Tacrolimus-induced severe leukoencephalopathy: evidence for an immune-mediated pathogenesis

C. Smeralda, [1] A. Marini, [1] A. Vogrig, [2] F. Janes, [2] P. Dolso, [2] G. Gigli, [1,2] M. Valente [1,2]

[1]*Clinical Neurology Unit, University of Udine Medical School, Udine, Italy.*

[2]*Clinical Neurology Unit, Department of Neurosciences, S. Maria della Misericordia, Udine, Italy.*

INTRODUCTION

Tacrolimus is an immunosuppressive agent widely used to prevent rejection after solid and non-solid organ transplantation. Minor neurological side effects such as headache, postural tremor, paresthesia and visual changes have been described after treatment initiation. One rare but potentially severe complication of tacrolimus is leukoencephalopathy, presenting with acute neurological symptoms such as seizures, hemiplegia and altered mental status. Brain imaging may reveal white matter lesions predominantly in the posterior cerebral regions, with features similar to PRES (Posterior Reversible Encephalopathy Syndrome). In a minority of cases, tacrolimus-induced encephalopathy shows a more diffuse and heterogeneous white matter's involvement. Rarely, it could resemble tumor-like lesions, demyelinating diseases or central pontine myelinolysis.

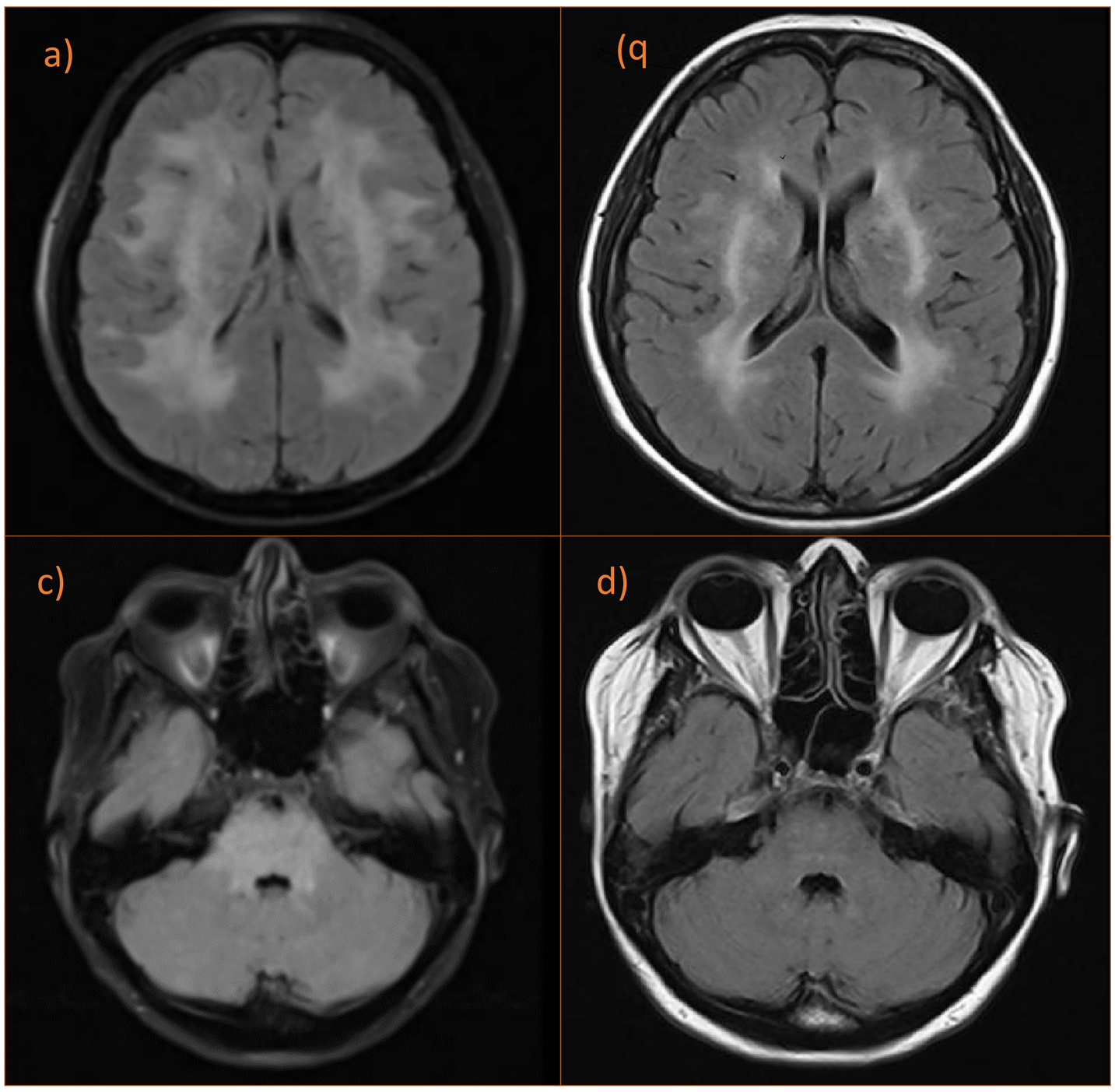
We present a case of extensive leukoencephalopathy as a rare complication of tacrolimus therapy in which serum drug levels were normal and no concomitant disease existed.

CASE REPORT

A 60-year-old woman presented to our Clinic with a 4-month history of severe analgesic-resistant headache. The pain was described as dull and bilateral. It often started in the occipital region, with subsequent anterior irradiation, and was exacerbated by supine position. She recently underwent kidney transplantation for chronic renal failure due to polycystic kidney disease. Headache started 4 months after organ transplantation, while the patient was taking 3.5 mg of tacrolimus per day. Neurological examination was normal. Complete blood count, electrolytes, CRP, liver and thyroid function tests were normal. Creatinine and urea blood levels were within normal range. Tacrolimus blood level was within therapeutic range (7.7 ng/mL; N.V. 5–12 ng/mL).

MRI scan showed T2-weighted and FLAIR diffuse and symmetric hyperintensity widely involving supratentorial and infratentorial white matter, without alterations on DWI and ADC map. The patient had no previous history of headache, stroke or CNS autoimmune diseases and her family history was unremarkable. Previous CMV infection (developed after transplantation) was reported. Serum analysis and CSF PCR for infectious diseases (Toxoplasma, Borrelia, CMV, EBV, HSV, VZV, HIV, HHV6, JCV) were all negative but elevated total protein level (1.7 g/dl) and oligoclonal bands (pattern type 3), were found in the CSF.

Diagnosis of tacrolimus-induced leukoencephalopathy was made. Treatment with steroid bolus, together with minor tacrolimus tapering, provided impressive clinical and radiological improvement at 5 months follow-up.



T2-weighted FLAIR MRI pre (a,c) and post (b,d) IV steroid treatment and tacrolimus tapering; a) diffuse and symmetric hyperintensity involving supratentorial white matter; c) subtentorial white matter involvement with swelling of the pons; b) and d) T2-weighted FLAIR MRI scan 5 months after treatment

DISCUSSION AND CONCLUSION

Our case presents interesting novelties: first, oligoclonal bands positivity and marked albuminocytologic dissociation in the CSF are unprecedented, suggesting a possible immune-mediated mechanism of tacrolimus-induced neurotoxicity; second, extension of white matter involvement, together with significant brainstem swelling, were much wider in this case compared to the Literature series. Finally, the marked clinical and radiological improvement following steroid bolus (with only minor tacrolimus dosage tapering) is in line with a drug-induced autoimmune reaction.

To our knowledge, this is the first case of neurotoxicity induced by tacrolimus, showing clear evidence for an immune-mediated pathogenesis. Additionally, our findings suggest that tacrolimus-induced leukoencephalopathy could benefit from high-dosage steroid treatment. Further studies are needed to understand the exact biological mechanism underlying tacrolimus neurotoxicity.

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