Invasive *Ureaplasma* Infection in Patients Receiving Rituximab and Other Humoral Immunodeficiencies—A Case Report and Review of the Literature

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*Ureaplasma* species are small, fastidious bacteria that frequently colonize the lower reproductive tract of asymptomatic hosts. These organisms have been well described to cause chorioamnionitis, neonatal infection, and urethritis, and to a lesser degree surgical site infection and infection in transplant recipients. Outside of these settings, invasive *Ureaplasma* infections are rare. We describe the case of a young woman receiving rituximab for multiple sclerosis who presented with fever and bilateral renal abscesses due to *Ureaplasma* spp., which was successfully treated with oral doxycycline. We searched the literature for cases of invasive *Ureaplasma* infection and found a patient population that predominates with humoral immunodeficiency, either congenital or iatrogenic. Diagnostic and therapeutic interventions are discussed.

**Keywords.** anti-CD20; humoral immunity; hypogammaglobulinemia; literature review; renal abscess; rituximab; septic arthritis.

**CASE REPORT**

A 27-year-old female with multiple sclerosis on rituximab with neurogenic bladder and frequent urinary tract infections (UTIs) presented to a community hospital with fevers, chills, and vomiting and a positive urinalysis. Despite empiric treatment with vancomycin and piperacillin-tazobactam, her fevers persisted. A computed tomography (CT) scan of the abdomen and pelvis revealed bilateral, small renal abscesses that were up to 2.1 cm in dimension.

Her therapy was broadened to vancomycin and meropenem, but a repeat CT scan 5 days after admission revealed enlarging abscesses. The bilateral collections were aspirated 7 days after admission, but all cultures including aerobic, anaerobic, fungal, and acid-fast cultures failed to isolate a pathogen. She had persistent intermittent fevers above 102°F, but remaining vital signs were stable.

She was transferred to our facility 8 days after admission. Vancomycin was transitioned to linezolid and levofloxacin was added, but her fevers persisted. She had repeat aspiration of the left renal abscess; however, no pathogen was isolated.

From a catheterized specimen, specialized urine culture techniques isolated *Ureaplasma* spp. (*Ureaplasma* culture, Quest Diagnostics, no further speciation). There was insufficient abscess aspirate remaining to be tested for the presence of *Ureaplasma* spp. Doxycycline was orally administered, and all fevers abated within 24 hours. She remained normothermic as the remainder of antibiotics were discontinued.

She was treated with doxycycline for 6 weeks total, as serial CT scans showed slow resolution of her abscesses. Her urinary symptoms improved quickly after initiation of doxycycline, and she remained asymptomatic at follow-up in clinic.

**LITERATURE REVIEW**

We searched PubMed and Embase for the last 30 years for patients with *Ureaplasma* infections outside of urethritis, neonatal, and pregnancy (Appendix). From this search, we excluded patients with transplant (solid organ or bone marrow), surgical site infection, peritoneal dialysis catheters, and children (<18 years old). We subsequently excluded 1 patient ultimately diagnosed with reactive arthritis that improved on immunosuppression [1]. Table 1 summarizes the remaining 24 cases.

**RESULTS**

Excluding patients with other known risk factors, humoral immunodeficiencies, either hypogammaglobulinemia or receipt of rituximab, are associated with the majority (17/24, 71%) of invasive *Ureaplasma* infections (Table 1). The remaining 7 patients (cases 1, 3, 6, 7, 11, 13, 14) were notable for 2 patients with lymphoma on unreported or other chemotherapy (3, 6), 1...
| Author (Year) | Case Presentation | Microorganism/Method of Diagnosis | Antimicrobial Treatment | Outcome | Risk Factors |
|---------------|-------------------|-----------------------------------|-------------------------|---------|--------------|
| 1 Rouard (2019) [2] | 88M prosthetic hip infection | *U. urealyticum*/*16S rRNA PCR and culture | None | Died of multiple comorbidities | No known immunocompromising conditions |
| 2 Gassiep (2017) [3] | 51F hip septic arthritis, necrotizing soft tissue infection | *U. urealyticum*/*16S rRNA PCR | Moxifloxacin | Improved | Mantle cell lymphoma; rituximab + hyper-CVAD, hypogammaglobulinemia |
| 3 Korytny (2017) [4] | 56M shoulder septic arthritis, orchitis, endocarditis | *U. parvum*/*16S rRNA PCR (on joint fluid and on aortic valve) | Doxycycline | Improved | CNS lymphoma with chemotherapy (regimen not reported) |
| 4 Roerdink (2016) [5] | 69F bilateral prosthetic knee infection | *U. urealyticum*/*16S rRNA PCR | Moxifloxacin + doxycycline | Improved | Hodgkin’s lymphoma/R-CHOP |
| 5 George (2015) [6] | 21F native knee and prosthetic hip infection | *Ureaplasma spp./16S rRNA PCR* | Azithromycin | Improved | JIA on rituximab |
| 6 Balsat (2014) [7] | 18F polyarthitis | *U. urealyticum*/*PCR/ESI-MS* | Levofloxacin + doxycycline | Improved | ALL on vincristine, steroids, daunorubicin, L-asparaginase, 1 dose tocilizumab |
| 7 Farrell (2014) [8] | 75M prosthetic knee infection | *U. parvum*/*PCR/*ESI-MS* | Doxycycline | Improved | No known immunocompromising conditions, colon adenocarcinoma, nephrolithiasis |
| 8 Deetjen (2014) [9] | 20 (gender not specified) brain abscess | *U. urealyticum*/*16S rRNA PCR* | Doxycycline + clarithromycin | Improved | Burkitt’s lymphoma, rituximab |
| 9 Yazdani (2012) [10] | 68F pyelonephritis, perinephric abscess, psoas abscess | *U. urealyticum*/*PCR (further tests not specified)* | Vancomycin + levofloxacin | Improved | Mantle cell lymphoma, rituximab |
| 10 Goulenok (2011) [11] | 74F prosthetic hip infection | *U. urealyticum*/*culture* | Doxycycline | Improved | SLE, rituximab |
| 11 Sköldenberg (2010) [12] | 54M polyarthritis, prosthetic hip infection | *U. parvum and Mycoplasma hominis*/*16S rRNA* | Moxifloxacin | Died (septic shock; other nosocomial infection suspected) | NHL, rituximab, hypogammaglobulinemia |
| 12 MacKenzie (2010) [13] | 50F spontaneous pericarditis, tamponade | *Ureaplasma spp./culture* | Doxycycline | Improved | No known immunocompromising conditions except age |
| 13 Tarrant (2009) [14] | 100F spontaneous pericarditis, tamponade | *Ureaplasma spp./culture* | Doxycycline | Improved | No known immunocompromising conditions except age |
| 14 Fenollar (2003) [15] | 57F prosthetic valve endocarditis | *U. parvum*/*16S rRNA PCR* | None | Died (heart failure) | No known immunocompromising conditions |
| 15 Heilmann (2001) [16] | 25M polyarthritis | *U. urealyticum*/*culture* | Doxycycline + ciprofloxacin + valneumulin (not available in US) | Died (pneumonia) | CVID, hypogammaglobulinemia |
| 16 Heilmann (2001) [16] | 34F prosthetic knee septic arthritis | *U. urealyticum*/*culture* | Doxycycline + valneumulin | Improved | CVID, hypogammaglobulinemia |
| 17 Lapusan (2001) [17] | 38M septic arthritis, pneumonia, empyema | *U. urealyticum*/*culture* | Erythromycin → doxycycline clindamycin | Died (disseminated disease) | Hypogammaglobulinemia |
| 18 Frangogiannis (1998) [18] | 31M ankle septic arthritis, endocarditis of unknown etiology | *U. urealyticum*/*culture* | Doxycycline and clarithromycin | Improved | CVID, hypogammaglobulinemia |
| 19 Asmar (1998) [19] | 18M knee septic arthritis, bacteremia | *U. urealyticum*/*culture* | Erythromycin, doxycycline, chloramphenicol → ofloxacin | Improved | Agammaglobulinemia |
| 20 Puéchal (1995) [20] | 30F septic polyarthritis | *U. urealyticum*/*PCR* | Doxycycline, IVIG | Improved | CVID |
Table 1. Continued

| Author (Year) | Case Presentation | Microorganism/Method of Diagnosis | Antimicrobial Treatment | Outcome | Risk Factors |
|---------------|-------------------|-----------------------------------|------------------------|---------|-------------|
| 21 Forgacs (1993) [21] | 53M wrist septic arthritis | *U. urealyticum, Mycoplasma hominis, Mycoplasma salvarium* culture | Doxycycline | Improved | CVID |
| 22 Lee (1992) [22] | 27M septic polyarthritis | *Ureaplasma* spp./PCR | Doxycycline | Improved | Hypogammaglobulinemia |
| 23 Lehmer (1991) [23] | 38M wrist septic arthritis | *U. urealyticum* culture | Tetracycline, rosaramicin (mac-Improved rolide) | Improved | CVID, hypogammaglobulinemia |
| 24 Mohiuddin (1991) [24] | 22M hip septic arthritis | *U. urealyticum* culture | Tetracycline | Improved | CVID, hypogammaglobulinemia |

Abbreviations: ALL, acute lymphoblastic leukemia; CVID, common variable immune deficiency; ESI-MS, electrospray ionization–mass spectrometry; F, female; hyper-CVAD, cyclophosphamide, doxorubicin, vincristine, dexamethasone; JIA, juvenile idiopathic arthritis; M, male; NHL, non-Hodgkin’s lymphoma; PCR, polymerase chain reaction; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; SLE, systemic lupus erythematosus.

centenarian (12), and 4 patients with a prosthetic implant infection: hip (1, 10), knee (6), and heart valve (13). Nineteen of 24 (79%) patients improved with therapy, and only 1 (4%) patient died of disseminated infection. Septic arthritis was the most common manifestation in this group (21/24, 88%).

**DISCUSSION**

*Ureaplasma* was discovered in 1954 and initially called T-mycoplasma, due to its similarities to *Mycoplasma* species, but notable for its small colony sizes (“T” to indicate “tiny”) [25]. Although our report depicts the rarity of invasive *Ureaplasma* infection, earlier cases may have been classified as *Mycoplasma* spp. [26], before the separation of these genera in 1974 [27]. *Ureaplasma* spp. are frequent colonizers in asymptomatic patients, but they have been implicated in chorioamnionitis, neonatal infection, urethritis [28, 29], surgical site infections [30], and post-transplant severe hyperammonemia [31, 32]. This case report and literature review identifies a subset of patients outside of these populations who are at risk for invasive disease:

1. Humoral immunodeficiency: Rituximab, a monoclonal antibody against CD20 found on B lymphocytes, was approved by the Food and Drug Administration in 1997 [33], and its use has significantly expanded in recent years to treat a variety of autoimmune and malignant processes. Rituximab has been associated with serious infections as a result of a variety of mechanisms including prolonged B-cell depletion and hypogammaglobulinemia [34]. Interestingly, most reported cases of invasive *Ureaplasma* disease since 2010 have been observed in patients receiving this therapy. Prior studies have shown that patients with hypogammaglobulinemia are more likely to be colonized with *Ureaplasma* and *Mycoplasma* [35]. Furthermore, although neutrophils can phagocytose *Ureaplasma* and *Mycoplasma*, the bacteria remain viable in the absence of antibody. It has been postulated that neutrophils with viable bacteria may facilitate dissemination, tracking to areas of inflammation; however, further studies are needed [36].

2. Prosthetic implant: We found 4 cases of prosthetic implant infection, 3 joints and 1 heart valve, in patients without known immunodeficiencies. Although rare, *Ureaplasma* may be considered in culture-negative implant infections failing standard therapy.

*Ureaplasma* does not grow on routine media or appear on gram stain; therefore, a specialized culture or 16S rRNA polymerase chain reaction (PCR) assay must be employed. Empiric therapy may be indicated in settings of severe infection, owing to these tests’ long turnaround times. Tetracyclines, macrolides, and quinolones all have activity against *Ureaplasma* spp. Although susceptibility testing is not widely available, there has been concern for increasing resistance globally [37]. Consequently, despite treatment with levofloxacin, our patient only improved when doxycycline was administered. In patients with severe illness due to suspected or confirmed *Ureaplasma* spp. infection, agents from 2 different classes can be used to increase the likelihood of therapeutic success [38].

**CONCLUSIONS**

This case review should alert providers to consider *Ureaplasma* spp. in infected patients with negative standard cultures, who have humoral immunodeficiency, whether it be congenital (eg, hypogammaglobulinemia) or iatrogenic (eg, anti-CD20 therapy). Specialized culture or PCR is necessary for confirmation of diagnosis. Therapy involves selection of an agent from the tetracycline, macrolide, and/or quinolone classes.

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M.L. provided guidance and editing. Both were involved in the clinical care for the patient. Both authors have reviewed the final manuscript and approved its contents.

APPENDIX

The following terms were used for the literature search on PubMed and Embase:

“Ureaplasma infections”[MeSH] OR “Ureaplasma infections”[Title/Abstract] NOT “neonatal infection”[Title/Abstract] NOT “peripartum”[Title/Abstract] NOT “peri-partum period”[MeSH] NOT “urethritis”[Title/Abstract] NOT “urinary tract infection”[Title/Abstract] NOT “chorioamnionitis”[Mesh] AND (Case Reports[ptyp]

AND “humans”[MeSH Terms] AND English[lang]).

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