good adherence to the prescribed immunosuppressants (mycophenolate mofetil [500 mg/day] and tacrolimus [0.5 mg/day]) and good graft function.

In January 2018, after experiencing insomnia for a few months, the woman began to suffer persecutory delusions and auditory hallucinations. She claimed, "I cannot go out all the time because I am being watched," or "I hear a voice telling me what to do." She also began to exhibit various bizarre behaviors. For example, she forced her parents to remove their clothes "because they were infected with bacteria." In the beginning of March 2018, she visited our psychiatric clinic accompanied by her parents. Because of psychomotor agitation without meaning and the psychotic symptoms, the patient was involuntarily hospitalized in our psychiatric ward the same day.

Physical examination on admission revealed significant edema of both lower limbs and jaundice. Laboratory tests revealed the following: white blood cell count, 3650/ μ L; red blood cell count, 2.47×10^6 / μ L; hemoglobin, 8.9 g/dL; hematocrit, 26.1%; platelet count, 7.6×10^4 / μ L; prothrombin time, 19.7 seconds; total protein, 5.5 g/dL; albumin, 2.7 g/dL; total bilirubin, 10.0 mg/dL; direct bilirubin, 2.6 mg/dL; aspartate aminotransferase 56 U/L; alanine aminotransferase 54 U/L; alkaline phosphatase 1193 U/L; cholinesterase, 85 U/L; blood urea nitrogen, 20.8 mg/dL; C-reactive protein, 0.90 mg/dL; serum copper, 47 μ g/dL (normal, 68–128 μ g/dL); ceruloplasmin, 13 mg/dL (normal, 21–37 mg/dL); tacrolimus, <2.0 ng/mL; mycophenolate mofetil, <0.4 μ g/mL. Overall, the laboratory tests results indicated exacerbation of liver dysfunction, pancytopenia, hypoalbuminemia, hyperammonemia, and decreased trough concentrations of the prescribed

immunosuppressive drugs. Chest radiography revealed cardiac enlargement. Thus, acute rejection due to nonadherence to the immunosuppressive agents was diagnosed, and the patient was given steroid pulse therapy (methylprednisolone, 0.5 g/day for 2 days) ([Supplementary Table](#)).

Six days after admission, the patient was transferred from the psychiatric ward to the transplant ward. A psychiatric liaison team visited her daily to manage her psychotic symptoms, which included auditory hallucinations, persecutory delusions, and psychomotor excitement. She did not appear disoriented. Risperidone was administered orally up to 4 mg/day, and when she refused it, haloperidol (5 mg) was injected intravenously.

We looked carefully for secondary causes of the psychosis. We performed brain magnetic resonance imaging, and, with the exception of a small high-intensity area in the right paramedian body of the corpus callosum, no abnormalities, including pathological copper accumulation, were detected. In addition, there was no evidence of abnormal copper metabolism (per ceruloplasmin, serum copper, and urinary copper excretion levels). Therefore, psychosis due to the recurrence of Wilson disease⁷ was ruled out. Tacrolimus-induced psychosis was also ruled out because the trough tacrolimus concentration had not increased before onset of the psychosis, and the psychosis persisted after the trough value decreased. No evidence of other medical conditions or a substance use disorder that could cause psychotic symptoms was found. Therefore, we suspected schizophrenia, but it was not diagnosed officially because the duration of psychotic symptoms did not meet the DSM-5 criteria for schizophrenia.

The patient's psychotic symptoms alleviated gradually, and by the middle of April we were able to communicate rationally with her. On the Mini-Mental-State Examination she scored 30. However, refractory ascites had set in, a result of the hepatic dysfunction. Further, severe hematemesis and melena developed. Thus, it was assumed that gastrointestinal bleeding had occurred, but the origin remained obscure. These developments led, unfortunately, to the patient's death in June 2018. The family consented to autopsy, which was performed on the day of death. Significant liver atrophy, marked pleural ascites, and splenomegaly were observed, and the examiner noted that a cause of death other than liver failure could not be specified. Our final diagnosis was that of schizophrenia because, by the time of the patient's death, the symptoms had lasted more than 6 months, meeting the DSM-5 diagnostic criteria.

Discussion

Our patient's first episode of schizophrenia occurred over 20 years after liver transplantation. The very long period during which she functioned well socially after her liver transplant delayed the discovery and treatment of her psychosis, although she had become noncompliant in terms of her immunosuppressant regimen. Considering the occurrence of psychiatric symptoms and the change in the blood concentration of tacrolimus, it is likely that the patient had stopped taking one or both immunosuppressants in January 2018. Her non-compliance led to graft rejection and ultimate graft loss.

Although we performed a comprehensive differential diagnostic work up, some secondary causes of psychosis, such as limbic encephalitis, could not be completely ruled out. However, no symptom typical of encephalitis, such as disorientation or altered consciousness, was evident. Therefore, based on the DSM-5 criteria, the final diagnosis was that of schizophrenia. For women, there are two reported peak ages for onset of schizophrenia, one between 25 and 30 years, and the other after 45 years, whereas for men, there is a single peak age for onset, which is between 21 and 25 years.⁸ The age distribution for onset in women supports our diagnosis.

In a large cohort study based on the United States Renal Data System (USRDS) data recorded between 1994 and 1998 ($n = 39,628$),⁹ hospitalizations for psychoses occurring after renal transplant were independently associated with increased risk of death and graft loss, possibly mediated by medication nonadherence. However, subjects included in the study were mainly those with psychotic depression or delirium, both of which differ from a longstanding psychotic disorder such as schizophrenia. In addition, it is unclear whether the patients' psychoses developed newly after transplantation or pre-existing psychoses had recurred.

Recently, two multicenter retrospective studies from France ($n = 8750$)³ and the United States using USRDS ($n = 3680$)⁴ examined the effects of a pretransplant history of psychosis (schizophrenia or bipolar disorder) on the outcome of renal transplantation. Both studies found no evidence of increased risk of medication nonadherence, rejection, or death in these patient populations. Therefore, even if an existing psychiatric disorder is controlled, careful long-term psychiatric follow up after transplant is necessary.

As for liver transplantation in particular, psychotic disorders have been reported in only a few cases.^{10–13} In

each of the four reported cases, the psychosis existed before transplantation. Long-term outcomes were good in three of the four cases. The fourth patient had schizotypal personality disorder and committed suicide 3 months after transplantation, although he showed complete psychiatric recovery before the transplantation, and no evidence of the disorder was found during posttransplant follow up examinations.¹² Psychosis occurring for the first time after liver transplantation has not been reported previously.

The case we report herein highlights the possibility that a first episode of psychosis can occur long after liver transplantation and can result in graft loss and death due to medication nonadherence. Thus, awareness of the possibility of this rare clinical scenario is critical.

Abbreviations

DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th edition; USRDS, United States Renal Data System.

Consent for Publication

For the publication of this case report, written informed consent was obtained from the patient.

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Author Contributions

YA, RA, SM, and KN were involved in the psychiatric management of the patient. AS was the transplant surgeon involved in the physical assessment, management, and follow-up of the patient. This report was written by YA, RA, and KN. All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

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