

Late Fulminant Posterior Reversible Encephalopathy Syndrome After Liver Transplant

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Abstract

Objectives: Posterior leukoencephalopathy due to calcineurin-inhibitor-related neurotoxicity is a rare but severe complication that results from treatment with immunosuppressive agents (primarily those administered after a liver or kidney transplant). The pathophysiologic mechanisms of that disorder remain unknown.

Case: We report the case of a 46-year-old woman who received a liver transplant in our center as treatment for alcoholic cirrhosis and in whom either a fulminant course of posterior leukoencephalopathy or posterior reversible encephalopathy syndrome developed 110 days after transplant. After an initially uneventful course after the transplant, the patient rapidly fell into deep coma.

Results: Cerebral MRI scan showed typical signs of enhancement in the pontine and posterior regions. Switching the immunosuppressive regimen from tacrolimus to cyclosporine did not improve the clinical situation. The termination of treatment with any calcineurin inhibitor resulted in a complete resolution of that complication.

Conclusions: Posterior reversible encephalopathy syndrome after liver transplant is rare. We recommend a complete cessation of any calcineurin inhibitor rather than a dose reduction.

Key words: *Calcineurin inhibitor, Adverse event, Neurotoxicity, Immunosuppression, Tacrolimus*

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Posterior reversible encephalopathy syndrome due to calcineurin-inhibitor-related neurotoxicity is a rare but severe complication of treatment with immunosuppressive agents (primarily those administered to patients who have received a liver or kidney transplant). The pathophysiologic mechanisms of that syndrome, 50 cases of which have been described in the literature, remain unknown. The onset of posterior reversible encephalopathy syndrome in more than 80% of the cases described developed within the first 90 days after transplant (1). The clinical features of that syndrome are seizure (74% of patients), altered mental status (50%), and visual abnormalities (28%). To treat that complication, most investigators recommend only a reduction in the calcineurin inhibitor dosage, but others suggest that the termination of therapy with all calcineurin inhibitors is essential.

The diagnosis of posterior reversible encephalopathy syndrome is based on the results of a magnetic resonance imaging scan. Relying on the findings from computed tomographic scans, electroencephalograms, lumbar puncture, and stereotactic biopsies, which in the diagnosis of that syndrome are unspecific and useless, can be dangerous. One death associated with posterior reversible encephalopathy syndrome has been reported (2).

We describe the case of a 46-year-old woman who received a liver transplant in our center as treatment for alcoholic cirrhosis and in whom either a fulminant course of posterior leukoencephalopathy or posterior reversible encephalopathy syndrome developed 110 days after transplant. The termination of treatment with calcineurin inhibitor resulted in the patient's complete recovery.

Case report

A 46-year-old woman received a liver transplant in our institution as treatment for alcoholic cirrhosis at Child-Pugh stage C. The operation and initial clinical course were uneventful. Immunosuppressive treatment was initiated with tacrolimus (blood level, 10-15 $\mu\text{g/L}$) and prednisolone. Acute renal failure developed within the first week after orthotopic liver transplant. In the following weeks, this patient experienced a second-degree acute rejection episode (which was successfully treated with steroids) and severe hyperbilirubinemia that remained unexplained and resolved without treatment. She recovered slowly but steadily, her kidney function resumed, and she was transferred to a peripheral station on postoperative day 80. Until then, only minor neurologic adverse effects of tacrolimus (tremor, headache) had been diagnosed. On postoperative day 108, the patient was found in her bed confused and somnolent. No seizure was documented. On postoperative day 110, she became deeply comatose and exhibited no clinical reaction to pain, sound, or light. Cyclosporine was substituted for tacrolimus with no benefit. The patient remained comatose, paraplegic, and clinically decerebrated. Neurologists and radiologists diagnosed severe, irreversible brain damage. After the termination of treatment with calcineurin inhibitors and the initiation of immunosuppression with mycophenolate mofetil and prednisolone, however, the patient experienced a full recovery.

Diagnostics

In the patient described in this report, the results of all laboratory and serologic tests were negative, and lumbar puncture revealed no abnormalities. An electroencephalogram showed severe brain dysfunction, but that finding was too unspecific to contribute to the diagnosis. Epileptiform activity was not noted in the results of any electroencephalographic examination. A computed tomographic scan showed abnormal gray matter. T2-weighted FLAIR magnetic resonance imaging examinations of the brain revealed occipital, parietal, temporal, and pontine gray and white matter abnormalities (Figures 1 and 2). Contrast medium enhanced magnetic resonance

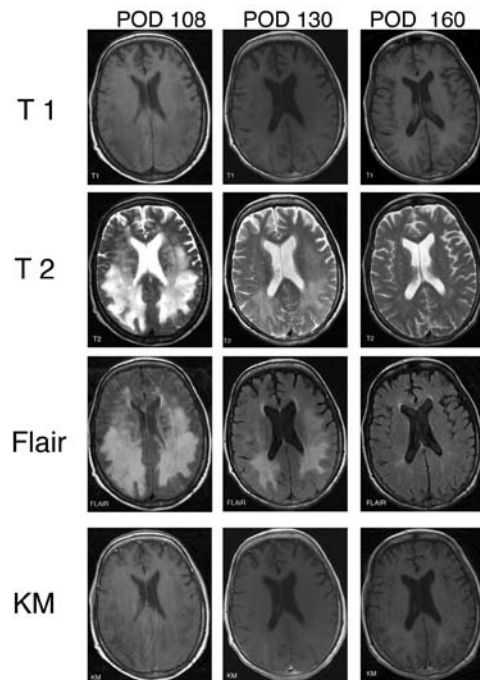


Figure 1. MRI-scan of the brain. From each MRI scan, T1, T2, FLAIR and contrast media-enhanced pictures are shown. The patient was clinically decerebrated on POD 108. T2 and FLAIR series show severe enhancement of the grey matter. Contrast media MRI detects an impairment of the blood-brain barrier. Occipital and parietal damage was classified as irreversible after the first 2 MRI-scans. All pathologies regressed almost totally within 52 days. On POD 130 and POD 160, the patient was awake and adequate.

Abbreviations: FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance image; POD, postoperative day.

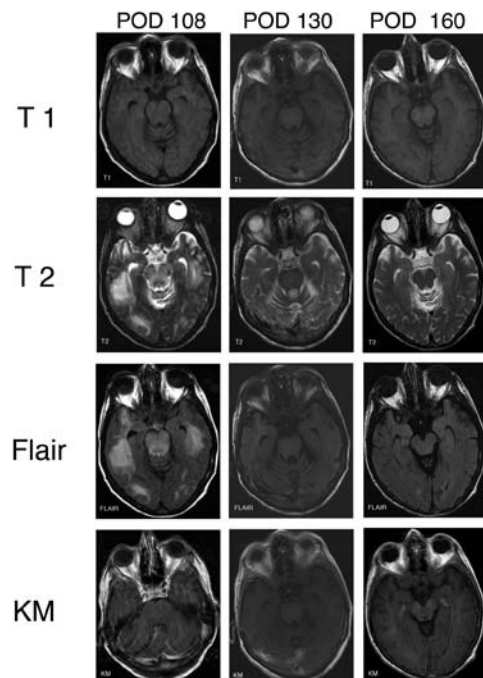


Figure 2. MRI-scan of the brain stem. Pontine structures and brain stem show severe and diffuse enhancement on POD 108. This brain damage was considered irreversible, too. On POD 160, only minimal damage remained detectable.

Abbreviations: MRI, magnetic resonance image; POD, postoperative day.

imaging showed impairment of the blood-liquor barrier and leakage of the contrast medium.

Discussion

Neurotoxicity and nephrotoxicity are the major adverse effects of calcineurin inhibitor therapy (3, 4). Posterior reversible encephalopathy is the most severe and dramatic consequence of calcineurin inhibitor neurotoxicity. Data indicate that posterior reversible encephalopathy syndrome develops most often in patients who have undergone a liver transplant (70% of all such patients) and less often in those who have received a kidney or heart transplant. That risk seems to increase after liver retransplant. The incidence of posterior reversible encephalopathy syndrome ranges from 1% to 6% in transplant patients and occurs in 80% within the first 90 days after the initiation of calcineurin inhibitor therapy (1). Cyclosporine and tacrolimus seem to have an equal potential to cause posterior reversible encephalopathy syndrome, but in cyclosporine-treated patients, dose dependency, and a correlation of serum drug levels is suspected. That syndrome, which seems more likely to develop in female and elderly liver transplant patients, also occurs in pediatric patients who have received a liver transplant (5). One patient death due to posterior reversible encephalopathy syndrome has been described in the literature; thus the mortality rate associated with that condition is about 1% to 2% (2). As a pathogenetic mechanism, an impairment of the blood-liquor barrier of the brain seems to be relevant (6).

Of all the various diagnostic procedures, magnetic resonance imaging seems to yield the most relevant information about posterior reversible encephalopathy syndrome. That procedure poses no risk to the patient but is relatively expensive, and its availability may be limited. Magnetic resonance imaging findings in T2-weighted sequences show the typical findings of bright enhancement of the occipital, parietal, or temporal white matter. In our patient, even the pontine structures were extensively affected. If radiologists or neurologists are not familiar with the clinical or radiologic picture of posterior reversible encephalopathy syndrome,

then misdiagnosis can result and more-extensive diagnostics might wrongly be recommended. However, relatively more-invasive diagnostics such as liquor puncture or stereotactic brain biopsy do not seem to be justified (7). From the data reported thus far, neither an obvious benefit nor a therapeutic consequence resulted in such patients who underwent those procedures (8, 9).

If the excellent prognosis of patients with posterior reversible encephalopathy syndrome is unknown to the managing clinicians, the discussion of further treatment may not arise. We emphatically caution physicians against acting on statements about irreversible brain damage or resulting mental disabilities.

There is no consensus in the literature regarding the best possible treatment of posterior reversible encephalopathy syndrome. Some authors recommend terminating treatment with calcineurin inhibitor, and others suggest that reducing the dosage of a calcineurin inhibitor should be enough. After the dosage of those agents has been reduced, patients can recover completely from posterior reversible encephalopathy syndrome but retain the advantage of standard calcineurin inhibitor-based immunosuppression with favorable and reproducible results. In our patient, the initial medication switch from tacrolimus to cyclosporine on day 110 was almost fatal. Either the dose reduction or complete cessation of treatment with a calcineurin inhibitor should be the therapy of choice in patients with posterior reversible encephalopathy syndrome.

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