Case Report: Hyperammonemic Encephalopathy Linked to Ureaplasma spp. and/or Mycoplasma hominis Systemic Infection in Patients Treated for Leukemia, an Emergency Not to Be Missed

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Background: Hyperammonemic encephalopathy caused by Ureaplasma spp. and Mycoplasma hominis infection has been reported in immunocompromised patients undergoing lung transplant, but data are scarce in patients with hematological malignancies.

Case Presentation: We describe the cases of 3 female patients aged 11–16 years old, developing initially mild neurologic symptoms, rapidly evolving to coma and associated with very high ammonia levels, while undergoing intensive treatment for acute leukemia (chemotherapy: 2 and hematopoietic stem cell transplant: 1). Brain imaging displayed cerebral edema and/or microbleeding. Electroencephalograms showed diffuse slowing patterns. One patient had moderate renal failure. Extensive liver and metabolic functions were all normal. Ureaplasma spp. and M. hominis were detected by PCR and specific culture in two patients, resulting in prompt initiation of combined antibiotics therapy by...
INTRODUCTION

Hyperammonemic encephalopathy (HE) is a rare and often lethal complication of intensive chemotherapy or hematopoietic stem cell transplantation (HSCT), in patients treated for hematologic pathologies. It was first described by Watson et al. in 1985, as “transient idiopathic hyperammonemia (IHA)” (1), in patients without any liver nor metabolic disorder. There are few data regarding its occurrence. Davies et al. published in 1996 the largest series of adult patients undergoing HSCT, and presenting with IHA, with an incidence of 0.5% (12/2,358 patients) and a mortality rate of 83% (10/12 patients) (2). Most common symptoms are those of a metabolic encephalopathy, with abrupt alteration in the mental status, sometimes seizures, confusion, and lethargy, leading to coma. The diagnosis is often made when severe neurologic symptoms occur, in the absence of liver or metabolism impairment. Despite ammonia-scavenging drugs associated with dialysis, the prognosis remains poor.

Several causes of IHA have been proposed during the last decades, such as iatrogenic toxicity (chemotherapy (3, 4), steroids, supportive care medications) and an increased catabolic state during acute severe illness. Recently, U. parvum and U. urealyticum infections have been determined to cause hyperammonemia in adult lung transplant recipients, responsible for numerous neurological manifestations (5). This infectious hypothesis has been later described in three patients treated for acute myeloblastic leukemia (AML), aged 21, 16, and 12 years old, following HSCT or not, with prompt resolution of hyperammonemic encephalopathy after the initiation of appropriate antibiotic therapy (6–8). Recently, Tawfik et al. described the case of a 53-year-old patient, receiving chimeric receptor antigen T-cell (CAR-T) therapy for relapsing B acute lymphoblastic leukemia (B-ALL), who died of brain damage following a systemic U. parvum infection (9).

Here, we report the case of 3 immunocompromised patients treated for acute leukemia, aged 11–16 years old, diagnosed with systemic Ureaplasma spp. or M. hominis infections, responsible for HE. Pooling these cases to the ones described in the literature allowed us to make some recommendations for the diagnosis and treatment of this misleading, rare, and severe condition.

CASE PRESENTATION

During these last three years (January 2019–December 2021), 361 patients were treated for a newly diagnosed acute leukemia in the pediatric hematology department of the Hôpital Universitaire Robert Debré (Paris, France) and the adolescent/young adult unit of the Hôpital Universitaire Saint Louis (Paris, France). We report here on 3 patients presenting with HE observed while undergoing intensive treatment for B-ALL (n=1) or AML (n=2), corresponding to an incidence of 0.8%. Clinical, main biological, and imaging feature characteristics are detailed in Table 1 and treatment/outcome in Table 2.

Patient #1

A 15-year-old female patient treated for B-ALL underwent haplo-identical HSCT following a myeloablative conditioning regimen in first remission. From day 6 post-HSCT, she presented with refractory thrombocytopenia responsible for hematocolpos (blood-filled dilated vagina). Opioids were started for a grade IV mucositis, complicated by iatrogenic acute urinary retention requiring indwelling catheter between day 11 and day 15 post-
On day 20, mental status changes were observed, shortly leading to coma (Glasgow Coma Scale [GCS] score of 8) followed by seizure and pyramidal syndrome. The brain computerized tomography (CT) scan was normal. Routine biological exams showed acute kidney injury (creatinine level at 142 µmol/L), a mildly elevated total bilirubin level (38 µmol/L), inflammatory markers (CRP level 287 mg/L), and a highly increased ammonia level at 342 µmol/L (normal 14-38 µmol/L). Ammonia-scavenging drugs were immediately started. The patient was then transferred to the intensive care unit (ICU) and was intubated for airway protection and placed on continuous venovenous hemofiltration to decrease ammonia levels. Other extensive liver and metabolic tests were normal. Ammonia levels plateaued for 6 days after ICU admission, and her neurological state worsened with abnormal respiratory patterns and the absence of corneal reflex. The MRI performed on day 25 post-HSCT showed a bilateral cerebral edema with a right frontal microbleeding. Electroencephalograms (EEGs) showed diffuse slowing patterns. On day 27 post-HSCT, blood, tracheal, urine, and vaginal samples were sent for *Ureaplasma* spp./*M. hominis*.

**TABLE 1 |** Clinical, biological, and imaging characteristics at onset of the three newly reported patients.

|                       | Patient #1 | Patient #2 | Patient #3 |
|-----------------------|------------|------------|------------|
| **Clinical characteristics** |            |            |            |
| Age at time of complication (years) | 15 | 11 | 16 |
| Gender | Female | Female | Female |
| Disease | B-ALL | AML | AML |
| Intensive chemotherapy | No | Yes | Yes |
| HSCT | No | No | No |
| Aplasia ongoing at the time of infection | Yes | Yes | Yes |
| Fever ongoing at time of complication | No | Yes | Yes |
| Perineal complication ongoing at time of complication | Yes | Yes | Yes |
| Initial neurological symptoms | Irritability/confusion/ seizure | Irritability/confusion | Psychomotor slowing |
| GCS score | 8 | 12 | 12 |
| **Biology** |            |            |            |
| NH4 level max in µmol/L (normal range) | 533 (14-38) | 1,420 (14-38) | 656 (18-72) |
| CRP max (mg/L) | 287 | 410 | 276 |
| Liver biology | Bilirubin 1.5N | ASAT/ALAT 2.5N | Gamma GT 17N |
| **Imaging** |            |            |            |
| Liver imaging (normal/abnormal) | Normal | Normal | NA |
| EEG abnormality | Yes | Yes | Yes |
| Cerebral Imaging Abnormalities | MRI | MRI | CT scan |
| Abnormalities | (bilateral cerebral edema with a right frontal microbleeding) | (left cerebellar microbleeds with hemorrhagic sequelae) | (cerebral edema) |
| **Bacterial documentation** |            |            |            |
| Species | *U. parvum*, *U. urealyticum*, *M. hominis* | *U. parvum*, *M. hominis* | *M. hominis* |
| Method | PCR (vagina, blood, urine, trachea) and culture (trachea) | PCR (vagina, blood, urine) and culture (blood) | 16S rRNA PCR (vagina) |

*B-ALL, B acute lymphoid leukemia; AML, acute myeloid leukemia; HSCT, hematopoietic stem cell transplant; GCS score, Glasgow Coma Scale score; NA, not applicable; EEG, electroencephalogram; MRI, magnetic resonance imaging; CT scan, computed tomography scan; U, ureaplasma; M, mycoplasma.*

**TABLE 2 |** Therapeutics and outcome of the 3 newly reported patients.

|                       | Patient #1 | Patient #2 | Patient #3 |
|-----------------------|------------|------------|------------|
| **Treatment** |            |            |            |
| Antibiotherapy | Levofloxacin + azithromycin | Levofloxacin + clarithromycin switched to josamycin | None |
| NH4 chelation* | Yes | Yes | Yes |
| Renal replacement therapy | Yes | Yes | Yes |
| **Outcome** |            |            |            |
| Alive | Yes | Yes | No |
| Cause of death | Cerebral edema | Cerebral edema | NA |
| Neurological sequelae | No | No | NA |
| Follow-up (year) | 1.5 | 0.8 | NA |

*NH4 chelation: sodium phenylbutyrate and/or sodium benzoate. NA, not applicable.*
specific culture and PCR. Empiric antibiotics (levofloxacin and azithromycin) were started on the same day. Within 48 h, her neurological status improved and ammonia levels normalized, allowing to stop life-sustaining therapies in the ICU. PCR was positive for *U. parvum* (blood, trachea, urine, and vagina), *U. urealyticum* (urine and vagina), and *M. hominis* (urine, vagina, and trachea). The latter was also positive in the culture of tracheal aspiration, allowing the determination of antibiotic susceptibility. *Ureaplasma* spp. were susceptible to erythromycin, tetracycline, levofloxacin, and moxifloxacin, with intrinsic resistance to clindamycin. *M. hominis*, intrinsically resistant to erythromycin and azithromycin, was susceptible to tetracycline, clindamycin, and moxifloxacin but had acquired resistance to levofloxacin. Levofloxacin and azithromycin were discontinued 4 and 20 days later, respectively, with a strict monitoring of neurological examination and ammonia levels, which both remained normal. Eighteen months post-HSCT, the patient is still in remission, with a normal mental status and neurological exam. Clinical, biological, and imaging features are summarized in Figure 1A.

**Patient #2**

An 11-year-old female patient was diagnosed with AML, presenting with cauda equina syndrome. Given the neurological presentation, steroids and chemotherapy were started promptly but dysuria remained a major issue, requiring an indwelling urinary catheter. On day 24 of chemotherapy, she developed mental status changes with irritability and confusion...
(GCS score of 14). The brain CT scan was normal. Routine biological exams revealed mild anicteric cholestasis (elevated gamma GT up to 407 UI/L with normal bilirubin levels), inflammatory markers (CRP level 179 mg/L), and extremely high ammonia levels at 1,118 µmol/L (normal 14-38 µmol/L). Given the previous case observed earlier, samples for the Ureaplasma spp./M. hominis-specific culture and PCR were promptly performed. Empirical antibiotic therapy combining levofloxacin and clarithromycin was immediately started. PCR performed on urine, vaginal, and blood samples was positive for U. parvum and M. hominis. The latter was also detected in blood culture. Antibiogram showed susceptibility to tetracycline, clindamycin, levofloxacin, and moxifloxacin and intrinsic resistance to erythromycin. Other extensive liver and metabolic tests were normal. The patient was transferred to the ICU and placed under continuous venovenous hemofiltration, with ammonia-scavenging drugs. Despite 48 h of intensive treatment, ammonia levels remained elevated and the neurological examination worsened, leading to a coma (GCS score of 6) with EEG showing diffuse slowing patterns. She was intubated the same day and benefited from two intermittent hemodialysis sessions. Clarithromycin was switched to josamycin. Within 72 h of newly combined antibiotics, ammonia levels started to decrease, and her mental status improved, allowing to stop life-sustaining therapies a few days later. MRI performed on day 32 post-chemotherapy showed left cerebellar microbleeds with hemorrhagic sequelae. Josamycin and levofloxacin were stopped after 21 and 47 days, respectively, with a strict monitoring of ammonia levels and neurological examination, which both remained normal. After 10 months of AML treatment, the patient is in remission without any sequelae. Clinical, biological, and imaging features are summarized in Figure 1B.

**Patient #3**

A 16-year-old female patient was diagnosed with AML and received leukoreductive therapy followed by conventional chemotherapy. On day 9 post-chemotherapy, she presented sepsis while being profoundly neutropenic and was started on empirical antibiotics (cefepime plus vancomycin). No detectable microorganism was documented in repeated blood cultures and local samplings. Despite broad spectrum antibiotics (meropenem, amikacin and ornidazole) the infection kept on evolving. Antibiotic resistance to erythromycin. Other extensive liver and metabolic tests were normal. The patient was transferred to the ICU and placed under continuous venovenous hemofiltration, with ammonia-scavenging drugs. Despite 48 h of intensive treatment, ammonia levels remained elevated and the neurological examination worsened, leading to a coma (GCS score of 6) with EEG showing diffuse slowing patterns. She was intubated the same day and benefited from two intermittent hemodialysis sessions. Clarithromycin was switched to josamycin. Within 72 h of newly combined antibiotics, ammonia levels started to decrease, and her mental status improved, allowing to stop life-sustaining therapies a few days later. MRI performed on day 32 post-chemotherapy showed left cerebellar microbleeds with hemorrhagic sequelae. Josamycin and levofloxacin were stopped after 21 and 47 days, respectively, with a strict monitoring of ammonia levels and neurological examination, which both remained normal. After 10 months of AML treatment, the patient is in remission without any sequelae. Clinical, biological, and imaging features are summarized in Figure 1B.

**DISCUSSION**

IHA occurring in patients treated for malignancies, while receiving intensive chemotherapy or HSCT, has been described over the last decades but with difficulties to identify one predominant etiology (3, 4). Evidence came from immunocompromised patients post-lung transplant who experienced HE associated with M. hominis or Ureaplasma spp. infections. All 3 patients were females, pre-pubescent or pubescent, with urogenital complications occurring while being profoundly neutropenic. The first symptoms of HE began around day 20 after chemotherapy initiation or HSCT, quickly leading to severe neurological symptoms without major liver or metabolic complications. When M. hominis or Ureaplasma spp. infections were diagnosed and treated, their neurological state quickly returned to normal (<96 h), without any sequelae, even with extremely high ammonia levels and worrying cerebral imaging. Ammonia-scavenging drugs and renal replacement therapies seemed insufficient to improve a patient’s clinical status.

Only 4 similar cases in patients treated with intense therapy and immunosuppression for hematologic malignancies have been recently described in the literature (Table 3) (6–9). We report here the second case during an HSCT procedure. Combined with our 3 cases, they show a strong trend among female (6 females vs. 1 male) and pediatric patients (age 11–21 years old, n=6). No other pelvic/perineal complication is described. Ureaplasma spp. was more frequently involved (n=6), and all microbiologic documentations were performed by PCR. Once an infection is suspected and/or documented, empiric antibiotic therapy combining fluoroquinolones with macrolide or tetracycline was used, with the normalization of ammonia levels and neurological status in 5 out of 6 patients. The last patient was a 53-year-old woman treated with CAR T-cell therapy for B-ALL. She developed HE while under levofloxacin prophylaxis. Once elevated ammonia levels were identified, doxycycline was introduced to cover ammonia-producing bacteria without any clinical or biological efficacy. PCR from broncho-alveolar lavage returned positive for U. parvum, and levofloxacin was started again, as a combined targeted antibiotic therapy. The cerebral MRI performed the same day showed diffuse cerebral edema, and the patient’s family elected to the discontinuation of care (9).
HE linked to *Ureaplasma* spp. or *M. hominis* systemic infection is rarely reported in literature and may be underestimated. In a recent study, Zaho et al. (12) published a series of 265 adults treated in ICU for sepsis, 107 of whom had non-hepatic hyperammonemia. They compared the characteristics of this group to the non-hyperammonemia group. The median white blood cell count was similar for both groups and well above bone marrow aplasia criteria. Patients with non-hepatic hyperammonemia had more intestinal and urinary tract infections (23.4% vs. 13.3%, p=0.034 and 45.8% vs. 24.7%, p<0.001, respectively) and had a higher rate of non-hepatic hyperammonemia had more intestinal and urinary tract infections (23.4% vs. 13.3%, p=0.034 and 45.8% vs. 24.7%, p<0.001, respectively) and had a higher rate of non-hepatic hyperammonemia had more intestinal and urinary tract infections (23.4% vs. 13.3%, p=0.034 and 45.8% vs. 24.7%, p<0.001, respectively) and had a higher rate of non-hepatic hyperammonemia had more intestinal and urinary tract infections (23.4% vs. 13.3%, p=0.034 and 45.8% vs. 24.7%, p<0.001, respectively) and had a higher rate of non-hepatic hyperammonemia had more intestinal and urinary tract infections (23.4% vs. 13.3%, p=0.034 and 45.8% vs. 24.7%, p<0.001, respectively) and had a higher rate of non-hepatic hyperammonemia had more intestinal and urinary tract infections (23.4% vs. 13.3%, p=0.034 and 45.8% vs. 24.7%, p<0.001, respectively) and had a higher rate of non-hepatic hyperammonemia had more intestinal and urinary tract infections (23.4% vs. 13.3%, p=0.034 and 45.8% vs. 24.7%, p<0.001, respectively) and had a higher rate of non-hepatic hyperammonemia had more intestinal and urinary tract infections (23.4% vs. 13.3%, p=0.034 and 45.8% vs. 24.7%, p<0.001, respectively) and had a higher rate of non-hepatic hyperammonemia had more intestinal and urinary tract infections (23.4% vs. 13.3%, p=0.034 and 45.8% vs. 24.7%, p<0.001, respectively) and had a higher rate of non-hepatic hyperammonemia had more intestinal and urinary tract infections (23.4% vs. 13.3%, p=0.034 and 45.8% vs. 24.7%, p<0.001, respectively) and had a higher rate of non-hepatic hyperammonemia had more intestinal and urinary tract infections (23.4% vs. 13.3%, p=0.034 and 45.8% vs. 24.7%, p<0.001, respectively) and had a higher rate of non-hepatic hyperammonemia had more intestinal and urinary tract infections (23.4% vs. 13.3%, p=0.034 and 45.8% vs. 24.7%, p<0.001, respectively) and had a higher rate of non-hepatic hyperammonemia had more intestinal and urinary tract infections (23.4% vs. 13.3%, p=0.034 and 45.8% vs. 24.7%, p<0.001, respectively) and had a higher rate of non-hepatic hyperammonemia had more intestinal and urinary tract infections (23.4% vs. 13.3%, p=0.034 and 45.8% vs. 24.7%, p<0.001, respectively) and had a higher rate of non-hepatic hyperammonemia had more intestinal and urinary tract infections (23.4% vs. 13.3%, p=0.034 and 45.8% vs. 24.7%, p<0.001, respectively) and had a higher rate of non-hepatic hyperammonemia had more intestinal and urinary tract infections (23.4% vs. 13.3%, p=0.034 and 45.8% vs. 24.7%, p<0.001, respectively) and had a higher rate.

### TABLE 3 | Comparison of cases of hyperammonemic encephalopathy due to *Ureaplasma* spp. and/or *Mycoplasma hominis* in immunocompromised patients treated for a malignant hemopathy found in the literature.

| Age (Y) | Gender | Disease/Treatment | Perineal Complication | Bacteria | Method of Detection | Antibiotics | Outcome |
|---------|--------|------------------|----------------------|----------|--------------------|-------------|---------|
| This Study | 15 | Female | B-ALL/HSCT | Yes | *U. parvum, U. urealyticum, M. hominis* | PCR (vagina, urine, blood, trachea) and culture (trachea) | Levofoxacin + azithromycin | Alive |
| | 11 | Female | AML/CT | Yes | *U. parvum, M. hominis* | PCR (vagina, urine, blood) and culture (blood) | Levofoxacin + clarithromycin/josamycin | Alive |
| | 16 | Female | AML/CT | Yes | *M. hominis* | Post-mortem 16sRNA PCR (vagina) | None | Dead (cerebral edema) |
| Placone et al. (6) | 16 | Female | AML/CT | No | *U. parvum* | PCR (blood) | Azithromycin then doxycycline | Alive |
| Smith et al. (7) | 12 | Female | AML/CT | No | *U. parvum* | PCR (blood, urine, and trachea) | Culture failure | DOD/normalization of NH4 level |
| Graetz et al. (6) | 21 | Male | AML/HSCT | No | *U. parvum* | PCR (trachea) | Azithromycin + levofoxacin | Alive |
| Tavfik et al. (9) | 53 | Female | B-ALL/CAR T cells | No | *U. parvum* | PCR (BAL fluid) | Doxycycline (D1) + levofloxacin (D5) | Dead (discontinuation of care due to the severity of the brain damage) |

Y, years; B-ALL, B acute lymphoid leukemia; HSCT, hematopoietic stem cell transplant; U, ureaplasma; M, mycoplasma; AML, acute myeloid leukemia; CT, chemotherapy; DOD, died of disease; CAR-T cells, chimeric antigen receptor-modified T cells; BAL, fluid, bronchoalveolar lavage fluid.
treated for a malignant hemopathy. *Ureaplasma* spp. is found in 40%–80% of healthy adult women’s genital flora (21), whereas 21%–53% of sexually active women are colonized with *M. hominis* (22); both bacteria are less diagnosed in men. The colonization rate is maximal at puberty and is linked to a low socio-economic level, oral contraception, sexual activity, and multiple partners (22). Prospective studies on patients experiencing HE while undergoing intensive treatment for a malignant hemopathy should allow a better estimate of its incidence. If higher than described in literature, it should be interesting to discuss a systematic screening in this population, especially in young women, with urogenital complications.

In conclusion, HE due to *Ureaplasma* spp. and *M. hominis* infection in patients treated for acute leukemia is a rare but possibly underestimated complication that can lead to death if not recognized and managed promptly. Thus, in this population, any neurological symptoms should lead to the measurement of ammonia levels. If increased, and in the absence of an obvious cause, this should prompt to search for *Ureaplasma* spp. and *M. hominis* by PCR in various sites (vagina, urine, blood, and trachea if possible). Immediate empiric antibiotic therapy combining fluoroquinolones (levofloxacin) and macrolides (josamycin) or tetracycline for older patients should be initiated. Supportive care in ICU is required, including ammonia-scavenging drugs and potential kidney replacement therapies. Appropriate antibiotics seem to allow a rapid and complete recovery in 72-96 h, even when ammonia levels are very high and brain imaging worrying.

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**DATA AVAILABILITY STATEMENT**

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

**ETHICS STATEMENT**

The studies involving human participants were reviewed and approved by Comité Local d’Ethique pour la Recherche Clinique des HUPSSD Avicenne-Jean Verdier-René Muret. Written informed consent to participate in this study was provided by the participants’ legal guardian/next of kin.

**AUTHOR CONTRIBUTIONS**

MD and AB contributed to the conception of the study, the interpretation of data, and manuscript writing. JG and AMF wrote sections of the manuscript. All authors contributed to the collection and assembly of data and the final approval of the submitted version.

**ACKNOWLEDGMENTS**

We thank SP, SB, and ABI for providing their expertise on mycoplasma and ureaplasma infections. We thank the patients and their families.
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