A 16-year-old transplant patient with amnesia, insomnia, and visual hallucinations

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A 16-year-old boy with T-cell acute lymphoblastic leukemia received induction (vincristine, prednisone, pegylated asparaginase, and daunorubicin) and consolidation chemotherapy (systemic and intrathecal methotrexate, cytarabine, 6-mercaptopurine, vincristine, pegylated asparaginase, and nelarabine). He achieved complete remission and proceeded to total body irradiation, fludarabine, and cyclophosphamide with an unrelated double cord stem cell transplant. He received cyclosporine as prophylaxis against graft vs host disease and acyclovir as prophylaxis against herpetic infections. Three weeks later, he developed retrograde and anterograde amnesia, visual hallucinations, and insomnia. He was found to be intermittently confused with staring spells. He reported brief episodes of visual hallucinations consisting of déjà-vu, sometimes accompanied by a perception that objects would gradually recede and become smaller (teleopsia). Mini-Mental State Examination was notable for impaired recall of objects at 5 minutes despite preserved registration. He had impaired concentration and attention and was only able to follow simple requests of up to 3 steps. The remainder of the neurologic examination was normal. EEG showed no epileptic discharges but intermittent, medium amplitude 4 to 5 Hz polymorphic activity of the left hemisphere, predominantly in sleep. MRI showed increased fluid-attenuated inversion recovery signal in the medial temporal lobes (figure, A–C). Cyclosporine level was 1,190 ng/mL, having been between 93 and 253 ng/mL over the last week (normal range 100–400 ng/mL).

Cyclosporine was held and the next morning cyclosporine level was 265 ng/mL and remained in a therapeutic range without improvement in the patient's condition. Levetiracetam was started with resolution of visual hallucinations and staring spells. Serum PCR titers of human herpesvirus-6 (HHV-6) peaked at 118,000 copies/mL while the patient was encephalopathic. Serum testing for Epstein-Barr virus, varicella zoster virus, cytomegalovirus, and herpes simplex virus was negative. CSF was not obtained due to thrombocytopenia. A presumptive diagnosis of HHV-6 encephalitis was made. Foscarnet therapy (60 mg/kg) was initiated, with immediate decline in serum HHV-6 levels. The patient made a full recovery over the next week, but remained amnesic for most events of the preceding days. Subsequent MRI 3 months later (figure, D) showed chronic gliotic changes in the medial right temporal

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Figure Imaging

Fluid-attenuated inversion recovery image demonstrates increased signal in the bilateral medial temporal lobes (A, B) with restricted diffusion (C), which resolved into chronic gliotic changes after treatment with foscarnet (D).

lobe. The patient remains in complete remission more than 2 years later and has not had subsequent seizures after tapering off levetiracetam.

DISCUSSION

The differential diagnosis of encephalitis is especially challenging in transplant patients, as numerous chemotherapies and medications used in this population can cause encephalopathies. In addition, radiation toxicity can cause confusional states. Patients can also have a panoply of metabolic abnormalities, systemic infections, and other medications that can cause delirium. Metastatic leptomeningeal cancer may be occult on MRI. Limbic encephalitis can also be paraneoplastic, frequently with normal MRI and nonspecific CSF findings. The clinical picture and MRI suggested acute limbic encephalitis and HHV-6 was strongly suspected based on the characteristic clinical scenario and MRI findings.

HHV-6 is a beta-herpes virus that infects 90% of the population by 2 years of age.¹ Most patients are asymptomatic, but others develop roseola infantum or exanthem subitum or aseptic/viral meningitis.¹ Asymptomatic HHV-6 reactivation in serum is seen in up to one-third of transplant patients, and is associated with delayed engraftment and CMV reactivation.^{1,2} HHV-6 encephalitis is an early consequence of transplant, and may be more common with unrelated cord blood transplants (~16% vs ~3% of bone marrow or peripheral blood transplants) and higher at subsequent unrelated cord blood transplants (~30%).^{2,3}

The majority of patients with HHV-6 present with symptoms of limbic encephalitis (confusion, memory deficits, seizures), but other neurologic syndromes, including myelitis and leukoencephalopathy, have been described.¹⁻⁴ MRI typically shows bilateral temporal changes restricted to the limbic system with corresponding areas of restricted diffusion, but changes in the orbitofrontal cortex, brainstem, and leptomeninges have also been seen.⁵ Other herpesviruses, notably herpes simplex, also have a propensity to involve the temporal lobes, but HHV-6 is more likely to exclusively involve the mesial temporal lobe structures, as opposed to diffuse temporal lobe involvement seen in herpes simplex.⁶ There are limited data on treatment for HHV-6 encephalitis, but foscarnet, ganciclovir, and cidofovir have in vitro activity against the virus. When ganciclovir is used as cytomegalovirus prophylaxis in

transplant patients, there may be some protection against HHV-6 reactivation.⁷ Prognosis is generally good with full neurologic recovery; however, fatality and permanent neurologic sequelae are possible, especially in severe cases that fail to respond to initial therapy.¹

Neurologic care of transplant patients is challenging, given their impaired immune status, polypharmacy, and frequency of metabolic abnormalities. Careful attention to unusual neurologic complications in transplant patients is important to provide proper care and improve outcomes.

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