Background: During the past 10 years, acute disseminated encephalomyelitis has been reported a few times after organ transplantation.

Objective: To report a case of acute disseminated encephalomyelitis as a complication of liver transplantation.

Design: Case report.

Setting: The University of North Carolina Hospital and Medical Center, Chapel Hill.

Patient: A 49-year-old woman admitted because of acute onset of paresthesias, sensory loss, and weakness after liver transplantation. Acute clinical presentation, results of imaging studies, and comprehensive laboratory evaluation were consistent with acute disseminated encephalomyelitis.

Interventions: High-dose intravenous corticosteroid therapy followed by maintenance oral dosing.

Main Outcome Measures: Clinical and magnetic resonance imaging improvement.

Results: Corticosteroid therapy halted clinical progression, with partial resolution of lesions on magnetic resonance images of the brain and spinal cord.

Conclusions: This is, to our knowledge, the first report of acute disseminated encephalomyelitis after liver transplantation. Possible pathogenic mechanisms include a cross-reactive immune response to foreign antigens present within the transplanted organ, or an inflammatory response triggered by viral infection in an immunocompromised host.

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Acute disseminated encephalomyelitis (ADEM) is characterized by the acute onset of disseminated, immune-mediated central nervous system (CNS) demyelination that typically begins within 3 to 6 weeks of an antigenic challenge such as vaccination or viral infection. It usually occurs in children and adolescents because of their more frequent immunization and exposure to antigens, but it is also reported in adult populations. Acute disseminated encephalomyelitis occurs rarely after organ transplantation, as a result of immunosuppressive therapy that is routinely administered after transplantation to prevent graft-vs-host disease. Acute disseminated encephalomyelitis has been seen as a complication after renal, blood stem cell, bone marrow, and heart-lung transplantation. In this study, we report a case of ADEM that occurred 14 weeks after liver transplantation in an adult female patient. The transplanted organ constituted an antigenic challenge that triggered an acute inflammatory response and subsequent ADEM.

A 49-year-old white woman with a history of end-stage liver disease secondary to cryptogenic cirrhosis underwent orthotopic liver transplantation. At a posttransplantation assessment 6 days before presentation, the patient was afebrile, complaining only of mild paresthesias in the left hand and forearm, correlating with mild sensory loss in the same distribution. After this visit, oral ganciclovir, oral prednisone, and cytomegalovirus immune globulin infusions were discontinued as part of the standard posttransplant protocol, and immunosuppressive treatment with tacrolimus was continued. Clinical and laboratory findings did not show evidence of an infectious process.

The patient’s sensory symptoms progressed during the next 6 days to involve paresthesias and sensory loss in all extremities. Neck pain and stiffness without constitutional symptoms or fever began 4 days after symptom onset. On examination, the patient was alert and oriented and had nor-
She had decreased grip strength on the left, hyperesthesia to fine touch below T1, reduced vibratory sensation in the lower extremities bilaterally, mild dysynergia in the left upper extremity, diffusely brisk reflexes, and an extensor plantar response on the left. Magnetic resonance images of the brain and spinal cord showed changes consistent with an acute disseminated demyelinating process (Figures 1, 2, and 3) (all images were downloaded from the University of North Carolina Hospitals, Chapel Hill, picture archiving and communications system without further modification).

Cerebrospinal fluid analysis showed 12 nucleated cells per microliter (64% neutrophils) and a protein level of 69 mg/dL but was otherwise unremarkable, including a comprehensive viral panel. Results of an extensive medical and laboratory workup performed to rule out infectious, toxic, inflammatory, metabolic, and other causes were negative.

High-dose intravenous methylprednisolone sodium succinate treatment was started 48 hours after admission and almost immediately halted the progression of the patient’s neurologic symptoms, followed by slight improvement in her sensation and strength. Intravenous corticosteroid infusion was followed by an extended course of oral prednisone.

A follow-up magnetic resonance image of the brain 2 days after the initiation of corticosteroid therapy showed reduced contrast enhancement of the lesions. The size and signal intensity of the lesions on T2-weighted images were unchanged, but they did exhibit new hyperintensity on diffusion-weighted imaging. A repeat magnetic resonance image of the spinal cord showed resolution of the patchy contrast enhancement, with no change in the size or signal intensity of the diffuse cord enlargement. A third imaging study obtained 1 month after admission showed significant reductions in lesion size and signal intensity. After a hospital course complicated by adult respiratory distress syndrome, the patient was discharged home with intensive physical therapy.

This is, to our knowledge, the first documented case of ADEM after liver transplantation. Posttransplant ADEM is rare. The appearance of the spinal cord lesion on magnetic resonance images in this patient invoked a differ-
ential diagnosis of CNS lupus, neurosarcoidosis, and vitamin B<sub>12</sub> deficiency, but the acute fulminant monophasic course, cerebrospinal fluid findings, and results of other laboratory studies were most consistent with ADEM.

The imaging and pathological findings in ADEM tend to resemble those in multiple sclerosis (MS).<sup>5,9</sup> In comparison with MS, ADEM lesions are disseminated more peripherally in the subcortical area and frequently spare the periventricular region. They are more extensive, enhance after contrast administration, and occasionally involve gray-matter structures including thalami.<sup>10</sup> Spinal cord involvement is as common as in MS.<sup>11</sup> However, the lesions seen on spine imaging in this case were different from the lesions usually seen in MS, which are commonly multiple, span 1 or 2 spinal segments, and occupy less cross-sectional area. In this case, the diagnosis of ADEM was differentiated from MS on the basis of the imaging characteristics noted previously, as well as the absence of previous symptoms to suggest MS, the acuteness and severity of presentation, and the lack of subsequent relapses.

Although no controlled therapeutic trials for ADEM exist, the short-term prognosis of ADEM may improve with corticosteroid treatment.<sup>12</sup> Corticosteroid therapy is usually associated with partial resolution of the lesions, and clinical recovery may be followed by apparent remyelination. Plasmapheresis and cytotoxic agents, which have been used in cases where corticosteroids have failed,<sup>13</sup> have not been used extensively enough to draw firm conclusions regarding efficacy.

Long-term prognosis is generally reported to be good. Recurrences of ADEM are rare,<sup>14</sup> typically respond to corticosteroid treatment, and tend to involve the sites of previously established lesions.<sup>15</sup>

The immune mechanisms of posttransplant ADEM may be similar to those putatively involved in classic ADEM. Experimental allergic encephalitis, an animal model of ADEM and MS, has been useful in studies of mechanisms of autoimmune response. Experimental allergic encephalitis is induced in animals by immunization with myelin antigens that induce an autoimmune T-cell response toward CNS myelin, the development of inflammatory demyelinating CNS lesions, and clinical symptoms that are consistent with ADEM. The activation of autoreactive T cells may be mediated by several mechanisms. Molecular mimicry, in which T cells that have been activated by a foreign (viral) antigen cross-react with self-antigens, has been hypothesized to play a role in multiple sclerosis. In a seminal study of molecular mimicry, Fujinami and Oldstone<sup>16</sup> reported that rabbits immunized with hepatitis B polymerase peptide, which shares 6 amino acids with myelin basic protein, developed an antibody and T-cell response to myelin basic protein and CNS lesions pathologically resembling experimental allergic encephalitis. In addition, local inflammation induced by an infectious agent may lead to tissue damage and myelin protein presentation by local antigen-presenting cells that are nonspecifically activated through the early innate immune response to the infectious agent.<sup>17</sup> In this context, several mechanisms, all involving aberrant activation of T cells, seem likely in posttransplant ADEM. Such activation could involve (1) occult viral infection in a chronically immunosuppressed host resulting in postviral ADEM; (2) non-specific activation of quiescent autoreactive T-cell clones; (3) exposure of endogenous T cells to foreign antigens in transplanted tissue resulting in a hypersensitivity reaction; and (4) molecular mimicry between immunogenic foreign antigens in the transplant and endogenous myelin epitopes. Further studies of cellular and molecular mechanisms involved in initiation of the autoimmune response in ADEM are needed to develop more selective therapeutic approaches in the future.

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REFERENCES


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