Pearls & Oy-sters: Seronegative Eastern Equine Encephalitis in an Immunocompromised Stem Cell Transplant Recipient

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Abstract

Altered mental status in immunosuppressed patients has a wide differential diagnosis. In this case, a 27-year-old man presented with encephalopathy, nausea, vomiting, and fevers. His medical history was significant for acute myeloid leukemia in remission after allogenic hematopoietic stem cell transplantation 17 months prior complicated by graft vs host disease affecting his skin treated with sirolimus. A lumbar puncture was performed with a lymphocytic pleocytosis, mildly elevated protein, and negative Gram-stain and bacterial and fungal cultures. His examination deteriorated, and he became comatose with loss of pupillary and corneal reflexes. An MRI of his brain demonstrated T2/fluid-attenuated inversion recovery signal abnormality involving the bilateral basal ganglia, mesial temporal lobes, and entire brainstem along with bilateral temporal parenchymal and leptomeningeal enhancement. Ultimately, diagnosis was made through metagenomic PCR sequencing from his CSF. This case highlights diagnostic challenges in immunosuppressed patients because antibodies against the causative antigen were negative (potentially related to decreased antibody production in the setting of immunosuppression).

Pearls

- Eastern equine encephalitis (EEE) is a rare arthropod-borne viral encephalitis which has been increasing in incidence in the past few years.
- Imaging findings associated with EEE include bilateral thalamic and basal ganglia T2 hyperintensities, which should raise concern for potential arboviral encephalitis.
- Metagenomic next-generation sequencing can be helpful in the diagnosis of uncommon infection, especially in immunosuppressed patients.

Oy-sters

- Diagnosis of infection by antibodies against the causative organism may be limited by delayed antibody response or diminished antibody production in the setting of immunosuppressive medications resulting in falsely negative serologic studies.
- Initial clinical presentation and imaging of encephalitis may be unremarkable or nonspecific and a high index of suspicion must exist for CNS infection in immunosuppressed patients.

Case

A 27-year-old right-handed man presented to emergency department with nausea, vomiting, fatigue, and fevers for the preceding 4 days. While a resident of Ohio, he had returned only days prior after travelling to rural North Carolina. His past medical history was significant for acute myeloid leukemia in remission after receiving an allogenic stem cell transplantation 17 months prior which was complicated by graft vs host disease (GVHD) affecting the skin. He had a prior

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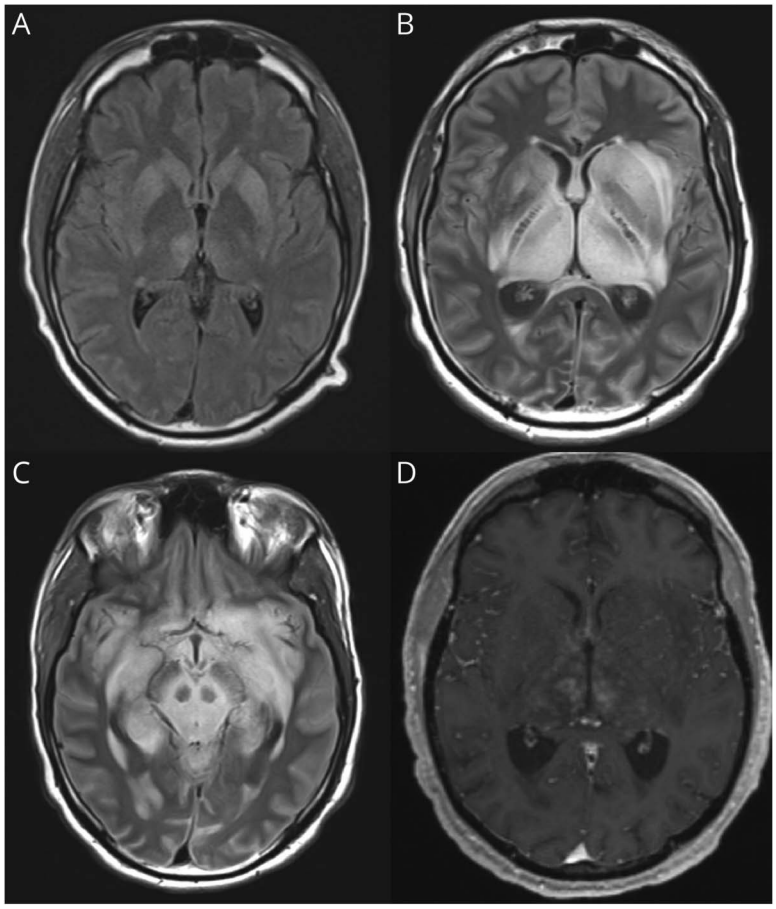
Figure Magnetic Resonance Images on Hospital Days 3 and 8



(A) MRI obtained 3 days after presenting to the hospital. Fluid-attenuated inversion recovery (FLAIR) hyperintensities are present in the bilateral caudate nuclei, putamina, and thalamus. No restricted diffusion or contrast enhancement was identified (not pictured). (B–D) Repeat MRI obtained 8 days after initial presentation demonstrating significant progression of previously seen FLAIR signal intensities within the caudate, putamina, thalami, and external capsules (B), with new extension into the midbrain and bilateral mesial temporal lobes (C) as well as pons, medulla, and cerebellum (not pictured). Contrast-enhanced T1 sequence (D) with focal parenchymal enhancement within the bilateral thalami and putamina as well as enhancement of the bilateral cortical leptomeninges.

episode of orthostatic syncope 18 months before this presentation, with a loss of consciousness lasting seconds in association with an abrupt positional change and orthostatic hypotension identified on vital sign assessment. A MRI of the brain obtained after this episode of syncope was unremarkable. Prior CSF obtained during intrathecal chemotherapy administration (4 total doses of cytarabine with cumulative dose 280 mg with last dose 2 years prior) was normal without the evidence of CNS involvement of his malignancy or GVHD. His immunosuppressive regimen included sirolimus (0.5 mg daily, stable dose for several months), and he had chronic hypogammaglobulinemia for which he received intravenous immunoglobulin infusions monthly.

In the emergency department, he was noted to be tachycardic and febrile. He was drowsy and generally uncooperative and disoriented, but no focal neurologic deficits were seen on examination. CT of his brain was normal. He was initially empirically treated with vancomycin and cefepime due to concerns for sepsis of unknown etiology, and he was transferred to the tertiary care center where he previously underwent care for his leukemia and allogenic stem cell transplantation. Shortly after transfer, he developed focal onset right arm tonic seizures with secondary generalization for which he was treated with intravenous lorazepam and eventually intubated because of inability to protect his airway. After intubation, the patient was transferred to the neurologic intensive care unit for further evaluation and management.

Continuous EEG monitoring revealed infrequent nonconvulsive seizures arising from the left frontotemporal region for which levetiracetam was initiated and up-titrated with resultant cessation of seizure activity. MRI of the brain revealed bilateral basal ganglia fluid-attenuated inversion recovery hyperintensities (Figure, A) concerning for metabolic insult or infection. A lumbar puncture was obtained, which demonstrated a normal opening pressure, pleocytosis (28 cells/μL, lymphocyte predominant), normal glucose, and slightly elevated protein (48 mg/dL, reference range 15–45) with unremarkable cytology and flow cytometry (cell surface markers including CD3, CD4, CD5, CD7, CD8, CD13, CD19, CD34, and CD45). Extensive infectious studies in the CSF including bacterial and fungal cultures and antibodies for varicella zoster virus, herpes simplex virus (HSV), cytomegalovirus, enterovirus, syphilis, and EEE virus were negative. Infectious studies in the blood including PCR targeting HSV, CMV, toxoplasmosis, human herpes virus 6, and West Nile virus as well as antibodies against West Nile virus, California encephalitis virus, St. Louis encephalitis virus, Western equine encephalitis virus, and EEE

virus returned negative. After these negative infectious studies, he was started on intravenous methylprednisolone and IVIG due to concern for possible autoimmune encephalitis caused by the CNS involvement of GVHD given his previous history. Seven days after presenting to the hospital, his neurologic status deteriorated with loss of pupillary and corneal reflexes. A repeat MRI showed interval progression of the previously demonstrated signal abnormality with new involvement of the bilateral mesial temporal lobes and entire brainstem along with new parenchymal and leptomeningeal enhancement (Figure, B–D). A second lumbar puncture was performed which revealed worsening pleocytosis (75 cells/μL, lymphocyte predominant), markedly elevated protein (525 mg/dL), and metagenomic next-generation sequencing (MNGS) detected the presence of EEE virus RNA and no other bacterial, viral, or fungal DNA or RNA. The patient's clinical condition continued to worsen, and he ultimately died 9 days after admission when supportive care was withdrawn. Postmortem autopsy was offered but declined.

Discussion

EEE is an uncommon mosquito-borne encephalitis in the United States caused by the EEE virus, a single-stranded RNA virus of the *Togaviridae* family. Although EEE is exceedingly uncommon with an average of 11 cases reported annually, there has been a recent increase in its incidence with a record of 38 cases reported in 2019, with most cases identified in Michigan and Massachusetts.[1] No previous cases of EEE had been reported in Ohio, but EEE virus has been identified in birds and horses in Ohio suggesting its presence in the environment.[2,3] The differential diagnosis for EEE may include other flaviviruses (such as Japanese encephalitis virus, West Nile virus, and St. Louis encephalitis virus) as well as other infectious encephalitides and autoimmune encephalitis. For patients who develop clinical symptoms of EEE, outcomes are very poor with mortality in 12%–75% of cases and incomplete neurologic recovery in 30%–70% of survivors.[4-6] No specific therapy exists for EEE, and management is centered around supportive care for neurologic sequelae including cerebral edema and seizures.

Although the majority of patients with EEE are immunocompetent, there have been several reported cases in immunosuppressed patients. In 1 prior case, EEE virus was transmitted as a donor-derived infection unknowingly from a deceased donor to 3 solid organ recipients.[7] In 2 cases of EEE in patients on rituximab for lymphoma, antibodies against EEE were also negative and the diagnosis was ultimately made by PCR identifying EEE virus RNA.[8,9] The absence of antibody response may have been related to the patients' use of immunosuppressive medication; however, in at least 1 prior report, serologic response was maintained in an organ recipient with EEE.[10] Another possible explanation for the absence of antibody production may be delayed serum antibody production as has been previously reported in other flaviviral encephalitides.[11] However, in a series of sera from 20 humans with EEE, anti-EEE IgM was present in the sera of all 20 patients at a median of 5 days after the onset of symptoms and in some patients as early as 1 day after the onset of symptoms.[12] Antibody studies were obtained in our patient on day 9 of symptoms, which suggests that a measurable response should have been identified.

Serologic diagnosis may be prone to false negative results, leading to significant diagnostic delay and uncertainty resulting in initial ineffective treatment. MNGS refers to multiple techniques of high-throughput simultaneous sequencing of DNA and RNA using different primer sequences common to viral, bacterial, and fungal organisms allowing for the identification of the presence of any nonhuman genetic material in a patient sample. Due to its increased sensitivity and lack of reliance on a patient mounting a measurable antibody response, MNGS should be considered in immunosuppressed patients for the evaluation of suspected uncommon opportunistic infection.

Although the patient was ultimately diagnosed with EEE, CNS involvement of GVHD was initially a leading diagnostic consideration given his history of dermatologic GVHD. CNS involvement is an uncommon manifestation of GVHD, with 32 cases being identified between 1990 and 2015 and only 15 of those being histologically proven.[13] A wide variety of neurologic manifestations have been identified in CNS GVHD including stroke-like episodes, white matter abnormalities, and encephalitis. Proposed diagnostic criteria include both chronic GVHD affecting other organ systems and new neurologic symptoms without other explanation (such as an infectious, metabolic, vascular etiology), and the presence of 2 or more facultative criteria including corresponding MRI abnormality, abnormal CSF studies, identification of GVHD on brain biopsy or postmortem autopsy, or response to immunosuppressive therapy.[14] The diagnosis of CNS GVHD is somewhat controversial because, in the absence of histologic confirmation, it is a diagnosis of exclusion and the differential diagnosis for new neurologic symptoms and MRI and CSF abnormalities in immunosuppressed patients is exceedingly broad. As a result, patients may be misdiagnosed in the absence of histology and other more common diagnoses such as opportunistic infection must be ruled out before making the diagnosis.

EEE virus is an uncommon cause of encephalitis in the United States. Diagnosis in this immunocompromised case was made challenging because of the absence of antibodies. The use of metagenomic next-generation sequencing should be considered in cases of encephalitis because antibodies may be falsely negative related to delayed humoral response or diminished antibody production in immunosuppressed patients.

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Catherine Hassett, DO	Cerebrovascular Center, Neurological Institute, Cleveland Clinic	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design
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Aneela Majeed, MD	Department of Infectious Disease, Cleveland Clinic, Cleveland	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data

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