A case of eculizumab-induced hemophagocytic lymphohistiocytosis (HLH) in a myasthenia gravis patient

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ABSTRACT

Hemophagocytic lymphohistiocytosis (HLH) is an immune hyperactivation state that can occur in immunosuppressed patients and is associated with high mortality and worse prognosis. We present a case of 78-year-old patient on multiple immune suppressing medications, including eculizumab and azathioprine for myasthenia gravis, who presented to our hospital for evaluation of hyperbilirubinemia. She had extensive laboratory workup that was significant for anemia, thrombocytopenia, increased ferritin level, and hyponatremia. Additionally, she had increased CD25 and CXCL9 leading to the diagnosis of HLH. Investigations for triggering factors identified eculizumab after excluding multiple infectious and rheumatologic conditions. Unfortunately, the patient did not survive. We recommend evaluating for high ferritin as a reliable predictor for HLH for patients on myasthenia gravis on eculizumab.

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening immune response caused by hyperactivation of macrophages and cytotoxic T-lymphocytes. Due to the lack of down-regulation of these immune cells, cytokine storm with variable interleukins can cause multi-organ failure.[1] The triggers for HLH are still not fully understood. However, it is now known that the triggers can range from hyper-immune states such as Epstein-Barr virus to immune-suppressed states such as human immunodeficiency virus, malignancy and inherited immune deficiency disorders.[2-3] Drug-induced HLH has been reported as an immune-related adverse effect (irAE) from few drugs such anti-PD1 and anti-CTLA-4 cancer immunotherapy.[4] There were reports of eculizumab therapy being associated with meningococcal infection and other infections as possible adverse events.[5] However, there is no published literature about HLH as an irAE of eculizumab. We present a case of a myasthenia gravis (MG) patient on eculizumab who developed HLH after an extensive workup to exclude any other possible triggers.

Case description

A 78-year-old female who presented to our hospital from an outside institution for evaluation of a pancreatic cancer found on her magnetic resonance cholangiopancreatography (MRCP). The patient initially presented to the outside hospital with a two-week history of jaundice; MRCP revealed pancreatic divisium and pancreatic duct dilation concerning for cancer. Upon presenting to our hospital, our gastroenterology service was consulted, and recommended a second read of the MRCP. Surprisingly, the second read did not show any evidence of pancreatic duct dilation, common bile duct dilation or pancreatic cancer. Instead, it showed multiple hepatic cysts and splenomegaly (Figure 1).

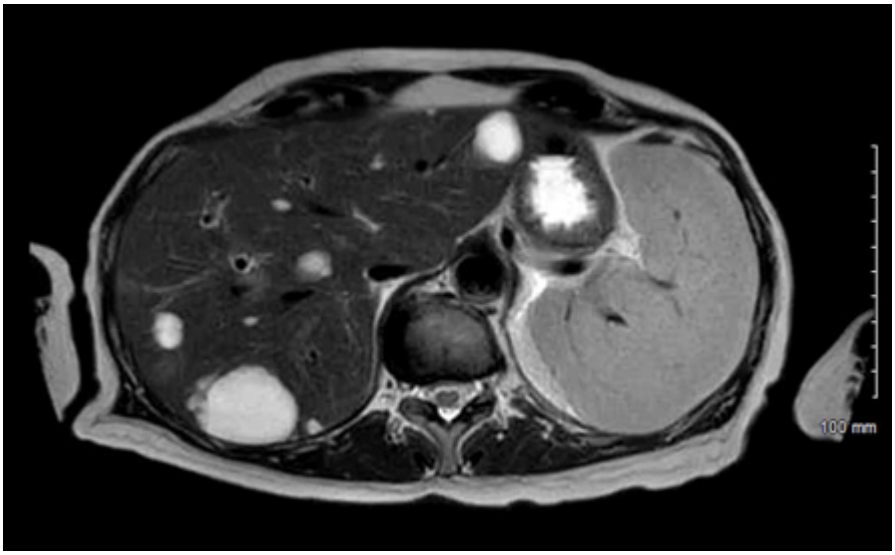

Figure 1. Multiple hepatic cysts and splenomegaly demonstrated on magnetic resonance cholangiopancreatography

Upon further history taking, patient reported having three days of sore throat and fever before her jaundice started. She reported occasional nausea, but no vomiting or abdominal pain. She denied any recent travels, illnesses, or medications. She reported a past medical history of remote seizure on phenytoin, thalassemia with no prior transfusions, and MG being treated with prednisone, pyridostigmine, azathioprine, and biweekly eculizumab infusions. She was diagnosed with MG in 2008. She was initially started on azathioprine, then started on eculizumab in 2020 with her last dose on the day prior to admission. When evaluated by the inpatient neurology service, there was no noticeable weakness in bilateral upper and lower extremities. However, she had an element of fatiguability on some provocative maneuvers. She was continued on eculizumab during hospitalization, but azathioprine was stopped given concern of liver injury.

Physical examination was negative for pertinent signs except for severe jaundice. Vital signs were stable except for occasional spiking fevers with Tmax of 38.6°C. Labs were significant for low white blood cells 3.4 X10 (9)/ L, low hemoglobin 7.3 g/dL, low mean corpuscular volume 64.1 fL, low platelet count 103 x 10^9/L, low sodium of 126 mmol/L and total bilirubin of 15.03 mg/dL. Infectious Disease service and Hematology-Oncology service were consulted for evaluation of infectious causes of hyperbilirubinemia and thrombocytopenia, respectively. Nephrology service was consulted for management of hyponatremia after initial attempts to correct by primary team. To simplify the presentation of our diagnostic approach, all workup performed by the primary team and consult services are presented in Figure 2 . After an extensive week-long workup during hospitalization, infectious etiology was ruled out. HLH was suspected at this time, and soluble CD25 (soluble IL-2 receptor) and CXCL-9 were ordered. They came back high at 8288 pg/ml and 15,989 pg/ml, respectively. At this point, the patient was transferred to another tertiary center for further evaluation and consideration of liver transplantation. Results were communicated, and patient was started on etoposide after transfer. However, the patient passed away after around two weeks of transfer. Cause of death was communicated to be related to HLH.

Discussion

Eculizumab is a humanized monoclonal antibody that works against complement factor 5 to prevent the complement fixation of acetyl-choline receptor antibodies in seropositive MG patients.[6-7] Per the American Academy of Neurology guidelines, eculizumab is indicated in severe, refractory seropositive MG after unsuccessful trials of other immunologic agents.[8] There is no published literature on the long-term safety profile of eculizumab in MG patients; however, it is reportedly generally well-tolerated. Frequent reported adverse effects include headache and upper respiratory tract infection. Less common but serious adverse effects include MG crisis and exacerbation. To our knowledge, there are no published reports whether eculizumab can trigger HLH. On the contrary, eculizumab has been reported as a treatment for complement-mediated thrombotic microangiopathy (TMA) in case series of refractory HLH with complete resolution of their symptoms. It was reported by the authors that eculizumab probably worked against the activated complements implemented in TMA.[8]

HLH is a primarily pediatric disorder which certain genetic predispositions can trigger its primary form. Recurrent attacks could be expected in primary HLH. In the adult population, secondary HLH is more common in states of immunosuppression or conversely, hyperactivation with viruses or infections.[9] In our patient's case, an extensive workup was able to rule out infectious causes of hyperbilirubinemia, elevated liver enzymes or pancytopenia. However, she was immunosuppressed in the setting of prednisone, azathioprine, and eculizumab intake. Azathioprine was discontinued upon admission, but her course was progressive. She did not develop any of her symptoms in the past, so HLH recurrence from a primary source was excluded. The only association in her case with HLH was the eculizumab.

Perhaps, earlier diagnosis could be anticipated in the setting of high ferritin. In a large pediatric study in Texas, a ferritin level higher than 10,000 mg/L had a high sensitivity and specificity for HLH diagnosis of 90% and 98%, respectively.[10] In adults, there was a lower reported sensitivity of 28% with ferritin greater than 10,000 mg/L.[11] Ferritin was independently associated with higher mortality in HLH patients.[12]

Conclusion

We recommend paying further attention to serum ferritin as a predictor of HLH and report that eculizumab therapy can be a possible etiology.

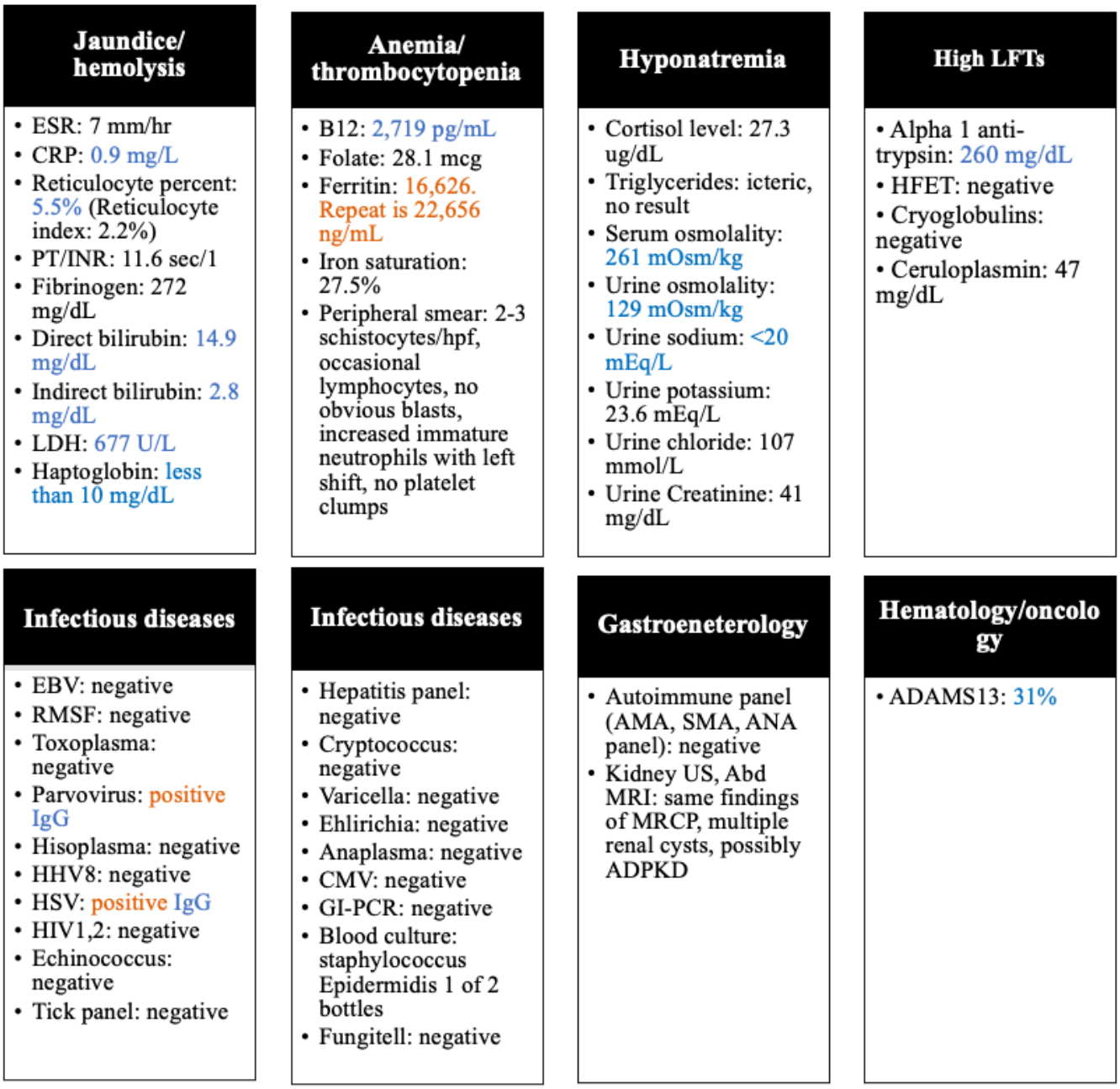

Figure 2. Above row indicates workup done for pertinent findings. Below row indicates workup by consulting services. Results in orange color indicates higher than normal values, and results in blue color indicates lower than normal values. ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, PT: prothrombin time, INR: international normalized ration, LDH: lactate dehydrogenase, EBV: Epstein-Barr virus, RMSF: rocky mountain spotted fever, HHV8: human herpesvirus 8, HSV: herpes simplex virus, HIV: human immunodeficiency virus, CMV: cytomegalovirus, GI-PCR: gastrointestinal polymerase chain reaction, AMA: antimitochondrial antibody, SMA: smooth muscle antibody, ANA: antinuclear antibody, US: ultrasound, MRI: magnetic resonance imaging, MRCP: magnetic resonance cholangiopancreatography, ADPKD: autosomal dominant polycystic kidney disease.

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