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Cerebral Complications of Murine Monoclonal CD3 Antibody (OKT3): CT and MR Findings

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Summary: Treatment of acute renal allograft rejection with mouse monoclonal antibody (OKT3) is associated with systemic and neurologic side effects. We describe cerebral abnormalities in a 13-year-old boy with steroid-resistant renal allograft rejection. After treatment with OKT3, an acute neurologic syndrome developed, including seizures, lethargy, and decreased mental function. CT and MR imaging revealed confluent cerebral lesions at the corticomedullary junction. Contrast-enhanced MR images showed patchy enhancement, indicating blood-brain barrier dysfunction. The diagnosis of OKT3-induced encephalopathy with cerebral edema and capillary leak syndrome was made. Although CT and MR findings are nonspecific, neuroradiologists should be aware of this condition in transplant patients treated with OKT3.

Index terms: Brain, diseases; Iatrogenic disease or disorder; Transplants

Orthoclone OKT3 (Ortho Pharmaceutical Corp, Raritan, NJ) is a mouse monoclonal antibody directed against human T-lymphocytes (1). This intravenously administered immunosuppressive drug is mostly used to treat acute corticosteroid-resistant allograft rejection in posttransplant patients. The target antigen of OKT3 is CD3, a 17- to 20-kDa protein in the human T-lymphocyte receptor complex. OKT3 is a biochemically purified IgG2a-immunoglobulin with a heavy chain of 50 kDa and a light chain of 25 kDa.

An increasing number of systemic and neurologic adverse reactions and complications have been reported with use of OKT3 (2–10). The purpose of this article is to report computed tomographic (CT) and magnetic resonance (MR) imaging findings in OKT3-induced encephalopathy.

Case Report

Our patient is a 13-year-old boy with reflux nephropathy and dysplastic kidneys. Pertinent clinical features include failure to thrive and growth retardation (weight and height below third percentile), delayed bone maturation, and hypophosphatemic and renal rickets (the orthopedic complications of which have been treated). At age 13, end-stage renal failure developed and he was admitted for treatment with peritoneal dialysis. After 4 months, renal transplantation was performed with two kidneys from a 2-year-old donor.

Six weeks after transplantation, the patient experienced acute renal allograft rejection. He was treated for 3 days with high-dose corticosteroids (methylprednisolone 1 g per day). Because of insufficient clinical response, intravenous treatment with OKT3 was initiated in a dosage of 3 mg/day (bolus injection).

After 7 days, the patient's neurologic status worsened acutely, with two episodes of generalized seizures, increasing somnolence and lethargy, and decreased mental function. No focal neurologic signs were present. His condition deteriorated rapidly, with progression to coma, and signs and symptoms of intracranial hypertension developed (somnolence, hypertension, bradycardia).

A noncontrast CT examination of the brain showed patchy, confluent areas of decreased attenuation at the gray-white matter junction, involving both cerebral hemispheres (Fig 1A). There was generalized brain swelling.

Within 12 hours of the onset of neurologic symptoms, MR imaging was performed on a 1.5 T system. Proton density- and T2-weighted images as well as T1-weighted images before and after intravenous injection of meglumine gadoterate were obtained. Axial T2-weighted images revealed multifocal areas of increased signal intensity in the subcortical white matter and corticomedullary junction of both cerebral hemispheres (Fig 1B). Coronal T1-weighted images showed areas of low signal intensity (Fig 1C). Axial and coronal T1-weighted images after contrast administration revealed patchy multifocal enhancing ar-

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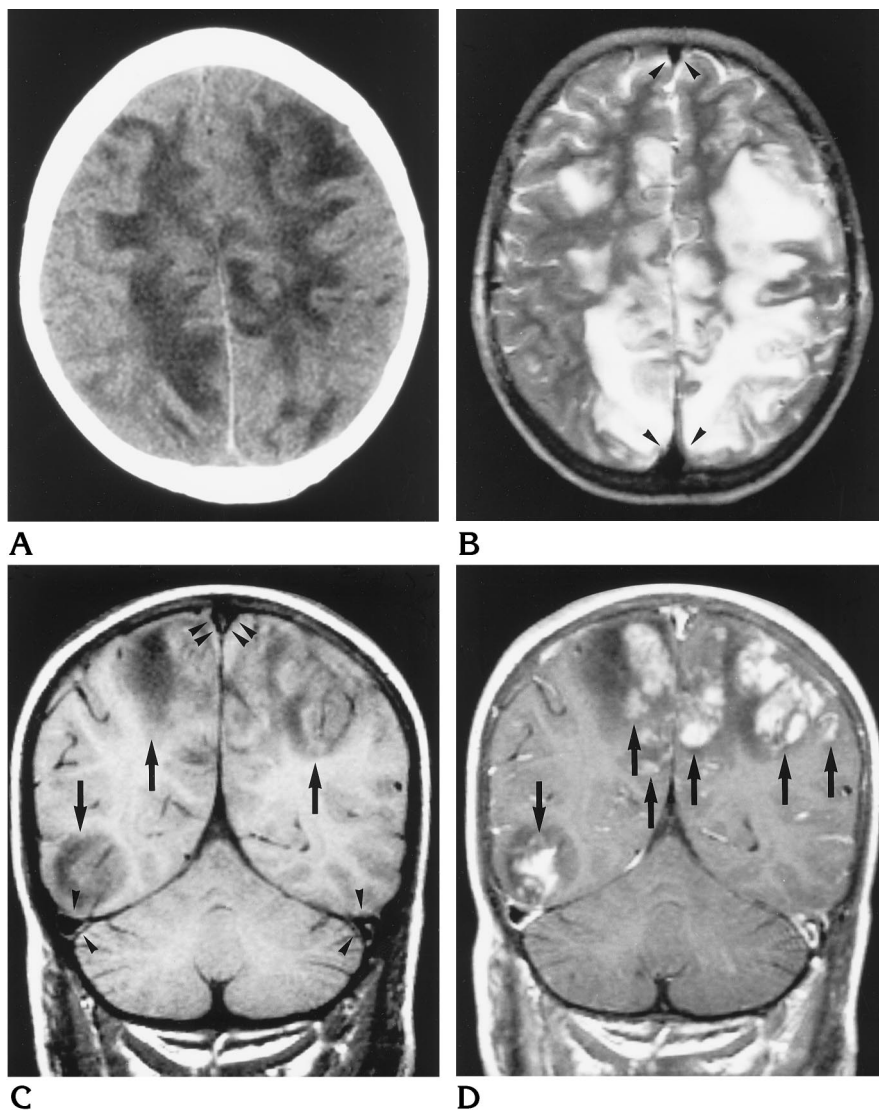
Fig 1. A 13-year-old boy with OKT3 neurotoxicity after treatment for acute renal allograft rejection.

A, Axial noncontrast CT scan of the brain through the centrum semiovale shows patchy and confluent hypodense areas at the gray-white matter junction in both hemispheres. There is generalized brain swelling, and the lesions are not confined to a vascular territory.

B, Axial T2-weighted fast spin-echo MR image (3500/93/2 [repetition time/echo time/excitations]) shows multifocal areas of high signal intensity at the corticomedullary junction bilaterally. There is involvement of both gray and white matter. The angulation of the MR image is slightly different from the CT scanning plane. The superior sagittal sinus is patent, as evidenced by the presence of flow voids (*arrowheads*).

C, Coronal T1-weighted spin-echo MR image (580/15/2) shows confluent lesions of low signal intensity in both parietal lobes and in the right occipitotemporal region (*arrows*). There is no sign of dural sinus thrombosis; flow voids are recognized in the transverse (*single arrowheads*) and superior sagittal sinuses (*double arrowheads*).

D, Coronal contrast-enhanced T1-weighted spin-echo MR image (580/15/2) reveals multiple patchy foci of contrast enhancement, indicating breakdown of the blood-brain barrier (*arrows*). The enhancing areas involve both gray and white matter, and are surrounded by a hypointense halo of edema.



eas, indicating that the lesions had produced blood-brain barrier dysfunction (Fig 1D). The neuroradiologic differential diagnosis of the intracerebral lesions included central nervous system (CNS) infection, lymphoma, vasculitis or vasculopathy, dural sinus thrombosis, hypertensive encephalopathy, or drug-induced encephalopathy. Presence of a flow-void sign in the superior sagittal and transverse sinuses on MR images excluded the possibility of dural sinus thrombosis (Fig 1B and C). In the months before the acute episode, systemic blood pressure had been normal, thereby excluding the hypothesis of renovascular encephalopathy. Laboratory findings showed evidence of prior exposure to Epstein-Barr virus. A CT-guided stereotactic needle biopsy of the brain was performed to establish histologic diagnosis. The stereotactic target was chosen in the left frontal subcortical region, within an area that appeared abnormal at imaging. The brain biopsy specimen showed edematous white matter. No lymphoma cells or infection were found.

On the basis of literature data, and by exclusion of other possibilities, a hypothesis of OKT3-induced encephalopathy with cerebral edema and capillary leak syndrome was proposed. Intravenous treatment with the immunoglobulin was discontinued. Under supportive therapy, the patient's neurologic status improved rapidly and normalized within 10 days. Repeat CT scans showed progressive disappearance of the brain edema.

Discussion

OKT3 suppresses graft rejection by depleting T-lymphocytes, which play an essential role in acute graft rejection (1). OKT3 binds to the CD3 antigen, which is part of the multimolecular T-lymphocyte antigen receptor complex and plays a role in signal-transduction after antigen recognition. Binding of OKT3 to CD3 initially

activates T-lymphocytes, which results in the massive release of cytokines. The acute reaction is followed by a depletion of T-cells and profound immunosuppression. After the end of treatment with OKT3, T-cell functions usually normalize within a week (1, 4, 10).

After the initiation of treatment with OKT3, some patients suffer an acute clinical syndrome, known as cytokine-release syndrome (CRS) (6). The frequency and severity of CRS are highest after the first administration of OKT3. CRS is believed to be caused by the massive release of cytokines by activation of lymphocytes. This affects the permeability of blood vessel walls, including brain capillaries, and leads to a drug-induced vascular leak syndrome. Typically, clinical symptoms of CRS develop within 30 to 60 minutes after the start of OKT3 treatment, and may last for several hours or days. Symptoms range from mild to severe. The most common adverse effect is an influenzalike syndrome characterized by fever, chills, headache, myalgia, arthralgia, nausea, and vomiting (11). Life-threatening reactions involve primarily the cardiovascular system and the CNS. The most frequent neurologic complication is aseptic meningitis, manifested by severe headache, photophobia, and meningism (3, 11). The other common neurologic complication is acute encephalopathy, with a depressed level of consciousness, impaired cognition, hallucinations, or acute psychosis (4, 5, 7, 11). This complication has been associated with the occurrence of cerebral edema (2, 4). Generalized seizures may occur (7, 10, 11). Ophthalmologic complications (visual loss, cortical blindness, and swelling of the optic disk) have been described in the context of acute encephalopathy (9, 10). Late complications of OKT3 treatment include an increased prevalence of infectious complications, especially cytomegalovirus and posttransplant lymphoproliferative disease.

The case presented here provided two challenging features. First, although acute neurologic effects of treatment with OKT3 are well known, the late onset of neurologic symptoms in our patient, 7 days after the start of treatment with OKT3, was unusual. Second, the striking CT and MR findings merited reporting, although they are not specific to OKT3-associated encephalopathy.

Neuroimaging findings in OKT3 neurotoxicity are presumably related to the increased vascu-

lar permeability induced by the immunosuppressive drug. They include evidence of brain edema and blood-brain barrier breakdown with enhancement of brain tissue in diffuse or gyri-form patterns. In addition to the obvious white matter changes, there may be gray matter involvement, as observed in our patient, especially on contrast-enhanced images (see Fig 1D). The pattern of imaging findings showed some similarities to those previously reported in patients with hypertensive encephalopathy or cyclosporine-induced neurotoxicity: low-attenuation areas on CT scans and high signal intensity on T2-weighted MR images (12, 13). In cyclosporine neurotoxicity, the posterior subcortical white matter (occipital and posterior parietal lobes) is preferentially affected (14). Gray matter changes in areas of subcortical white matter involvement are not infrequently observed, especially in more severe cases of cyclosporine neurotoxicity (14, 15) (K. B. Remley, C. L. Truwit, M. M. Casilimas, "Cyclosporine A—Related Neurotoxicity: Spectrum of Findings with MR Imaging," In: *Proceedings of the 34th Annual Meeting of the American Society of Neuroradiology*, Seattle, Wash: 1996:72; and W. E. Zimmer, H. Z. Wang, J. R. Schriber, "Cyclosporine A Neurotoxicity in Allogeneic Bone Marrow Transplantation for Hematological Malignancy: Magnetic Resonance Imaging and Clinical Correlation," In: *Proceedings of the 34th Annual Meeting of the American Society of Neuroradiology*, Seattle, Wash: 1996:73).

In conclusion, clinicians and neuroradiologists should be aware of CNS complications associated with OKT3 treatment. In patients with nonfocal cerebral abnormalities, drug-induced encephalopathy should be added to the gamut of the neuroradiologic differential diagnosis, which also includes CNS infection, primary cerebral lymphoma, cerebral vasculitis or vasculopathy, venous thrombosis, and renovascular hypertensive encephalopathy.

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