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Two Cases of Fatal Hyperammonemia Syndrome due to *Mycoplasma hominis* and *Ureaplasma urealyticum* in Immunocompromised Patients Outside Lung Transplant Recipients

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Hyperammonemia syndrome (HS) in immunocompromised patients was originally described in 1985 [1]. The original cases were three patients with acute leukemia in the absence of underlying liver diseases.

The mechanisms of HS were unknown until Bharat et al [2] shed light on *Ureaplasma* spp. as the potential culprits of HS in a case series of lung transplant recipients in US transplant centers. A total of six lung transplant recipients, retrospectively or prospectively collected, developed hyperammonemia due to *Ureaplasma urealyticum* or *Ureaplasma parvum*. Mycoplasma *hominis* was reported as a coinfected pathogen or a potential cause in HS [3, 4]. Most of the HS cases due to those fastidious organisms have been reported in lung transplant recipients. Here, we present two cases to add to the increasing evidence, outside of lung transplant recipients, of the relationship between *U urealyticum* and *M hominis* with HS.

CASE 1

The first case is a 32-year-old woman with a history of B-cell acute lymphoblastic leukemia and diabetes mellitus. The patient

denied any underlying liver diseases. Her cancer treatment course had been complicated with frequent episodes of neutropenic fever. She was admitted for initiation of salvage chemotherapy with methotrexate, vincristine, PEG-asparaginase, and dexamethasone, which led to episodes of neutropenic fevers related to a perirectal abscess due to extended-spectrum β-lactamases *Escherichia coli* and bacteremia due to *Stenotrophomonas maltophilia* from a skin and soft tissue infection of her right hand. While completing high-dose sulfamethoxazole/trimethoprim and ertapenem for these infections, she developed fevers, abrupt onset seizures, and shock requiring intubation. A computed tomography scan of the brain revealed diffuse effacement of the sulci and fissure consistent with diffuse cerebral edema. An ammonia level was checked and found to be severely elevated at 1643 μmol/L. Her blood work revealed continued profound leukopenia (<0.0 cm^2) over the previous two months, stable anemia, stable anemia, and severe thrombocytopenia. Levofloxacin was empirically initiated for concerns of HS due to infectious etiologies after a serum *Mycoplasma* and *Ureaplasma* polymerase chain reaction (PCR) was sent. Unfortunately, her low blood pressure and rapid clinical decline precluded aggressive dialysis for hyperammonemia management. She expired shortly after transition to comfort care. A serum *Ureaplasma* PCR panel returned positive for *Ureaplasma urealyticum* postmortem.

CASE 2

The second case is a 49-year-old female with a history of treated hepatitis C without cirrhosis and end-stage renal disease who had been on hemodialysis until she underwent a deceased donor kidney transplant. Her induction regimen included basiliximab, methylprednisone, mycophenolate mofetil, and tacrolimus. The immediate postoperative course was unremarkable until day 6 when she became acutely altered due to seizures requiring intubation for airway protection. Computed tomography and magnetic resonance imaging of the brain returned with bilateral thalamic edema. Cerebrospinal fluid analysis was within normal limits. Her ammonia level was 511 μmo/L, and she was started on continuous renal replacement therapy (CRRT), ammonia scavengers, and a protein-restricted diet. With concern of HS due to *M hominis* or *Ureaplasma* spp, empirical therapy with doxycycline and levofloxacin was initiated. Her liver function tests and liver ultrasound returned normal. Subsequently, she was found to have a large seroma as well as urinary leak due to severely necrotic transplant ureter, which required a washout and ureteropyeloplasty with a native ureter. PCRs for *M hominis* and *Ureaplasma* spp were sent from serum and urine, which came back positive for *M hominis* from both samples. Biochemical and molecular genetic testing for ornithine transcarbamylase deficiency and other urea cycle

disorder that might present with hyperammonemia were negative (Supplementary Table S1). After the initiation of aggressive therapy, her ammonia level had improved over 10 days. Despite completion of antimicrobial therapy without recurrence of HS, her hospital course was prolonged due to the neurological complications from hyperammonemia. She expired due to aspiration pneumonia after three months of hospitalization.

DISCUSSION

We described two cases of HS caused by *M hominis* and *Ureaplasma* spp. in immunocompromised patients. An additional case due to *U parvum* was recently reported in a stem cell transplant recipient [5]. Our cases highlight the importance of awareness of this syndrome even outside lung transplant recipients, especially because ammonia levels are not routinely measured for acute mental changes in immunocompromised patients without liver diseases.

Mycoplasma hominis and *Ureaplasma* spp. are frequently commensal urogenital organisms (up to 29% in men and 38%–75% in women) leading to urinary tract infections, urethritis, cervicitis, and pelvic inflammatory disease among other localized but extragenital infections such as pneumonia and septic arthritis [6, 7]. The disseminated disease does occur particularly among immunocompromised patients, notably solid organ transplants, acquired immune deficiency syndrome, and hematologic malignancies [8]. In addition, donor-derived transmissions have been reported in lung transplant recipients [9, 10]. The incidence of HS in immunocompromised patients is unknown. One to four percent of lung transplant patients may develop hyperammonemia with a 30-day posttransplantation mortality rate of 67% compared with 17% of those with normal ammonia levels [8]. The patients with hyperammonemia initially present with an abrupt onset of encephalopathy (i.e., lethargy, confusion, and agitation) early in the transplant postoperative course within the first two weeks (median 9.0 days) [11]. However, our first case developed HS after two months of severe neutropenia, which suggests this infection may occur anytime in the presence of severe immunosuppression. The original source of infection is unclear in our first case. In the second case, however, the urological source was highly suspicious because the patient had a severe necrotic ureter with a urinary leak as well as positive urine PCR. In addition, *M hominis* has been recognized as the cause of postsurgical infection in the renal transplant population [12]. Because only a case report reported *M hominis* as a possible cause of HS [3], other potential causes were sought in our second case. However, none of the tests was conclusive. Chemotherapy is also implicated as a potential cause of HS [13]. In our first case, the last chemotherapy was given four weeks before the event, which is outside of the typical reported range of HS postchemotherapy [13].

Ureaplasma spp. have a unique metabolic strategy that hydrolyzes urea into CO_2 and ammonia to obtain free energy,

which potentially leads to high serum ammonia level in bacteremic infections [13]. *Mycoplasma hominis* uses arginine during energy production, which may increase subsequent ammonia level as a byproduct [14, 15]. However, the exact mechanisms of HS are unknown. Because of their fastidious nature, these organisms require specific media with amino acids, nucleic acid precursors, urea, arginine, and serums that are not routinely used in culture [6]. Nucleic acid amplification assays, which detects *M hominis tuf* gene and *U urealyticum* or *parvum ureC* gene, are available in selected reference laboratories that will likely become the diagnostic standard in the future [6, 16–18]. The dedicated PCR tests for each organism were used in our cases through one of the US reference laboratories [17, 18].

Despite the treatability of this infection, which may ultimately lead to the control of the ammonia levels, the devastating neurologic consequences seen initially necessitates aggressive supportive measures to control ammonia levels and resultant brain edema with CRRT, nitrogen scavengers, nutrition modifications, and intensive care [2, 8, 11]. *Ureaplasma* spp. are generally susceptible to fluoroquinolones, macrolides, and tetracyclines, whereas *M hominis* is uniformly resistant to macrolides [6]. Combination therapy, such as tetracycline and fluoroquinolone, should be considered until there is a better understanding of resistant patterns in these pathogens [13]. The optimal duration of antimicrobial therapy is unknown. In our second case, a repeated *M hominis* PCR at day 14 after the initiation of therapy became negative and the therapy was continued for a total of 21 days.

CONCLUSIONS

Ureaplasma spp. and/or *M hominis* are emerging pathogens could be associated with hyperammonemia syndrome. The abrupt onset of neurological changes in immunocompromised patients should prompt ammonia level measurement, regardless of the suspicion of liver disease, and initiating empirical antimicrobial and supportive therapy if the level is significantly elevated until PCR results are available. Early diagnosis and aggressive therapy are the cornerstones of the management of this infection.

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