Open Forum Infectious Diseases

REVIEW ARTICLE

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

Vimal V. Jhaveri[1,2] and Mary T. LaSalvia[1,2]

[1]Division of Infectious Diseases, Department of Medicine, Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA, and [2]Harvard Medical School, Boston, Massachusetts, USA

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

Received 22 July 2019; editorial decision 3 September 2019; accepted 5 September 2019.

Correspondence: Vimal V. Jhaveri, MD, Beth Israel Deaconess Medical Center, 110 Francis Street, Suite GB, Boston, MA 02215 (vjhaveri@bidmc.harvard.edu).

Open Forum Infectious Diseases®

DOI: 10.1093/ofid/ofz399

Table 1. Reported Cases of Invasive *Ureaplasma* spp. Infection, Outside of Chorioamnionitis, Urethritis, Surgical Site Infections, and Transplant Recipients, 1989–2019

	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 polyarthritis	*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]	24M shoulder septic arthritis	*U. urealyticum*/culture	Doxycycline	Improved	SLE, rituximab
11	Sköldenberg (2010) [12]	74F prosthetic hip infection	*U. urealyticum*/culture	Doxycycline	Improved	No known immunocompromising conditions
12	MacKenzie (2010) [13]	54M polyarthritis, prosthetic hip infection	*U. parvum* and *Mycoplasma hominis*/16S rRNA	Moxifloxacin	Died (septic shock; other nosocomial infection suspected)	NHL, rituximab, hypogammaglobulinemia
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	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 (macrolide)	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.

Acknowledgments

The authors would like to acknowledge Megan McNichol, MLS, AHIP, from Beth Israel Deaconess Medical Center Knowledge Services for assistance with the literature review.

Financial support. There were no funding sources involved in the authorship of this article.

Potential conflicts of interest. The authors report no conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Author contributions. V.J. was involved in the entire process, including background research, initial drafting, and editing of the manuscript.

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 "peripartum period"[MeSH] NOT "urethritis"[Title/Abstract] NOT "urethritis"[MeSH] NOT "chorioamnionitis"[Title/Abstract] NOT "chorioamnionitis"[Mesh] AND (Case Reports[ptyp] AND "humans"[MeSH Terms] AND English[lang]).

References

1. Vittecoq O, Schaeverbeke T, Favre S, et al. Molecular diagnosis of *Ureaplasma urealyticum* in an immunocompetent patient with destructive reactive polyarthritis. Arthritis Rheum **1997**; 40:2084–9.
2. Rouard C, Pereyre S, Abgrall S, et al. Early prosthetic joint infection due to *Ureaplasma urealyticum*: benefit of 16S rRNA gene sequence analysis for diagnosis. J Microbiol Immunol Infect **2019**; 52:167–9.
3. Gassiep I, Gore L, Dale JL, Playford EG. *Ureaplasma urealyticum* necrotizing soft tissue infection. J Infect Chemother **2017**; 23:830–2.
4. Korytny A, Nasser R, Geffen Y, Friedman T, Paul M, Ghanem-Zoubi N. *Ureaplasma parvum* causing life-threatening disease in a susceptible patient. BMJ Case Rep **2017**; 2017:bcr-2017-220383.
5. Roerdink RL, Douw CM, Leenders AC, et al. Bilateral periprosthetic joint infection with *Ureaplasma urealyticum* in an immunocompromised patient. Infection **2016**; 44:807–10.
6. George MD, Cardenas AM, Birnbaum BK, Gluckman SJ. *Ureaplasma* septic arthritis in an immunosuppressed patient with juvenile idiopathic arthritis. J Clin Rheumatol **2015**; 21:221–4.
7. Balsat M, Galicier L, Wargnier A, et al. Diagnosis of *Ureaplasma urealyticum* septic polyarthritis by PCR assay and electrospray ionization mass spectrometry in a patient with acute lymphoblastic leukemia: FIG 1. Diekema DJ, ed. J Clin Microbiol **2014**; 52:3456–8.
8. Farrell JJ, Larson JA, Akeson JW, et al. *Ureaplasma parvum* prosthetic joint infection detected by PCR. J Clin Microbiol **2014**; 52:2248–50.
9. Deetjen P, Maurer C, Rank A, et al. Brain abscess caused by *Ureaplasma urealyticum* in an adult patient. J Clin Microbiol **2014**; 52:695–8.
10. Yazdani M, Thupili CR. Cystitis, pyelonephritis and perinephric abscess due to *Ureaplasma urealyticum*. J Urol **2012**; 188:2373–4.
11. Goulenok TM, Bialek S, Gaudart S, et al. *Ureaplasma urealyticum* destructive septic arthritis in a patient with systemic lupus erythematosus after rituximab therapy. Joint Bone Spine **2011**; 78:323–4.
12. Sköldenberg OG, Rysinska AD, Neander G, et al. *Ureaplasma urealyticum* infection in total hip arthroplasty leading to revision. J Arthroplasty **2010**; 25:1170.e11–3.
13. MacKenzie CR, Nischik N, Kram R, et al. Fatal outcome of a disseminated dual infection with drug-resistant *Mycoplasma hominis* and *Ureaplasma parvum* originating from a septic arthritis in an immunocompromised patient. Int J Infect Dis **2010**; 14(Suppl 3):e307–9.
14. Tarrant WP, Gonzalez-Berjon JM, Cernoch PL, et al. Spontaneous bacterial pericarditis with tamponade due to *Ureaplasma* spp. J Clin Microbiol **2009**; 47:1965–8.
15. Fenollar F, Gauduchon V, Casalta JP, et al. *Mycoplasma* endocarditis: two case reports and a review. Clin Infect Dis **2004**; 38:e21–4.
16. Heilmann C, Jensen L, Jensen JS, et al. Treatment of resistant mycoplasma infection in immunocompromised patients with a new pleuromutilin antibiotic. J Infect **2001**; 43:234–8.
17. Lapusan DL, Duffy L, Hamilos DL. Disseminated septic arthritis in a patient with common variable hypogammaglobulinemia. Ann Allergy Asthma Immunol **2001**; 86:368–72.
18. Frangogiannis NG, Cate TR. Endocarditis and *Ureaplasma urealyticum* osteomyelitis in a hypogammaglobulinemic patient. A case report and review of the literature. J Infect **1998**; 37:181–4.
19. Asmar BI, Andresen J, Brown WJ. *Ureaplasma urealyticum* arthritis and bacteremia in agammaglobulinemia. Pediatr Infect Dis J **1998**; 17:73–6.
20. Puéchal X, Hilliquin P, Renoux M, Menkès CJ. *Ureaplasma urealyticum* destructive septic polyarthritis revealing a common variable immunodeficiency. Arthritis Rheum **1995**; 38:1524–6.
21. Forgacs P, Kundsin RB, Margles SW, et al. A case of *Ureaplasma urealyticum* septic arthritis in a patient with hypogammaglobulinemia. Clin Infect Dis **1993**; 16:293–4.
22. Lee AH, Ramanujam T, Ware P, et al. Molecular diagnosis of *Ureaplasma urealyticum* septic arthritis in a patient with hypogammaglobulinemia. Arthritis Rheum **1992**; 35:443–8.
23. Lehmer RR, Andrews BS, Robertson JA, et al. Clinical and biological characteristics of *Ureaplasma urealyticum* induced polyarthritis in a patient with common variable hypogammaglobulinaemia. Ann Rheum Dis **1991**; 50:574–6.
24. Mohiuddin AA, Corren J, Harbeck RJ, et al. *Ureaplasma urealyticum* chronic osteomyelitis in a patient with hypogammaglobulinemia. J Allergy Clin Immunol **1991**; 87(1 Pt 1):104–7.
25. Shepard MC. The recovery of pleuropneumonia-like organisms from Negro men with and without nongonococcal urethritis. Am J Syph Gonorrhea Vener Dis **1954**; 38(2):113–24.
26. Taylor-Robinson D. Infections due to species of *Mycoplasma* and *Ureaplasma*: an update. Clin Infect Dis **1996**; 23(4):671–82; quiz 683–4.
27. Robertson JA, Stemke GW, Davis JW, et al. Proposal of *Ureaplasma parvum* sp. nov. and emended description of *Ureaplasma urealyticum* (Shepard *et al.* 1974) Robertson *et al.* 2001. Int J Syst Evol Microbiol **2002**; 52(Pt 2):587–97.
28. Sweeney EL, Dando SJ, Kallapur SG, Knox CL. The human *Ureaplasma* species as causative agents of chorioamnionitis. Clin Microbiol Rev **2017**; 30:349–79.
29. Gwee A, Curtis N. *Ureaplasma*—are you sitting comfortably? J Infect **2014**; 68(Suppl 1):S19–23.
30. Lucke K, Kuster SP, Bertea M, et al. A deep sternal wound infection caused by *Ureaplasma urealyticum*. J Med Microbiol **2010**; 59:1254–6.
31. Bharat A, Cunningham SA, Scott Budinger GR, et al. Disseminated *Ureaplasma* infection as a cause of fatal hyperammonemia in humans. Sci Transl Med **2015**; 7:284re3.
32. Nowbakht C, Edwards AR, Rodriguez-Buritica DF, et al. Two cases of fatal hyperammonemia syndrome due to *Mycoplasma hominis* and *Ureaplasma urealyticum* in immunocompromised patients outside lung transplant recipients. Open Forum Infect Dis **2019**; 6(X):XXX–XX.
33. Leget GA, Czuczman MS. Use of rituximab, the new FDA-approved antibody. Curr Opin Oncol **1998**; 10:548–51.
34. Mikulska M, Lanini S, Gudiol C, et al. ESCMID Study Group for Infections in Compromised Hosts (ESGICH) consensus document on the safety of targeted and biological therapies: an infectious diseases perspective (agents targeting lymphoid cells surface antigens [I]: CD19, CD20 and CD52). Clin Microbiol Infect **2018**; 24:S71–82.
35. Furr PM, Taylor-Robinson D, Webster ADB. *Mycoplasmas* and *Ureaplasmas* in patients with hypogammaglobulinaemia and their role in arthritis: microbiological observations over twenty years. Ann Rheum Dis **1994**; 53(3):183–7.
36. Webster ADB, Furr PM, Hughes-Jonest NC, Gorickt BD, Taylor-Robinson D. Critical dependence on antibody for defence against mycoplasmas. Clin Exp Immunol **1988;** 71(3):383–7.
37. Beeton ML, Spiller OB. Antibiotic resistance among *Ureaplasma* spp. isolates: cause for concern? J Antimicrob Chemother **2017**; 72:330–7.
38. Luo DQ, Liu JY, Yang W, et al. In vitro activities of erythromycin, tetracycline and levofloxacin alone and in dual combinations against *Ureaplasma* spp. Chemotherapy **2011**; 57:128–33.