Late presentation of posterior reversible encephalopathy syndrome following liver transplantation in the setting of tacrolimus and cannabis use

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ABSTRACT
A 45-year-old female presented to hospital with confusion and visual disturbances. She had undergone a liver transplant 3 years prior for cirrhosis secondary to primary biliary cholangitis. Computed tomography and magnetic resonance imaging of the brain showed features consistent with posterior reversible encephalopathy syndrome. Her medications included tacrolimus, sirolimus, and prednisone. She reported smoking 4 grams of cannabis per day. Following cessation of tacrolimus, the patient’s encephalopathy and visual disturbances resolved. To our knowledge, this case represents the longest time elapsed from liver transplantation to the development of tacrolimus-associated posterior reversible encephalopathy syndrome in the literature. This case highlights the potential danger of cannabis use in transplant recipients who are on immunosuppressants such as tacrolimus. Clinicians should have a high index of suspicion for posterior reversible encephalopathy syndrome in post-transplant patients presenting with altered mental status, even years after liver transplantation, and be familiar with potential interactions between cannabis and immunosuppressants.

KEYWORDS: cannabis; liver; marijuana; posterior reversible encephalopathy syndrome; tacrolimus; transplant

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CASE PRESENTATION
A 45-year-old female presented to the emergency department after an unwitnessed fall at home. She was confused and complaining of visual disturbances. Her past medical history was notable for a liver transplant 3 years prior for cirrhosis secondary to primary biliary cholangitis (PBC). Her immunosuppression consisted of tacrolimus 2 mg at breakfast and 3 mg at supper orally, sirolimus 1 mg once daily orally, and prednisone 2.5 mg once daily orally. Her only other medications were
alendronate and pantoprazole. One year prior to the patient’s presentation (two years post-transplant), the patient underwent liver biopsy because of abnormal liver enzymes; this showed recurrent PBC with stage 1 fibrosis and no evidence of rejection. At the time of biopsy, the patient was started on ursodiol, which resulted in normalization of her liver enzymes. However, the patient subsequently stopped taking ursodiol a few months prior to presentation to emergency.

Initial investigations in the emergency department revealed elevated alkaline phosphatase (ALP) of 386 U/L (nr 38–150 U/L) and gamma-glutamyl transferase (GGT) of 237 U/L (nr 0–49 U/L). Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were also elevated at 16.2 µmol/L (nr 0–20.4 µmol/L) and 7.7 µmol/L (nr 0–8.5 µmol/L), respectively. Total and direct bilirubin were normal at 16.2 µmol/L (nr 0–20.4 µmol/L) and 7.7 µmol/L (nr 0–8.5 µmol/L), respectively. Albumin was low at 30 g/L (nr 35–50 g/L). The international normalized ratio (INR) was normal at 1.0 (nr 0.8–1.2). Tacrolimus level was 2.4 ng/mL though this was taken 2 days after presentation.

Computed tomography of her head showed subcortical hypointensity within the white matter of the occipital lobes bilaterally, with no hemorrhage, hydrocephalus, shift, or herniation. Magnetic resonance imaging of the brain showed high T2/FLAIR (fluid-attenuated inversion recovery) signal in the subcortical white matter of the occipital lobes bilaterally, with no subcortical hypoattenuation within the white matter of the occipital lobes bilaterally, with no hemorrhage, hydrocephalus, shift, or herniation.

DISCUSSION

The occurrence of PRES in patients after transplantation secondary to tacrolimus is well-documented in the literature. This phenomenon has been observed in patients who have received liver (1–4), heart (5,6), kidney (7–9), and multivisceral transplants (10). In a retrospective chart review of 4,222 patients who underwent solid organ transplants, PRES developed in 21 (0.49%) patients (11). The time between transplantation and the development of PRES varied depending on the organ received. In 9 of 10 patients who underwent liver transplants, PRES developed within 2 months, while 8 of 9 patients who underwent kidney transplants developed PRES after 1 year (11). A 2016 review of PRES after liver transplantation also found that most cases developed 2 to 3 months after transplantation (12). In independent case reports, the longest time elapsed from transplantation to development of PRES was 110 days (3), though most were within the first month (1,2). To our knowledge, this case represents the longest documented time elapsed between liver transplantation and the development of PRES (3 years) in the existing literature. As with other reports, this case reinforces the importance of maintaining a high index of suspicion for PRES in patients presenting with altered mental status and visual disturbances, even long after transplantation.

In our case, we postulate that the patient’s substantial cannabis use contributed to this unique, late presentation of tacrolimus-associated PRES. While her tacrolimus level was only 2.4 ng/mL, this was drawn 2 days after her presentation; a 2010 review of PRES secondary to tacrolimus after transplantation noted that immunosuppressant blood levels do not appear to correlate with PRES (13). There are several proposed mechanisms for how cannabis use can alter the metabolism of tacrolimus and cause toxicity in transplant recipients. The constituents of cannabis are inhibitors of CYP 3A4, an enzyme that metabolizes tacrolimus (14). Cannabis also acts as a substrate for P-glycoprotein, a transport protein essential for pumping drugs into the gastrointestinal tract lumen for excretion (15). There are case reports of cannabis use influencing tacrolimus metabolism in a hematopoietic stem cell transplant patient (16) as well as a kidney transplant recipient (17). A 2019 case report documented the development of PRES 5 days post-liver transplantation in a patient who had been initiated on tacrolimus in the context of a history of ingesting 2–4 medical cannabis lozenges
Figure 1: (a) A 45-year-old woman underwent an emergent CT scan of her head for altered mental status and visual disturbances. There were areas of hypoattenuation in the subcortical occipital lobes bilaterally (white arrow). (b) Subsequent fat-saturated T2-weighted magnetic resonance images of the brain showed hyperintense signal in the subcortical white matter of the posterosuperior frontal (white arrowheads) and superior parietal (black arrowheads) lobes. There was also involvement of the occipital lobes and left cerebellum (not shown). (c) and (d) Axial T2-weighted FLAIR images demonstrate hyperintense signal in the posterior occipital (c, arrowheads) and parietal (d, arrowheads) lobes. The findings were favoured to represent posterior reversible encephalopathy syndrome.

CT = Computed tomography; FLAIR = Fluid attenuated inversion recovery

It is less clear if cannabis use in liver transplant recipients is associated with adverse clinical outcomes such as graft failure and mortality. In one retrospective study comparing liver transplant recipients who used cannabis versus those who did not, there were no significant differences in 5-year survival or inpatient complications (19). Another retrospective study found that survival rates were similar between liver transplant candidates who used cannabis versus those who did not (20).
There have been no large-scale or systematic studies on this topic, and more research in this area is needed.

To our knowledge, this case report describes the latest presentation of tacrolimus-associated PRES in a liver transplant recipient. Whereas most cases of PRES in the liver transplant population occur within a few months after transplantation, our patient presented 3 years after transplantation. We postulate that this patient’s late presentation was a result of her significant cannabis use. Our case reinforces the need to consider PRES in the differential diagnosis of liver transplant patients presenting with altered mental status, as well as a potentially dangerous association between cannabis use and tacrolimus-associated PRES. Cannabis use is common in the general population, with 10%–15% of adults and 25%–30% of youths having used cannabis, according to a Canadian study (21); these numbers are likely an underestimate given that cannabis has been legalized since this study was conducted. Health care providers should familiarize themselves with potential drug–drug interactions involving cannabis. This is particularly true for tacrolimus, given the increasing number of reports documenting tacrolimus toxicity associated with cannabis use in patients with solid organ transplants.

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