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Tacrolimus leukoencephalopathy: A neuropathologic confirmation

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Tacrolimus leukoencephalopathy has well documented clinical and neuroradiologic features.¹ The latter suggest endothelial dysfunction as the underlying etiology.² Confirmatory neuropathologic data have been lacking.

Case reports. A 40-year-old woman with biopsy-proven acute rejection was admitted 3 weeks after an orthotopic liver transplant for alcoholic cirrhosis. Alanine aminotransferase was elevated at 226 IU/L (<50 IU/L). She also had elevated cholesterol levels (237-411 IU/L) and was hypertensive (approximately 160/90). Erythrocytes showed anisocytosis and poikilocytosis (spiculated, fragmented, and targets). Tacrolimus 4 mg BID had been started the day after transplantation.

The patient had 2 days of toxic tacrolimus levels of 25 ng/mL and 29 ng/mL (>20 ng/mL), followed 4 days later by new onset seizures and mental status changes (lethargy to agitation). BP just after the seizure was 172/104. The last reading prior to her seizure was 144/88. MRI revealed two large white matter lesions in the right frontal lobe without mass effect (figure 1A). There was minimal peripheral enhancement, as well as scattered white matter lesions in the frontal and parieto-occipital lobes bilaterally (figure 1B). Her condition continued to deteriorate over the next 2 days with increasing seizure activity culminating in unresponsiveness. Brain biopsy was performed to exclude a treatable infectious process. Her platelet count at this time was 329,000/ μ L (445,000/ μ L upon admission); her prothrombin time and partial thromboplastin time were normal. However, that same day bleeding at the biopsy site necessitated a craniotomy for evacuation of a hematoma. The patient remained unresponsive for the next few days, and she died 2 months after her admission as a result of transplant rejection and hemorrhagic necrosis of the entire right centrum semiovale.

Neuropathologic findings. The small biopsy sample consisted of abnormal white matter that had no evidence of infection even with an antibody to cytomegalovirus (DAKO Envision Plus System; DAKO, Carpenteria, CA; 1:100 with proteinase K pretreatment). There was a diffuse decrease in the staining of myelin with Luxol Fast Blue, but not with an antibody to myelin basic protein (Research Diagnostics, Flanders, NJ; Monoclonal, 1:300, no pretreatment), and without appreciable periodic acid-Schiff (PAS)- or CD68-positive macrophages (DAKO Envision Plus System; Monoclonal, 1:100) (figure 1C). A comparable decrease in Bodian stained axons was observed (figure 1D). Oligodendrocytes appeared to be numerically reduced but were not activated caspase-3-positive (R & D Systems, Minneapolis, MN; Polyclonal, 1:1000). A mild increase in glial fibrillary acidic protein-positive astrocytes (GFAP) (DAKO Envision Plus System; 1:1000 with proteinase K pretreatment) and CD68-positive microglia was noted. Several small veins were surrounded by PAS-positive material that was present within the vascular lumen (figure 1E). Another vessel showed a marked perivascular decrease in myelin and axonal staining with replacement by a pale PAS-positive background stain (figure 1F). That same vessel showed strongly positive intravascular and extravascular PAS-positive droplets, focal endothelial hyperplasia, and swelling with prominent nucleoli and fibrin transudation (figure 1G). The endothelium was immunoreactive

for tumor necrosis factor-alpha (Santa Cruz Biotechnology, Santa Cruz, CA; Monoclonal, 1:5) but not for interleukin-1 (Genzyme, Cambridge, MA; Polyclonal, 1:300).

Discussion. Tacrolimus leukoencephalopathy has been included within the reversible posterior leukoencephalopathy syndrome (RPLS), which is also caused by cyclosporin, eclampsia, malignant hypertension, renal failure, and drug-induced thrombotic thrombocytopenic purpura (TTP).¹ The most common clinical features include the sudden onset of seizures, headache, altered mental status, visual abnormalities, aphasia, and hemiparesis.¹

Neuroradiologic findings are most commonly located in white matter of the posterior cerebrum, but also in the white matter of the cerebellum, frontal lobes, and brainstem.¹ Radiologic imaging provides evidence of vasogenic edema and generalized cerebrovascular dysregulation.²

Neuropathologic confirmation of the neuroradiologic interpretations, however, has been lacking. Cortical and subcortical infarcts, areas of diffuse neuronal necrosis, coagulative necrosis containing numerous macrophages, neutrophilic invasion of small cortical arteries and perivascular space, thrombi with perifocal edema³, and areas of "demyelination" with minimal reactive astrocytosis have been reported.⁴

Our patient had toxic levels of tacrolimus and neuropathologic evidence of endothelial damage with vasogenic edema in white matter in the absence of infarcts or demyelination. The myelin pallor in our patient and in a previous report does not constitute active demyelination (i.e., myelin breakdown with phagocytosis of myelin debris), and is more consistent with vasogenic edema as has been reported in HIV leukoencephalopathy.⁵

The precise etiology of tacrolimus leukoencephalopathy is not known. Tacrolimus toxicity has been implicated in cases of drug-induced thrombotic thrombocytopenic purpura (TTP); nephrotoxicity also has been reported in both animal and human studies. The precipitating event for both is most likely endothelial cell damage, which includes a microangiopathy with fibrinoid degeneration and endothelial swelling,⁶ comparable to that seen in our patient. Further evidence for endothelial dysfunction in our patient can be deduced from her erythrocytic abnormalities. Polymorphisms in the *ABCD1* gene that encodes the P glycoprotein transporter, a multidrug efflux pump acting to exclude tacrolimus from the brain, may render some patients genetically susceptible to the adverse neurologic effects of tacrolimus.⁷

One common precursor of RPLS is hypertension and hypocholesterolemia. The posterior circulation is purportedly more vulnerable to alterations in blood pressure because of its relative paucity of sympathetic innervation.³ In our patient, neither hypocholesterolemia nor the sympathetic innervation seem operative because at least some of the leukoencephalopathy and endothelial damage was located in the frontal lobe and she was hypercholesterolemic. The temporal linkage of her leukoencephalopathy to toxic drug levels suggests that tacrolimus was the main determinant for the endothelial lesions, but mild hypertension may have played a synergistic role in the genesis of the vasogenic edema. Additional references may be found on line at www.neurology.org.

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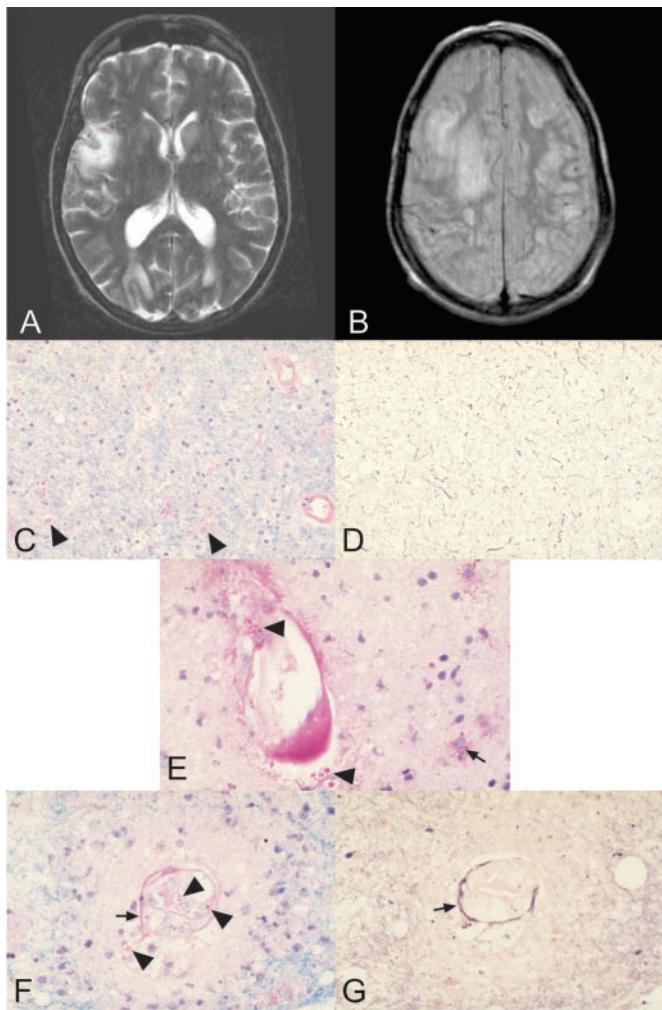


Figure. Neuroradiologic and neuropathologic features. (A) Axial T2-weighted image shows focal high intensity lesions in right frontal subcortical white matter and bilateral occipito-parietal, deep and subcortical white matter lesions. (B) Axial proton density weighted image shows bilateral deep and subcortical fronto-parietal white matter lesions. (C) Myelin pallor in the absence of periodic acid-Schiff (PAS)-positive macrophages, but a few reactive astrocytes (arrowheads). Luxol Fast Blue-PAS, original magnification, $\times 90$. (D) A comparable decrease in stainable axons in a serial section of A, without axonal abnormalities (e.g., spheroids). Bodian, original magnification, $\times 90$. (E) Small vein with a rim of PAS-positive material and both intravascular and extravascular PAS-positive droplets, probably composed of serum glycoproteins (arrowheads); some of these are within glial cells, presumably astrocytes (arrow). Diastase-PAS, original magnification, $\times 150$. (F) Another small vein with both intravascular and extravascular PAS-positive droplets (arrowheads) and linear material (arrow), the absence of perivascular myelin staining and replacement by a faint PAS-positivity. Duplicate, swollen endothelial cells with prominent nucleoli. Luxol Fast Blue-PAS, original magnification, $\times 150$. (G) Fibrin transudation in wall of same vessel as in D (arrow). Phosphotungstic acid-hematoxylin; original magnification, $\times 150$.

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Natural history of conservatively treated meningiomas

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Asymptomatic brain meningiomas are often diagnosed incidentally during investigations for minor neurologic symptoms. Their management is controversial because not enough data have been collected on the growth rate,^{1–7} and it may vary according to tumor location or patient age. We reviewed the natural history of conservatively treated brain meningiomas with a focus on the features associated with tumor growth.

Patients and methods. The files of 43 patients with 51 brain meningiomas that were treated conservatively at Beilinson hospital between 1989 and 1999 were reviewed. The diagnosis was based on a finding of an extra-axial dural-based enhancing mass on CT or MRI. Follow-up was performed 6 to 9 months after

diagnosis and yearly thereafter. Tumor size was calculated according to largest diameter in the antero-posterior, medio-lateral, or oblique dimension (perpendicular analysis). Growth was defined as a change in tumor size of at least 2 mm. The tumors were classified as growing or nongrowing, and the groups were compared for the following features: patient age, sex, tumor location, size, calcification, and duration of follow-up.

Statistical analysis. Student's *t*-test was used to analyze the significant differences in mean continuous variables, and χ^2 or Fisher's Exact Test was used, as appropriate, to analyze differences in categorical variables between groups. *p* Values ≤ 0.05 were considered significant.

Results. **Patient and tumor data.** The clinical data are reported in the table. The study group consisted of 8 men and 35 women aged 39 to 83 years (mean 65 years). Four patients had two tumors, and two patients had three. In all but two patients, the symptoms were not caused by the tumor itself. Average tumor size at diagnosis was 17 ± 8 mm (range 3–45 mm). Twelve tumors

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