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TACROLIMUS ASSOCIATED HEMORRHAGIC POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME: A RARE CASE IN THE LATE PERIOD AFTER RENAL TRANSPLANTATION

TAKROLİMUS İLİŞKİLİ HEMORAJİK POSTERİOR REVERSİBL ENSEFALOPATİ SENDROMU: BÖBREK TRANSPLANTASYONU SONRASI GEÇ DÖNEMDE PREZENTE OLAN NADİR BİR OLGU

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ABSTRACT

Immunosuppressive agents such as calcineurin inhibitors, which are commonly used in transplant patients may play a role in the development of posterior reversible encephalopathy syndrome (PRES), one of the rare neurological complications after organ and tissue transplantation. This complication, which is often seen in the early period after transplantation, occurs in the late period in a small number of cases. In this case report, to draw attention to this dramatic side effect of calcineurin inhibitors, we present a case of hemorrhagic PRES, which developed in the late period after kidney transplantation most likely associated with tacrolimus treatment.

Keywords: PRES, tacrolimus, calcineurin inhibitors, transplantation

ÖZET

Organ ve doku transplantasyonu sonrası nadir görülen nörolojik komplikasyonlardan birisi olan posterior reversible ensefalopati sendromunun (PRES) gelişiminde, transplantasyon hastalarında sıkça kullanılan kalsinörin inhibitörleri gibi immünsüpresif ajanlar rol oynayabilmektedir. Sıklıkla transplantasyon sonrası erken dönemde görülen bu komplikasyon az sayıda olguda geç dönemde meydana gelebilmektedir. Bu olgu sunumunda, kalsinörin inhibitörlerinin bu şiddetli ve dramatik yan etkisine dikkat çekmek için, böbrek nakli sonrası geç dönemde gelişen, kuvvetle muhtemel takrolimus tedavisi ile ilişkili hemorajik PRES olgusunu sunmaktayız.

Anahtar Kelimeler: PRES, tacrolimus, kalsinörin inhibitörleri, transplantasyon

INTRODUCTION

Posterior reversible encephalopathy syndrome (PRES) is characterized by mostly reversible subcortical vasogenic edema and occasionally irreversible cytotoxic edema without infarction in the brain parenchyma. Clinical symptoms include headache, nausea, vomiting, altered mental status, epileptic seizures, visual disturbances and focal neurological deficits (1, 2). Immunosuppressive agents such as calcineurin inhibitors (cyclosporine and tacrolimus) and mTOR inhibitors (sirolimus and everolimus) are among the etiological factors (3). Among these agents, tacrolimus has been the most frequently reported to have an association with PRES (4). We aimed to draw attention to the severe and dramatic side effect of tacrolimus by discussing a case of hemorrhagic PRES that was highly likely associated with tacrolimus therapy in the late period following kidney transplantation.

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CASE

A 36-year-old male patient who had received a kidney from his mother five years earlier due to kidney failure secondary to membranoproliferative glomerulonephritis, presented to the organ transplant clinic with weakness, fatigue and swollen legs. He was receiving tacrolimus 2.5 mg/day, mycophenolate sodium 300 mg/day, prednisolone 5 mg/day, acetylsalicylic acid 100 mg/day, amlodipine 20 mg/day, doxazosin 16 mg/day and carvedilol 50 mg/day. Upon examination, he had high blood pressure (BP) (150/90 mmHg), +3 pretibial edema in the lower extremities, fine crackles at the lung bases and increased body weight when compared to the previous follow-up visit. Laboratory tests were normal other than normocytic normochromic anemia, elevated blood urea (184 mg/dl), elevated creatinine (1.85 mg/dl) and hypoalbuminemia (1.98 g/dl). After being admitted to the Transplantation Service and treated with intermittent furosemide, his examination findings consistent with volume overload were improved, while graft functions remained stable.

On the seventh day of admission, the patient's BP increased (190/110 mmHg) and 30 minutes later, he had a 2-minute focal seizure characterized by clonic contractions in the right arm. A following generalized tonic-clonic seizure stopped after the administration of intravenous (IV) diazepam. The patient was mechanically ventilated due to respiratory distress, BP was controlled by IV esmolol and furosemide and levetiracetam was initiated. Neurological examination at 24 hours following extubation revealed apathy, tendency to sleep, disorientation, impairment of attention, disorganized thinking and generalized muscle weakness (3/5 in all extremities). He complained of blurred vision and headache. Laboratory tests revealed hypomagnesemia (1.48 mg/dl, range: 1.7–2.55 mg/dl) and elevated creatinine (2.5 mg/dl), while coagulation tests were within normal ranges. Brain computed tomography (CT) imaging revealed areas of hemorrhage in the left parietal and right occipital regions, and hypodense areas in both the parietal and occipital white matter (Figure 1). Brain magnetic resonance imaging (MRI) in T2-FLAIR-weighted sections revealed areas of hematoma in the left parietal and right occipital regions, as well as hyperintense lesions in the bilateral parietal, occipital, cerebellar regions and in the brainstem with no diffusion restriction, which is typically associated with PRES (Figures 2, 3). His blood tacrolimus level was 10 ng/ml (normal range: 5–20 ng/ml).

Despite the BP control, intermittent hemodialysis and magnesium replacement, neither neurological examination findings nor the patient's headache and blurred vision did not change. Brain MRI performed 3 days after the first one showed no changes in the initial findings, including hematoma areas and hyperintense lesions. Tacrolimus therapy was discontinued and to prevent graft rejection, mycophenolate sodium dose was increased to 600 mg/day and prednisolone dose to 10 mg/day. His headache, blurred vision and generalized muscle weakness resolved within a week after discontinuation of tacrolimus. Neurological examination performed one week after the discontinuation of tacrolimus revealed that apathy, tendency to sleep, disorientation, impairment of

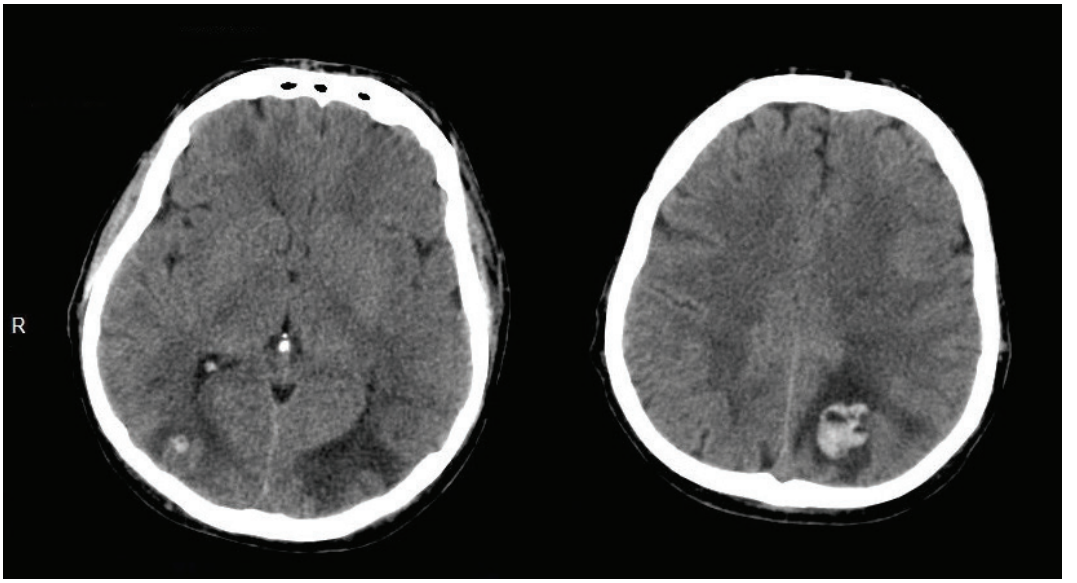

Figure 1: Post-seizure axial non-contrast CT showing hypodense areas in the bilateral occipital lobes and intracerebral hemorrhage in the left parietal and right occipital lobes

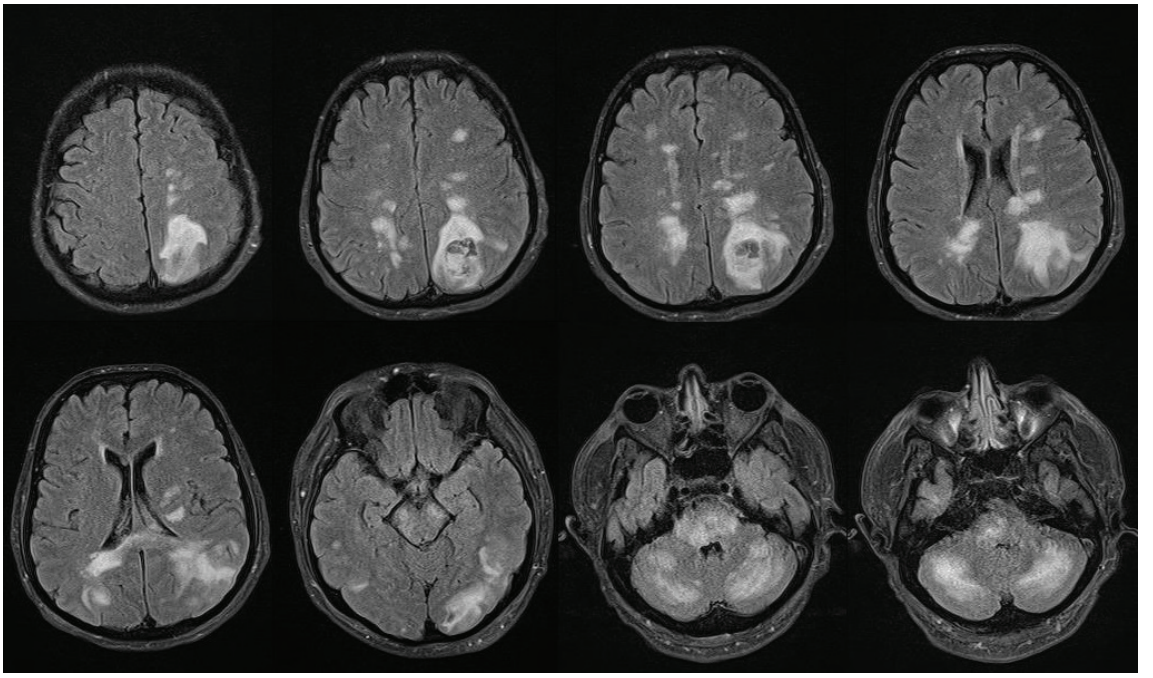

Figure 2: T2-FLAIR weighted axial MRI sections revealing left parietal hematoma, bilateral hyperintense lesions in the brainstem, cerebellum, and occipital lobes

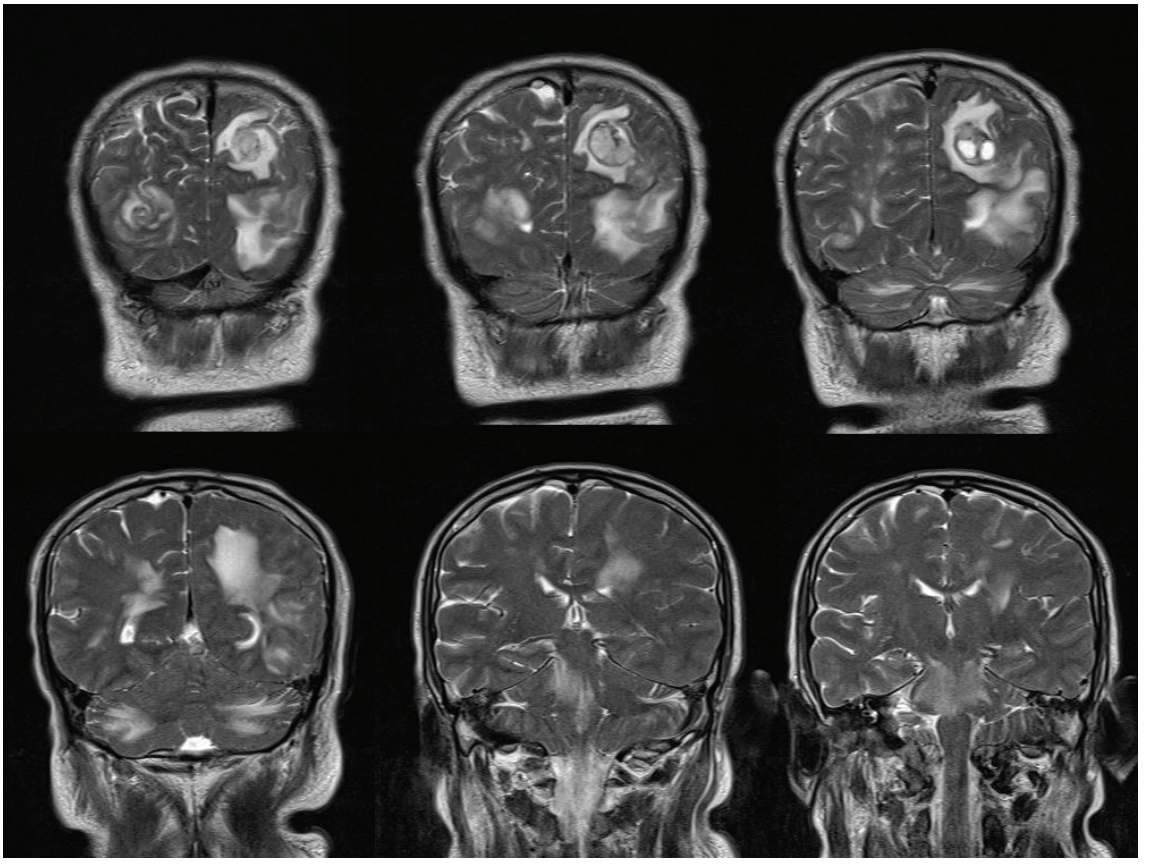

Figure 3: T2 weighted coronal MRI sections showing left parietal hemorrhage and bilateral hyperintense lesions.

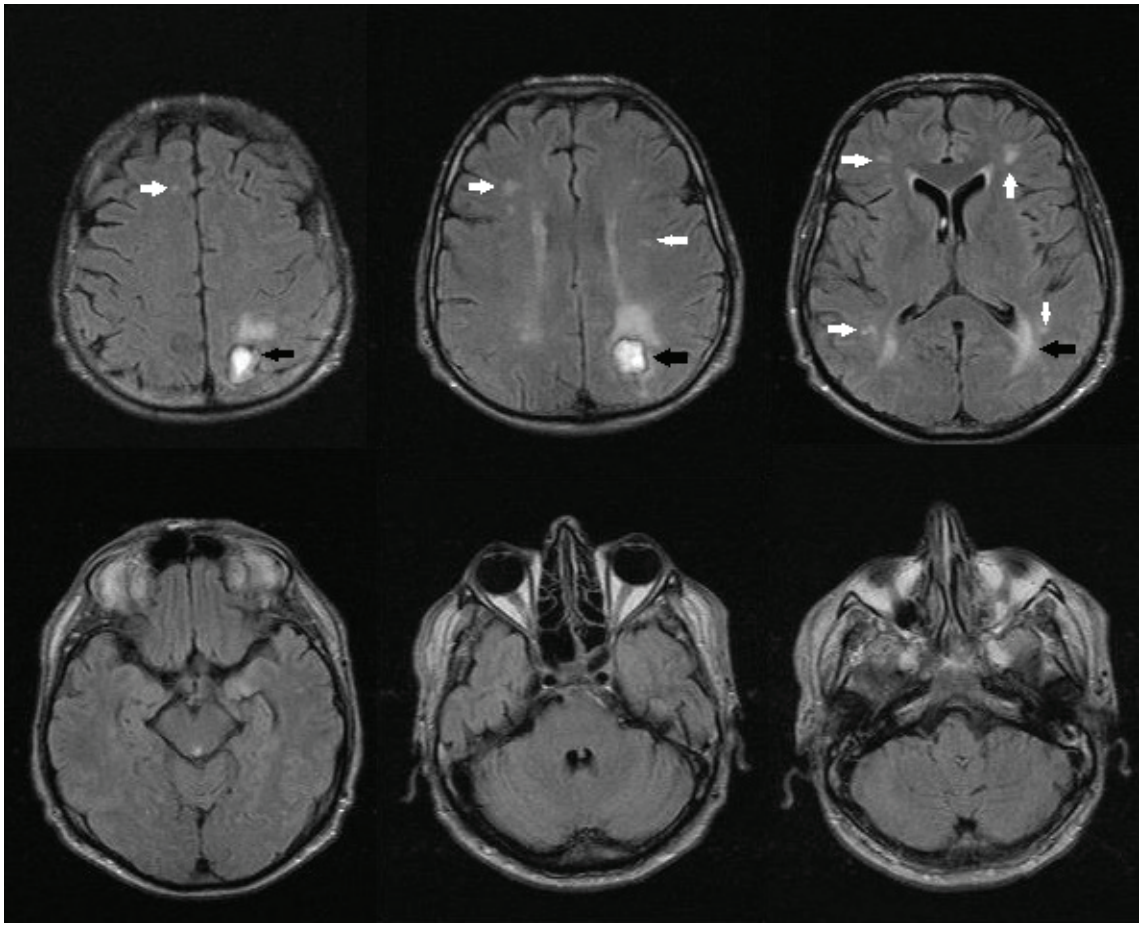

Figure 4: 1-month follow up MRI findings of the case: 1) The sequelae of the hematoma in the left parietal and right occipital lobes. 2) Chronic lesions also observed in MRI performed for headache before PRES (white arrows)

attention, disorganized thinking disappeared. Brain MRI performed one month later revealed no abnormality except chronic lesions that had been observed before PRES and the sequelae of the hematoma in the left posterior parietal and right occipital lobes (Figure 4). The patient was discharged and has been under follow-up with stable graft functions without the need for dialysis.

DISCUSSION

PRES, which developed in our patient resolved after the discontinuation of the tacrolimus therapy. We believe that acute renal failure, hypertension and hypomagnesemia in this patient also contributed to the development of PRES, but the absence of clinical or radiological improvement despite the control of BP, hemodialysis and the initiation of magnesium replacement therapy suggests that the main responsible factor was tacrolimus therapy.

The incidence of neurotoxicity is higher in patients receiving tacrolimus and PRES after solid organ transplantation seems to be most commonly associated with tacrolimus therapy (4). There is a lack of correlation between neurotoxicity and the levels of tacrolimus in the blood, and blood drug levels are mostly within the therapeutic range, as seen in our case (5-7). The drug level in the cerebrospinal fluid (CSF) was found to be much higher than the simultaneous serum level of the drug in a case with tacrolimus-associated PRES, suggesting that the drug accumulates in the central nervous system by crossing the blood-brain barrier, and that the CSF level of the drug is more closely associated with clinical symptoms than its serum level (5).

Calcineurin-associated PRES is most common in the early period after transplantation (median: 17 days, 24 hours–5 years), and occurs one year after the start of use in only 7.3% of cases (8). IV administration of the drug, hypomagnesemia, hyperlipidemia and concurrent high-dose steroid therapy increase the risk of neurotoxicity (9). Hypomagnesemia causes hypertension, impaired renal functions and encephalopathy (10, 11). Urinary magne-

sium loss is more common and severe in patients receiving tacrolimus than in those receiving cyclosporine. This partially explains why tacrolimus causes PRES more frequently than other agents (11). Therefore, agents known to be associated with hypomagnesemia, such as proton pump inhibitors, should be used with caution in these patients (12).

The risk of hemorrhage is increased in cases with tacrolimus-associated PRES, and has been reported in patients who have undergone stem cell, bone marrow and heart transplants (13). According to the literature review, our patient is the first reported case of tacrolimus-associated hemorrhagic PRES after kidney transplantation.

Treatment includes controlling BP and seizures, correcting metabolic disturbances, temporarily dose reducing or discontinuing of tacrolimus, and switching to another calcineurin inhibitor or an agent with a lower risk of neurotoxicity, such as sirolimus, everolimus, mycophenolate mofetil or hydrocortisone (8). It is important to closely monitor patients who are on tacrolimus therapy for hypomagnesemia, hypertension and hyperlipidemia, which have been identified as potential risk factors for neurotoxicity.

CONCLUSION

Despite being rare and having often a benign course, tacrolimus-associated PRES in transplant patients can lead to serious outcomes if diagnosed late. Patients who have received transplantations from unrelated and unmatched donors are at particular risk. It should be kept in mind that the condition may develop even years after transplantation.

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