

# Rapidly Reversible Leukoencephalopathy After Acute Kidney Graft Rejection in a Patient With Systemic Lupus Erythematosus

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## Abstract

The finding of white matter damage on brain magnetic resonance imaging may correspond to a wide variety of etiologies. The differential diagnosis may be particularly difficult in immunocompromised patients with a specific autoimmune disease or who are receiving medications after a solid-organ transplant. Herein, we describe the case of a 22-year-old woman who developed serious neurological complications after an acute rejection of a kidney graft that she had received a few months previous to treat a systemic lupus erythematosus-related nephritis. We discuss the possible hypotheses underlying the development of acute leukoencephalopathy in this setting.

**Key words:** *Acute kidney injury, Autoimmune disease, Central nervous system impairment, Encephalopathy, Renal transplantation, Solid-organ transplantation*

## Introduction

The diagnosis of acute central nervous system (CNS) disorders may be difficult in patients who present with multiple diseases, such as immunocompromised patients receiving medications for an autoimmune disease or for organ transplant. Brain magnetic resonance imaging (MRI) is the most appropriate imaging modality to identify the specific types of brain tissue damage. Leukoencephalopathy is a

generic term to describe disease processes of various etiologies. Herein, we describe a case of acute toxic leukoencephalopathy (ATL) in a young patient with systemic lupus erythematosus (SLE) who had recently received a renal transplant for rapid worsening of SLE-related nephritis.

## Case Report

A 22-year-old African woman was admitted in August 2022 in the emergency department after a long flight back from Africa to Europe. She started to feel unwell during the flight, with abdominal pain, sleepiness, and rapid decrease of consciousness that required emergency admission. Shortly before this, while visiting Uganda for holidays, she had complained of asthenia, abdominal discomfort, and some episodes of diarrhea together with oliguria.

Her medical history showed that she had been diagnosed with SLE at the age of 14 years. Lupus nephritis developed as the main complication 4 years later. In July 2021, she had benefited from a kidney transplant from a living related donor (her mother). An initial episode of acute graft rejection occurred in November 2021 and was controlled by corticosteroids pulse therapy, plasma exchanges, and anti-T-lymphocyte globulins.

The patient was suspected of low adherence to the prescribed immunosuppressive therapy, which included prednisone 10 mg/day, tacrolimus 40 mg/day, and azathioprine 100 mg/day. Tacrolimus was not undetected at admission, and the accompanying relatives suspected that the patient had repeatedly omitted to take at least tacrolimus.

At admission to the emergency department, she had a temperature of 35.5   C, heart rate of 82 beats/min, blood pressure of 132/85 mm Hg,

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respiratory rate of 17 breaths/min, and pulse oximetry oxygen saturation of 100%. Her Glasgow coma scale score decreased from 14/15 to 8/15 within 1 hour and she presented with left-sided hemiparesia. She underwent orotracheal intubation. A brain computed tomography scan failed to reveal any lesion at that time (not shown). A lumbar puncture was then performed, and cerebrospinal fluid analysis only revealed 2 elements; multiplex polymerase chain reaction analysis remained negative for neurotropic viruses including JC/BK polyomavirus. Laboratory results showed arterial pH 7.11, bicarbonate level of 8 mmol/L, lactate of 0.5 mmol/L, potassium of 9.7 mmol/L, serum urea of 334 mg/dL, creatinine of 29.5 mg/dL, osmolality of 363 mmol/kg, hemoglobin of 6.2 g/dL, platelet count of  $229 \times 10^3$  cells/ $\mu$ L, lactate dehydrogenase of 329 IU/L, and schistocytes of 1.8%. Specific biomarkers for SLE revealed C3 complement, 0.78 g/L (reference range, 0.90-1.80 g/L); C4 complement, 0.17 g/L (reference range, 0.10-0.40 g/L); antibody against double-stranded DNA immunoglobulin G, 15.0 IU/mL (reference range, <10 IU/mL); and C-reactive protein, 133.4 mg/L (reference range, <5.0 mg/L).

The patient was transferred to the intensive care unit for continuous venovenous hemofiltration. Acute kidney rejection was suspected, so tacrolimus was reintroduced at a daily dose of 40 mg for 4 days and then tapered down to 16 mg/d together with methylprednisolone 4 mg/d, while azathioprine was stopped. The peak serum concentration reached 40.7 ng/mL for tacrolimus. A brain MRI was performed 3 days after admission, and diffusion-weighted imaging (DWI) revealed severe white matter (WM) cytotoxic edema involving diffusely the supratentorial compartment without any other focal parenchymal injury. Only a faint concomitant vasogenic edema was observed on fluid-attenuated inversion recovery (FLAIR) T2-weighted images (that is, FLAIR with longer TE and TR times, for which T2 is the transverse relaxation time, TR is the repetition time, and TE is time to echo) (Figure 1, A-C).

A continuous electroencephalogram recording showed focal ictal discharges within right temporo-occipital area, which were treated with valproic acid. Immunophenotyping excluded a circulating B-cell lymphoma or an immune reconstitution inflammatory syndrome (IRIS). The neurological status rapidly improved, which allowed extubation shortly after the cerebral MRI, and complete recovery

without neurological deficit occurred within the next 48 hours. A renal biopsy was performed on day 6 and confirmed acute cellular and humoral rejection. A follow-up brain MRI was performed 5 days after the initial MRI and revealed complete subsidence of cytotoxic edema (Figure 1, D-F). After evidence of the irreversible renal damage, a transplantectomy was initiated.

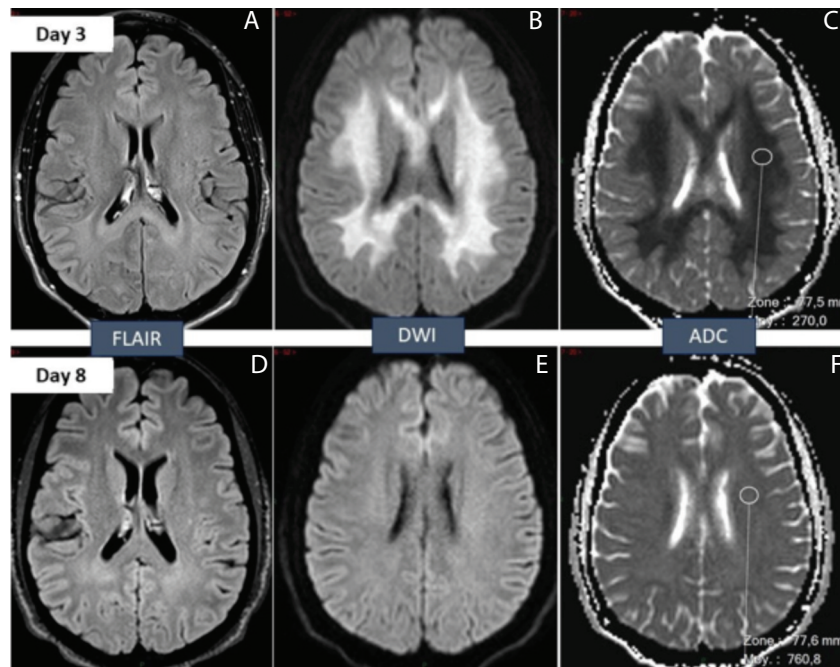
## Discussion

Our patient, a young African woman who had previously received a kidney transplant to treat SLE-related nephritis, presented with a combination of severe neurological dysfunctions including loss of consciousness, seizure, and hemiparesis together with high suspicion of acute kidney graft rejection due to low compliance to the immunosuppressive treatment. Brain MRI work-up demonstrated rapidly reversible leukoencephalopathy with a strong prominence of cytotoxic edema of the WM.

In SLE, a wide range of neurological symptoms may be present, including psychiatric disorders, stroke, seizures, myelopathy, chorea, and headaches. Also, a wide range of abnormalities may be observed on cerebral MRI views. The finding of "leukoencephalopathy" (ie, WM damage on brain MRI) may encompass different conditions in SLE.<sup>1</sup> Diffuse leukoencephalopathy on T2-FLAIR sequences with hyperintensity on DWI reflecting cytotoxic edema with free-water diffusivity reduction featured by a decrease in apparent diffusion coefficient (ADC) values is more frequently observed in young women.<sup>2</sup> It may be the first manifestation of juvenile-onset neuropsychiatric SLE. Contrary to the ischemic stroke-related cytotoxic edema, the edema observed in SLE may be fully reversible as illustrated by our patient (Figure 1, E to F). In addition, some patients with diffuse leukoencephalopathy may also present with signs of intracranial hypertension as the consequence of concomitant vasogenic edema, which is best seen on T2-FLAIR views.<sup>3</sup>

In our patient, a combination of vasogenic and cytotoxic edema was observed but with a strong prominence of the cytotoxic edema. Treatment of SLE-related diffuse leukoencephalopathy requires intravenous steroid pulse therapy alone in most cases, but some refractory patients may require an additional treatment regimen with rituximab or cyclophosphamide.

Figure 1. Magnetic Resonance Imaging Monitoring



**Abbreviations:** ADC, apparent diffusion coefficient; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; WM, white matter

Images in top row (A, B, C) show results from initial examination at day 3, with all 3 views in similar slice location through the supratentorial space. Images in bottom row (D, E, F) show results of follow-up examination 5 days later using similar sequences in similar slice location. (A) axial transverse FLAIR view shows faint hypersignal intensity of the WM prominently involving the parietal lobes (solid arrow) and the splenium of corpus callosum (dotted arrow) featuring only slight vasogenic edema. (B) DWI view shows diffuse abnormal hypersignal intensity within WM (asterisks) featuring strong cytotoxic (C) DWI-derived ADC map shows severe hypointensity of the WM (asterisks) with decreased ADC values at  $270 \times 10^{-6} \text{ mm}^2/\text{s}$  (reference range,  $700\text{--}800 \times 10^{-6} \text{ mm}^2/\text{s}$ ), which confirms strong restriction of free-water diffusivity. (D) axial transverse FLAIR view shows moderate subsidence of the vasogenic edema. (E) DWI view shows complete normalization, which indicates complete recovery of the cytotoxic edema. (F) DWI-derived ADC map confirms normalization of ADC value at  $760 \times 10^{-6} \text{ mm}^2/\text{s}$ .

Progressive multifocal encephalopathy (PML) is a rare and devastating demyelinating disease of the CNS caused by the so-called John Cunningham virus, of which immunological traces are observed in 70% of the general population. Progressive multifocal encephalopathy most often arises in patients with severe underlying immunosuppression, and SLE is associated with the highest risk for PML in patients with rheumatological conditions.<sup>4</sup> The PML complication of John Cunningham virus infection has also been described in kidney transplant recipients.<sup>5</sup> The prognosis of PML is poor, with a mortality rate reaching 60% to 75%.<sup>6</sup> Analysis by MRI plays a key role in the diagnosis of PML. In patients with severe immune deficiency, WM lesions do not enhance after intravenous perfusion of gadolinium-based contrast agent, and no restriction in water diffusion is observed. Conversely, the edges of the lesions can show contrast enhancement together with diffusion restriction in inflammatory PML. Treatment of PML

usually relies on reduction of immunosuppression, which could be difficult in patients with underlying autoimmune diseases.<sup>7</sup>

There is also an overlap between PML and the IRIS. This syndrome was initially described in patients with HIV who had received highly active antiretroviral therapy. Very rarely, PML and IRIS have been observed in kidney transplant recipients<sup>8</sup> or in patients with SLE.<sup>9</sup> The mechanism is linked to a reduction or removal of immunosuppression with a paradoxical worsening of neurological symptoms due to recovery of inflammatory capabilities well assessed on contrast-enhanced MRI scans. There is no firm recommendation for treatment of IRIS because pulse steroid therapy and immunosuppression withdrawal carry their own intrinsic risks.

Posterior reversible encephalopathy syndrome (PRES) is a clinical radiological condition characterized by headache, sight disturbances, seizure, and altered mental status together with “pure” vasogenic

edema mainly affecting the subcortical WM of the occipital and parietal lobes. The pathognomonic MRI pattern of the condition combines strongly positive T2-FLAIR images for vasogenic edema and negative corresponding DWI views for cytotoxic edema. A central-variant PRES has been described that involves the basal ganglia and brainstem, with sparing of the posterior lobes.<sup>10</sup> This subtype has been reported on the setting of both SLE and renal transplant, and differences in the radiological presentation at MRI examination allows differentiation between both PRES subtypes, IRIS, PML, and diffuse leukoencephalopathy illustrated by our patient.<sup>10</sup>

Immunosuppressive drugs (eg, mycophenolate, tacrolimus, cyclosporine) for treatment of patients with SLE or for solid-organ recipients can also induce some forms of ATL, which could occur in up to 12.6% of patients.<sup>11</sup> The MRI findings in the condition are described as confluent and symmetric hyperintense areas on DWI prominently involving the cerebral WM associated with restricted water diffusivity (low ADC values appear dark on ADC-mapped views) featuring cytotoxic edema, as observed in our patient (Figure 1, B and C). One putative mechanism for the pattern could be the drug-induced disruption of the cerebral vasculature, which may result in intramyelinic (and not interstitial) edema.

The influence of blood urea nitrogen levels on the pathophysiology of ATL is not precisely known. In the series of 101 patients reported by Ozutemiz and colleagues, serum blood urea nitrogen was increased in 26% of the patients.<sup>11</sup> Coexistence of PRES and ATL has also been discussed.<sup>12</sup> Uremic encephalopathy has been associated with symmetric superficial and deep T2 hyperintensities, but some observations have reported on selective periventricular WM involvement sparing the basal ganglia on DWI.<sup>13</sup>

Finally, there are also cases of obvious association between SLE and B-cell lymphoma and between lymphoproliferative disorders, including B-cell lymphoma from Epstein-Barr virus-driven polyclonal proliferations, with solid-organ transplantation.<sup>14</sup> In immunocompromised patients such as patients with SLE, primary CNS lymphoma can be seen as homogenous, heterogeneous, or sometimes peripheral enhancement of lesions with mass effect and variable water diffusivity restriction.<sup>1,15</sup>

In our observation, clinical and biologic signs indicated that the activity of the SLE disease was

weak. Therefore, diffuse demyelinating lesions due to the progression of SLE were deemed unlikely. Progressive multifocal encephalopathy, IRIS, PRES, and primary CNS lymphoma were reasonably excluded by the MRI work-up at admission and by the 5-day follow-up examination, which demonstrated complete subsidence of both types of cytotoxic edema. We concluded that the most likely cause was ATL due to toxic alterations of the blood-brain barrier synergistically caused by renal failure/hyperazotemia and by immunosuppressive drugs. As mentioned, azathioprine had been stopped, but a high dose of tacrolimus had been given immediately after hospital admission. A rapid clinical and radiological recovery together with improvement of the renal function after renal replacement therapy was observed, thereby rendering steroid pulse therapy unnecessary.

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