Common Variable Immunodeficiency with Angiosarcoma Associated with Hyperammonemia Secondary to High Dose IVIG Infusion

Yujie Li,[1] John Johnson,[2] Brian Peppers,[2] Haig Tcheurekdjian,[3] Robert Hostoffer[3]

[1]Lake Erie College of Osteopathic Medicine, Erie, PA; [2]Allergy/Immunology Fellowship, University Hospitals, Cleveland, OH; [3]Allergy/Immunology Associates, Mayfield Heights, OH

Abstract

Common Variable Immunodeficiency (CVID) is the most common symptomatic immunodeficiency, marked by a humoral deficiency and recurrent respiratory tract infections. It can be treated with regular infusions of gammaglobulin, which has been associated with post infusion side effects such as headaches. We report a 78 year old patient diagnosed with CVID and liver angiosarcoma who developed hyperammonemia secondary to high dose IVIG infusion.

The patient is a 78 year old Caucasian male with CVID, on biweekly high dose (1.1g/kg) IVIG treatment, who was initially admitted for generalized weakness secondary to a newly diagnosed encephalopathy from hyperammonemia. He became progressively drowsy during his hospital admission, and his ammonia level was 87. An abdominal CT showed multiple nodules in the liver. He was found to have hepatic angiosarcoma on biopsy. His discharge was delayed due to altered mental status. Despite a 1 week delay in his IVIG dose his immunoglobulin level remained at 1100. Once discharged, he received IVIG redeveloping encephalopathy 1 week later with an ammonia level of 81. No other causes of hyperammonemia were detected.

A previous case of hyperammonemia associated with high dose gamma globulin has been reported without the presence of an immunodeficiency. Additionally, there have been no reported cases of a liver angiosarcoma in an adult CVID patient. We report the first case of hyperammonemia secondary to high dose IVIG in a patient with hepatic angiosarcoma and CVID.

Introduction

Common Variable Immunodeficiency (CVID) is the most common, symptomatic immune deficiency. Patients with CVID are often managed with repetitive, life-long immunoglobulin (Ig) replacement therapy.

Although immunoglobulin replacement decreases the rate of infections, it has not been shown to decrease the rate of chronic lung disease, systemic granulomatous disease, gastrointestinal disease, lymphoma and development of cancer. Patient who receive intravenous immunoglobulin (IVIG) commonly experience many transient post-infusion adverse reactions such as headaches, flushing, malaise, fevers, chills, etc.

Encephalopathy secondary to hyperammonemia has never been reported after an IVIG infusion. We report a case of a 74 year old male with CVID, receiving biweekly high dose IVIG found to have hyperammonemia-induced encephalopathy associated with newly diagnosed liver angiosarcoma. The hepatic angiosarcoma compromised his ability to convert the ammonia, from his IVIG, to urea, resulting in encephalopathy.

Hospital course

The patient is a 74 year old, Caucasian male with a past medical history of hypertension, dyslipidemia, coronary artery disease status post multiple stent placements, colon cancer status post colonic resection, benign prostatic hyperplasia, osteoarthritis, cervical spondylosis presented to the ED with 2 days of decreased appetite and generalized weakness. He was admitted with working diagnoses of non-ST elevation myocardial infarction (NSTEMI) and urinary tract infection (UTI).

On day 3 of admission, the patient became progressively confused and lethargic. Subsequently, a CT and MRI of the brain were negative for cerebral vascular accident. A lumbar puncture was performed and a central nervous system infection was not likely after cerebral spinal fluid was negative for bacteria, fungus including Cryptococcus, HSV, HIV, and toxoplasmosis. On day 5 of admission, he was only arousable to sternal rub and was transferred to the ICU.

Subsequently, he was found to have an elevated alkaline phosphatase and ammonia level of 87. A viral hepatitis panel did not reveal abnormality. A CT of the liver without contrast revealed a suspicious mass. The patient was started on lactulose and rifaximin. His mental status began to improve as he became arousable to voice.

Recurrent colon cancer with metastasis to the liver was suspected given his history. A serum carcinoembryonic level was within normal limits. A CT guided core needle biopsy revealed angiosarcoma.

Due to the prolonged hospital stay, the patient's scheduled IVIG transfusion was delayed by a week after the IgG level was found to be 1340umol/L at post infusion day 7.

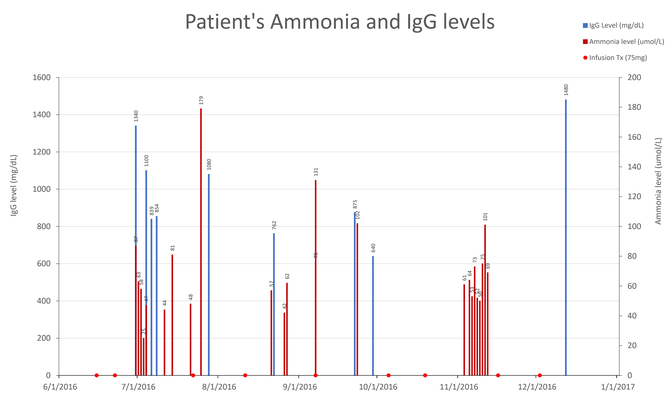

Figure 1: Patient's IgG and ammonia level collected since the date of diagnosis to end of 2016. Patient received 75mg of Gamunex C 10% usually every 2 weeks. Dates when patient received Gamunex are indicated by red dots.

Path report

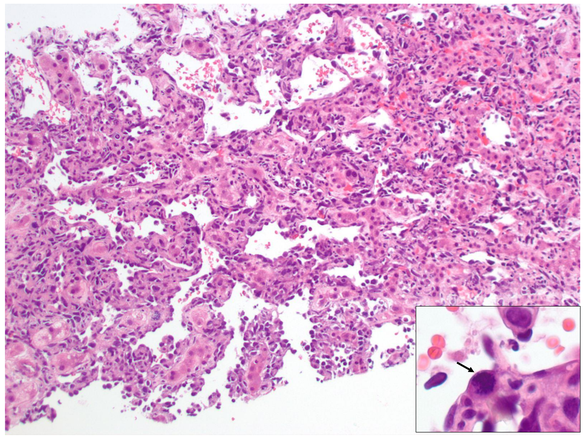

Figure 2: Hematoxylin and eosin stain of tissue collected from CT guided core needle biopsy of patient's hepatic lesion. The lesion is composed of distinct vascular channels of irregular size and shape. The neoplastic cells resemble normal endothelium to some extent; however, they have larger, hyperchromatic nuclei, and often higher up along the lumens, creating intraluminal buds or papillations. Tumor cells may display a characteristic growth pattern of spread along preexisting sinusoids. Some areas show highly pleomorphic spindle cells and epithelioid cells with rudimentary lumen formation and frequent mitosis. Intraluminal red blood cells or areas of hemorrhage is a feature of angiosarcoma. Inset: The arrow indicates a mitotic figure.

Immunohistochemical stains (not pictured) were also performed, which were positive for CD34 and ERG, which highlight the nuclei of neoplastic cells confirming their endothelial origin.

Imaging

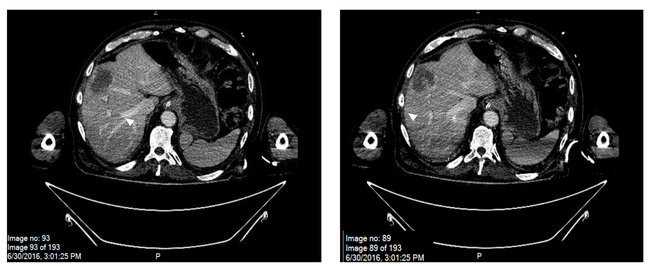

Figure 3: CT of abdomen shows a 5.2 x 5.2 cm heterogeneously enhancing lesion in the segment 8/4 A of the liver, few other hypodense lesions in the right lobe of the liver, changes likely related to metastasis. White arrow heads indicate the lesion.

Discussion

Each immunoglobulin monomer consists of four polypeptide chains, two heavy chain and two light chains connected by disulfide bonds. Each polypeptide chain is composed of 400-500 amino acids. Amino acids are rich in nitrogen, which are metabolized to ammonia. Ammonia, a toxic metabolite is quickly converted to urea by the liver. In the setting of liver dysfunction, such as cirrhosis, ammonia levels accumulate leading to encephalopathy.

In the case of our patient, his newly diagnosed hepatic angiosarcoma was confirmed after tissues collected from CT guided core needle biopsy was stained positive for CD34 marker, indicating that the neoplastic cells are of endothelial cells/vascular origin. His ability to metabolize proteins, including his IVIG, to urea was compromised by his the neoplasm in his liver.

From the our patient's course of diagnosis of the hepatic angiosarcoma and its correlation to his acute progressive encephalopathy due to hyperammonemia, we concluded that:

- Patients who receive high dose immunoglobulin infusion may be at increased risk of hyperammonemia, especially in the setting of compromised liver function.
- Patients with liver pathology, such as a hepatic neoplasm, can decrease their ability to metabolize proteins and may result in increased ammonia level, which may present clinically as acute encephalopathy.
- Clinicians should consider making adjustments to the dosage of immunoglobulin infusion or injection of large amount to protein products patients with underlying liver pathology.
- In patients with underlying liver pathology who receive high dose IVIG, clinicians should consider prescribing lactulose prophylactically to prevent hyperammonemia.

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