Case Report

Hyperammonemia Presenting as Refractory Status Epilepticus after Lung Transplant in a Patient Positive for Ureaplasma parvum

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Abstract

Hyperammonemia is a rare complication of lung transplant with a high mortality rate. It presents as encephalopathy and progresses to seizures, status epilepticus, coma, cerebral edema, and brain death. Multiple treatments have been documented including administration of medications, gut decontamination, and dialysis. However, no definitive treatments exist and mortality remains between 67% and 75%. We present the case of a 65-year-old male with idiopathic pulmonary fibrosis who developed refractory status epilepticus secondary to hyperammonemia following lung transplant. The patient presented on postoperative day 7 with super-refractory status epilepticus and normal computed tomography scan of the head. Hyperammonemia was suspected due to refractory seizures and confirmed with peak ammonia level >1000 µmol/L. Despite aggressive treatment, the patient developed global cerebral edema and died. Postmortem investigations revealed that the patient was positive for Ureaplasma parvum. Additional studies are needed to elucidate the exact mechanism of disease and investigate successful treatment options.

Keywords: Cerebral edema, hyperammonemia, lung transplantation, seizures, status epilepticus

Introduction

Hyperammonemia following lung transplant is a rare, but often fatal complication.[1] The majority of these patients have normal hepatic function. Some studies have linked the occurrence of hyperammonemia to a deficiency of hepatic glutamine synthetase activity; however, the exact pathophysiology is unknown.[2,3] Early and aggressive treatment with medications and dialysis may decrease mortality.[2,4,6] When diagnosed late, hyperammonemia is often accompanied by seizures, severe cerebral edema, and increased intracranial pressure and frequently leads to death.[1,2,7,8]

Case Report

A 65-year-old male underwent lung transplant for idiopathic pulmonary fibrosis. He progressed well following transplant; however, his mental status waned and he had other postoperative issues including atrial fibrillation, hypoxemia requiring reintubation, and periods of hypotension requiring vasopressors. His medication regimen included narcotics for postoperative pain and calcineurin inhibitors for immunosuppression.

On postoperative day (POD) 7, the patient had seizures. Continuous electroencephalogram (cEEG) revealed a prolonged focal motor seizure, suggestive of ongoing status epilepticus [Figure 1]. Computed tomography (CT) of the head was normal. Seizures were treated with phenytoin, midazolam, and propofol. Tacrolimus and voriconazole were discontinued for concerns of neurotoxicity. The patient remained in status epilepticus on POD 8; ketamine, lacosamide, and valproic acid (VPA) were added. Later that night, seizure activity stopped, and cEEG demonstrated severe encephalopathy with diffuse slowing. Serum ammonia level was 830 µmol/L. Lactulose, rifaximin, and continuous renal replacement
therapy (CRRT) were initiated. Despite these interventions, the patient’s ammonia level increased to >1000 µmol/L. Hours later, his pupils became fixed and dilated. Boluses of mannitol and 23.4% hypertonic saline were given, 3% hypertonic saline infusion started, and sedation discontinued. Physical examination revealed fixed and dilated pupils, absent brainstem responses, and near-isoelectric tracing on eEEG. Neurosurgery placed an external ventricular device which demonstrated intracranial hypertension. CT of the head showed diffuse cerebral edema and transtentorial and tonsillar herniation [Figure 2]. CRRT was discontinued and intermittent hemodialysis (IHD) was performed; however, his ammonia level remained >1000 µmol/L and examination unimproved. Multidisciplinary meeting was held with the family, and life-support measures were discontinued on POD 9. Bronchoalveolar lavage done at the time of transplant was positive for Ureaplasma parvum postmortem.

DISCUSSION

There are many potential causes of altered mental status following lung transplant. Hyperammonemia may not initially be considered. Common reasons include drug effects from calcineurin inhibitors and narcotics, Intensive Care Unit delirium, or hypoxia. Calcineurin inhibitors can cause altered mental status since they contribute to vasogenic cerebral edema as a result of hyperperfusion. Calcineurin inhibitor-associated hyperperfusion occurs when hypertension disrupts the myogenic and neurogenic response leading to cerebral vasoconstriction. This causes fluid shift into the brain parenchyma, resulting in vasogenic edema. After prolonged exposure to the drug, cytotoxic effects may also occur. In our case, hyperammonemia presented as seizures and progressed to cerebral edema, coma, and death, likely due to glutamine production in the brain from ammonia metabolism, which creates an osmotic effect and leads to cerebral edema. This phenomenon was reported in two cases where cerebral spinal fluid glutamine levels were measured and increased with dissociation between plasma glutamine levels, which were decreased. The etiology of this disease after lung transplant is not known. Some have hypothesized that hyperammonemia is triggered by major medical stressors, particularly gastrointestinal stress, hepatic glutamine synthetase deficiency, or a partial urea cycle deficiency unmasked by the stress of surgery. In our patient, medications such as VPA may have contributed to hyperammonemia by inhibition of the first stage of the urea cycle as a result of inhibition of carbamoyl phosphate synthetase 1 activation and resultant decrease of N-acetylglutamate availability.

Others have noted a causal relationship to Mycobacterium hominis and Ureaplasma infections. It is postulated that Ureaplasma contributes to hyperammonemia due to its production of amonia which leads to hydroyisis of urea with ammonia as a byproduct. While the presence of Ureaplasma in the human urogenital tract is usually not symptomatic, when this infection becomes systemic in lung transplant recipients, the ammonia production becomes too much to handle. In one study, bronchoalveolar lavage and plasma samples for Ureaplasma were collected in patients with and without hyperammonemia after lung transplant. This study demonstrated a causal relationship between Ureaplasma and hyperammonemia and adds to the growing body of literature regarding the etiology of this disease. While the true incidence of ureaplasma infection in lung transplant patients is unknown, one study that tested for Ureaplasma in both donor and recipient lungs had 4 of 28 donor lungs testing positive for Ureaplasma. All recipients of Ureaplasma-positive donor lungs developed lung infiltrates and required vasopressors for blood pressure support postoperatively. Ureaplasma-positive donor lungs were also associated with hyperammonemia in the transplant recipients, as well as higher incidence of primary graft dysfunction, acute rejection, acute renal failure, and 60-day mortality.

All treatment regimens include combinations of protein restriction, bowel decontamination, amino acids, dialysis, and nitrogen scavengers. Many medications have been used, including lactulose, rifaximin, metronidazole, levocarnitine, arginine, sodium phenylacetate, and sodium benzoate. The mainstay of treatment for hyperammonemia in hepatic encephalopathy has traditionally been lactulose,
a nonabsorbable disaccharide which decreases both the absorption and the production of ammonia in the gut. Antibiotics, such as rifaximin, have been used adjunctively to suppress ammonia-producing bacteria. Levocarnitine improves hyperammonemia caused by VPA because carnitine depletion changes the metabolism of VPA. Supplementation of carnitine returns VPA metabolism back to mitochondrial beta-oxidation and also improves urea cycle function. Arginine decreases serum ammonia by stimulating the urea cycle. Sodium phenylacetate and sodium benzoate are nitrogen scavengers that divert nitrogen from the urea cycle to alternate routes of secretion. Sodium phenylacetate acetylates glutamine forming phenylacetylglutamine, and sodium benzoate acetylates with glycine, forming hippuric acid, both of which are easily excreted by the kidneys. In addition, if an Ureaplasma infection is suspected, the combined use of fluoroquinolones and macrolides is recommended while polymerase chain reaction results are pending. Dialysis is a mainstay of treatment, and both IHD and CRRT are utilized with a preference for IHD, which was found to be more effective in clearing plasma ammonia. This has been the only case of hyperammonemia encountered in >400 patients who underwent a lung transplant at our institution. Our patient’s bronchial lavage was done at the time of transplant tested positive for U. parvum; however, these results were only available postmortem. This likely triggered the development of hyperammonemia and status epilepticus. Once hyperammonemia was suspected, treatment was promptly initiated. The patient did not improve despite aggressive treatment. Lichtenstein et al. described a period of irreversibility where intervention no longer improves outcome, and our patient’s hyperammonemic coma likely indicated that this point had been reached.

Conclusion
Early assessment of serum ammonia level when lethargy, agitation, or seizures are present could potentially be lifesaving. Early and aggressive intervention may prevent progression to cerebral edema and coma. In addition, patients should be screened carefully for Ureaplasma as this may be an inciting cause, and antibiotics initiated prophylactically if hyperammonemia is present. Further investigation of the etiology of hyperammonemia after lung transplant and of successful treatment regimens is needed.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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