An Unusual Suspect in a Case of Severe Hyperammonemia

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Introduction

- Hyperammonemic crisis is a neurologic emergency that if left untreated can lead to cerebral edema, increased intracranial pressures, and seizures, potentially leading to coma and death
- The most common cause of hyperammonemia is liver failure, and in patients with acutely decompensated liver cirrhosis can commonly present with hyperammonemia,
- Cryptococcus neoformans is a fungal pathogen that is known to be urease producing--we present a rare case of dissemnated C. neoformans causing hyperammonemia in a decompensated cirrhotic

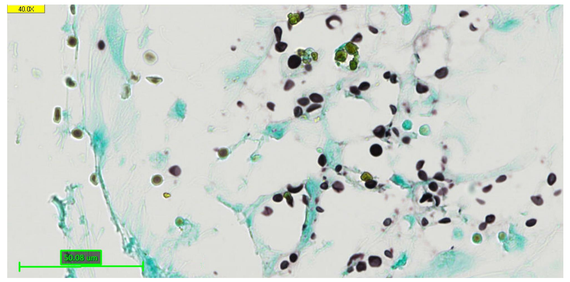
CASE REPORT

HPI: 69-year-old male s/p DDKT (approximately 1 year prior to presentation), distant history of hepatitis C infection, and cryptogenic cirrhosis presented after a fall 4 days prior along with generalized weakness and worsening SOB. At this time, patient had presented around once every 2-3 weeks for therapeutic paracenteses. He was noted to have a bilateral tremor in his hands that had been worsening since his fall, but no fevers, chills, nausea, vomiting, or diarrhea. The patient appeared confused but was otherwise alert and oriented to person, location, and time. Vital signs were unremarkable. Initial workup was significant for an elevated ammonia level to 466 while in the emergency department. CBC and chemistries were stable with his previously known baseline.

- Admitted to the hepatology service and started on lactulose for hyperammonemia. Immunosuppressive medications were continued, but diuretics were discontinued due to concerns for hypovolemia.
- On the second day of admission, patient appeared more somnolent and disoriented. EEG was obtained, showing mild encephalopathy. CT head was negative for signs of acute intracranial hemorrhage. Over the course of the next 24 hours, the patient's mental status improved to his baseline with lactulose therapy.
- Patient again became unarousable on the fourth day of admission. Ammonia level acutely elevated to above 758, and CBC was significant for neutropenia, with an absolute neutrophil count of 600k per uL. IV fluid resuscitation was started, and the decision was made to transfer the patient to the ICU for CRRT.
- CRRT was initiated, with the patient subsequently becoming bradycardic and hypotensive, requiring atropine and vasopressor support. Shortly thereafter, the patient went into polymorphic ventricular tachycardia, followed by a cardiac arrest.
- Patient had two subsequent cardiac arrest events. The patient's family decided to withdraw care and focus on comfort at this time, and the patient was extubated and pronounced dead on his 6th day of admission.

AUTOPSY FINDINGS

Grocott's Methenamine Silver (GMS), PAS (Periodic Acid Schiff), hematoxylin, and eosin stains of tissue from the patient's lung, pericardium, pancreas, liver, and adrenal glands demonstrated yeast, indicating disseminated infection with Cryptococcus neoformans, correlating with the final result from the patient's blood cultures.



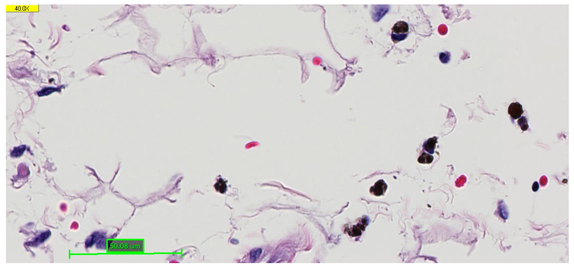
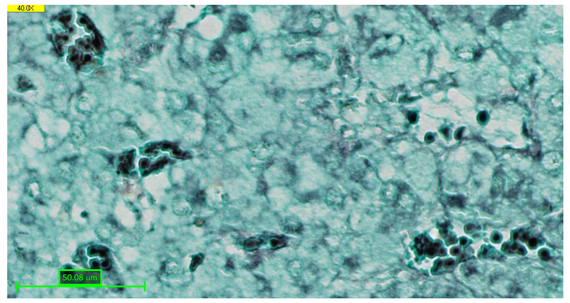


Figure 1: GMS (1A) and H&E (1B) stains of pericardial tissue. Round to oval fungal elements with variable size consistent with cryptococcus neoformans in the pericardium. 40x magnification.



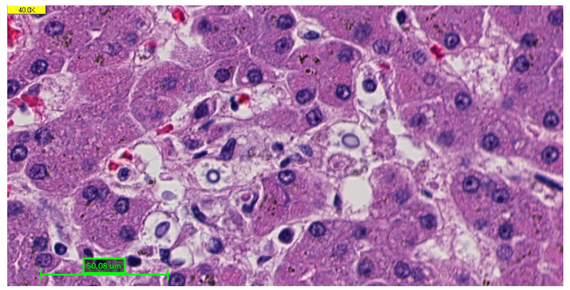


Figure 2: GMS (1A) and H&E (1B) stains of liver tissue. Narrow-based buds with soap bubble appearance consistent with cryptococcus neoformans in the liver. 40x magnification.

DISCUSSION

- Ammonia is normally produced through bacterial hydrolysis of urea and other nitrogenous compounds in the small intestine, from which is then absorbed and transported to the liver to be converted to the liver and converted to urea via the urea cycle
- Over 90% of cases of hyperammonemia in adults are attributed to cirrhosis
- Non-hepatic hyperammonemia can be caused by a broad range of conditions that decrease hepatic elimination of ammonia (defects in the urea cycle, portal vein thrombosis, or medications that disrupt the urea cycle e.g. valproic acid) or increase urea metabolism (multiple myeloma, high-stress states such as seizure, starvation, or trauma, or systemic infections involving urease-producing pathogens)
- Urease-producing bacteria such as Proteus mirabilis, Escherichia coli, and Klebsiella species are the predominant infectious cause of non-hepatic hyperammonemia
- Urease produced by these bacteria hydrolyze urea to ammonium ions, which are converted to ammonia in the alkaline environment created by the urinary infection. Ammonia is reabsorbed into the bloodstream via the venous plexuses of the bladder, which drain directly into systemic venous circulation, bypassing the portal venous system.
- Cryptococcus neoformans is the third most common cause of invasive fungal infection in solid organ transplant recipients and accounts for 8% of invasive fungal infections in solid organ transplant recipients. C. neoformans is a urease-producing pathogen, and urease has been implicated as one of the fungus' major virulence factors in both its infection of the lungs as well as its dissemination to the brain, causing meningoencephalitis
- C. neoformans has not commonly been reported as a cause of hyperammonemic crisis, and particularly not in patients with liver cirrhosis. It is worth considering in the differential diagnosis for susceptible patients

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