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

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Neurology® Published Ahead of Print articles have been peer reviewed and accepted for publication. This manuscript will be published in its final form after copyediting, page composition, and review of proofs. Errors that could affect the content may be corrected during these processes.

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Abstract

Altered mental status in immunosuppressed patients has a wide differential of potential etiologies. In this case, a 27-year-old male presented with encephalopathy, nausea, vomiting, and fevers. His medical history was significant for acute myeloid leukemia in remission after allogenic hematopoietic stem cell transplant 17 months prior complicated by graft versus 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/FLAIR 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 via metagenomic polymerase chain reaction sequencing from his cerebrospinal fluid. This case highlights diagnostic challenges in immunosuppressed patients as 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 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.
• 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 non-specific and a high index of suspicion must exist for central nervous system infection in immunosuppressed patients.

Case:
A 27-year-old right-handed male presented to emergency department with nausea, vomiting, fatigue, and fevers for the preceding four 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 transplant 17 months prior which was complicated by graft versus host disease (GVHD) affecting the skin. He had a prior episode of orthostatic syncope 18 months before to 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 magnetic resonance image (MRI) of the brain obtained after this episode of syncope was unremarkable. Prior cerebrospinal fluid obtained during intrathecal chemotherapy administration (four total doses of cytarabine with cumulative dose 280mg with last dose two years prior) was normal without evidence of central nervous system involvement of his malignancy or GVHD. His immunosuppressive regimen included sirolimus (0.5mg 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. Computed tomography 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 transplant. 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 due to 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 non-convulsive 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 FLAIR 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, slightly elevated protein (48 mg/dL, reference range 15–45) with unremarkable cytology and flow cytometry (cell surface markers including markers including CD3, CD4, CD5, CD7, CD8, CD13, CD19, CD34, and CD 45). Extensive infectious studies in the cerebrospinal fluid including bacterial and fungal cultures, antibodies for varicella zoster (VZV), herpes simplex (HSV), cytomegalovirus (CMV), enterovirus, syphilis, and Eastern Equine Encephalitis (EEE) virus were negative. Infectious studies in the blood including polymerase chain reaction 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 central nervous system (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 nine 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. While EEE is exceedingly uncommon with an average of 11 cases reported annually, there has been a recent increase in its incidence with a record 38 cases reported in 2019 with most cases identified in Michigan and Massachusetts. 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. 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\textsuperscript{4–6}. No specific therapy exists for EEE, and management is centered around supportive care for neurologic sequelae including cerebral edema and seizures.

While the majority of patients with EEE are immunocompetent, there have been several reported cases in immunosuppressed patients. In one prior case, EEE virus was transmitted as a donor-derived infection unknowingly from a deceased donor to three solid organ recipients\textsuperscript{7}. In two cases of EEE in patients on rituximab for lymphoma, antibodies against EEE were also negative and the diagnosis was ultimately made by polymerase chain reaction identifying EEE virus RNA\textsuperscript{8,9}. Absent antibody response may have been related to the patients’ use of immunosuppressive medication; however, in at least one prior report serologic response was maintained in an organ recipient with EEE\textsuperscript{10}. Another possible explanation for the absent antibody production may be delayed serum antibody production as has been previously reported in other flaviviral encephalitides\textsuperscript{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 onset of symptoms and in some patients as early as 1 day after onset of symptoms\textsuperscript{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 identification of the presence of any non-human 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 evaluation of suspected uncommon opportunistic infection

While the patient was ultimately diagnosed with EEE, CNS involvement of GVHD was initially a leading diagnostic consideration given his prior history of dermatologic GVHD. CNS involvement is an uncommon manifestation of GVHD, with 32 cases being identified between 1990-2015 and only 15 of these being histologically proven. 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 two or more facultative criteria including corresponding MRI abnormality, abnormal CSF studies, identification of GVHD on brain biopsy or post-mortem autopsy, or response to immunosuppressive therapy. The diagnosis of CNS GVHD is somewhat controversial as, 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.

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

References:


**Figure Title:** Magnetic Resonance Images on Hospital Days 3 and 8.

**Figure Legend:**

A. Magnetic resonance imaging (MRI) obtained three 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 eight 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, 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.