CLINICAL VIGNETTE

Success, So Short-Lived

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Case Presentation

A 72-year-old woman presented to our emergency department (ED) after her daughter noted her mentally altered with left sided gaze preference. Code stroke was activated in the ER without significant findings on CT brain, angiograms of head and neck, perfusion studies and subsequent MRI brain with and without contrast. While in the ER, patient vomited and aspirated causing respiratory failure requiring endotracheal intubation. Past medical history includes chronic lumbar spinal stenosis, partial seizure disorder, atrial fibrillation on dabigatran, morbid obesity, and type 2 diabetes mellitus. Patient's daughter reported she had difficulty swallowing with 30-pound weight loss in recent months and may have missed taking her medications including antiseizure medicines: eslicarbazepine, gabapentin and levetiracetam. Neurocritical care consultation started cenobamate in addition to her home antiseizure medicines. Cultures from the day of her admission grew Staphylococcus auricularis in both blood cultures, Proteus mirabilis in urine culture and Klebsiella aerogenes in respiratory culture. She was treated with vancomycin and cefepime and follow up blood cultures were negative. 2D echocardiogram revealed normal LV function and no significant valvular disease. Continuous EEG monitoring did not show seizure activity. However, the patient remained mentally altered. Cefepime was discontinued. Dabigatran was held and CT guided lumbar puncture was performed on the 10th hospital day. CSF was colorless with 4 nucleated cells, 8 RBCs in tube #4, glucose 69 and elevated protein of 73. CSF bacterial, acid fast bacilli and fungal cultures were negative. No oligoclonal bands were seen in the CSF. Meningitis-encephalitis panel, cryptococcal antigen, VDRL and oligoclonal bands were negative. Neuro intensivist lowered the dose and stopped eslicarbazepine. Eighteen days into hospitalization, patient received tracheostomy and PEG tube. There was a subtle improvement in her mental status, at the time of discharge to a long-term acute care hospital [LTACH] on day 25 of her hospitalization.

One month after her lumbar puncture, CSF autoimmune encephalitis reflexive panel was resulted, and glutamic acid decarboxylase antibody was >250 IU/mL [reference 0-5]. Patient's family and her attending physician at the LTACH were approached. Pulse dose steroids were given at the LTACH without much benefit and patient was moved back to the hospital, where she received plasmapheresis treatment and discharged back to LTAC.

She presented back to our hospital 6 months later with abdominal pain. To our delight, her prior altered mentation had completely resolved. She was without tracheostomy or a PEG tube, verbal with normal mentation and now living at home with her daughter. CT scan of the abdomen revealed pancreatic head mass. Lipase was within normal limits. CA 19-9 was elevated at 1023. Hepatobiliary surgery consultation was obtained. Pancreatic mass was inoperable with vascular involvement including the superior mesenteric artery and superior mesenteric vein. Endoscopic ultrasound guided biopsy was performed, and she was found to have poorly differentiated adenocarcinoma of the pancreas.

Next 4 months included 3 hospitalizations for different infections. On her last admission she presented with septic shock to another facility, found to have pulmonary embolism. With underlying cancer, and other comorbidities, accepted hospice at home. She passed away few days later in December 2022.

Discussion

Our patient presented with obtundation with known history of seizures, but continuous EEG monitoring in the ICU did not reveal seizures. In the process of further evaluating the acute encephalopathy, she was found to have anti-GAD antibody encephalitis.

Glutamic acid decarboxylase [GAD] is an enzyme that converts glutamate to gamma amino butyric acid [GABA], the main inhibitory neurotransmitter in the central nervous system. GAD in different isoforms is expressed not only in the central nervous system but also in the pancreatic beta cells, testes, fallopian tube, liver, kidney, and adrenal glands. Brain contains 2 isoforms GAD65 and GAD67. GAD65 is concentrated in the cell terminals, exists primarily in inactive form, undergoes autoactivation during circumstances that demand rapid surge in GABA synthesis and release. GAD67 is present in its active state in the cell cytoplasm and provides a steady basal production of GABA.[1] GAD67 is rarely detected in the absence of GAD65, has less autoantigenicity and autoantibodies in clinical practice use recognize the GAD65 isoform, which we will refer to GAD Ab in this paper.

GAD Ab is detected in 80% of patients with diabetes mellitus type 1, but in lower concentration compared to the neurological syndromes it is associated with. Antibodies to different epitopes

on GAD, sometime overlapping are seen in different diseases. GAD Ab is detected in about 60% to 80% of patients with Stiff Person Syndrome, 2%-12% of Cerebellar Ataxia cases and about 17% of Limbic Encephalitis. Limbic encephalitis commonly described with GAD Ab is characterized by subacute onset of seizures, confusion, behavioral changes with MRI of the brain showing bilateral hyperintensities in temporo-mesial structures on T2 weighted or fluid-attenuated inversion recovery [FLAIR] sequences with no contrast enhancement. In limbic encephalitis, CSF can show inflammatory changes with moderate pleocytosis, and mildly elevated protein and commonly detection of oligoclonal bands.[2] While our patient had the inflammatory CSF changes, but without oligoclonal bands. She had 2 brain MRI scans and neither depicted the classic changes noted in limbic encephalitis. However, GAD Ab associated encephalitis with a normal MRI has been previously reported.[3,4]

Treatment options for GAD Ab encephalitis include high dose steroids, intravenous immunoglobulins, and plasma exchange and recovery has been reported to be modest. In cases resistant to these treatments, immunotherapy with Rituximab or cyclophosphamide have been studied with moderate success. Our patient did not respond to high dose steroids at the LTACH. However, she received plasma exchange at the hospital, with complete recovery of her mental status and decannulation of her tracheostomy and removal of gastric tube.

Paraneoplastic Association

GAD Ab neurological syndromes have been associated with paraneoplastic syndromes. Specifically, in pancreatic neuroendocrine tumors, immunohistochemical staining has shown GAD Ab in tumor cells.[4] Overall, paraneoplastic cases association, however, is rare with various GAD Ab neurological syndromes, but relatively frequent with limbic encephalitis at 26%. Non-small cell lung cancer and neuroendocrine pancreatic tumors are most common. Male gender, older age, coexisting antibodies to cell surface antigens like GABA or glycine receptor antibodies are risk factors. Our patient was an elderly woman and encephalitis panel for GABA-B Receptor Ab in the CSF and was negative. Her presentation 6 months later with abdominal discomfort led to the finding of pancreatic tumor and subsequent biopsy to poorly differentiated adenocarcinoma. With typical pancreatic neuroendocrine tumor association, adenocarcinoma in our patient may be purely coincidental since we did not perform further testing to detect GAD Ab on tumor cells. However, adenocarcinoma in other organs such as lung and breast have been reported in paraneoplastic cases of GAD Ab associated neurological syndromes.

Our patient's story heart breaking and a humbling experience. After a complex initial hospitalization, she recovered to celebrate a remarkable recovery only to succumb to a deadly cancer a few months later. The initial CT of the abdomen and pelvis during her first admission prior to PEG placement did not show the pancreatic tumor. With a rare encephalitis and even rarer cancer association we wonder what we could have done differently to alter her outcome.

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