A case of oropharyngeal Ureaplasma urealyticum infection in a human immunodeficiency virus positive bisexual male co-infected with human papilloma virus and Treponema pallidum

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Abstract

Introduction. Management strategies for sexually transmitted infections (STIs) in their extragenital forms address Neisseria gonorrhoeae and Chlamydia trachomatis alone; whereas increased rates of isolation of other STI agents have been reported from various parts of the world. Their extragenital presence as a reservoir of infection emphasizes the need to screen and treat them at these sites.

Case presentation. A 35-year-old human immunodeficiency virus 1 infected bisexual male presented with urethral discharge and multiple ano-genital warts. He was reactive for the venereal disease research laboratory (VDRL) test. He tested positive for Ureaplasma spp. both by culture and PCR at urethral and oropharyngeal sites, but was negative at the rectal site. The patient was successfully treated with doxycycline and penicillin, and was followed up with a test of cure at 6 weeks.

Conclusion. In view of the disseminating infections that can be caused by Ureaplasma spp., it makes it important to screen for these infections even at non-genital sites, especially in the immunocompromised. STIs may be asymptomatic and can serve as a reservoir of infection in a population. This report should promote all efforts to formulate guidelines for extragenital screening of all STI pathogens.

INTRODUCTION

Screening of extragenital sites, including the oropharynx and rectum, is an emerging practice based on recent studies highlighting the prevalence of infection at these sites [1]. The presence of sexually transmitted infections (STIs) at non-genital sites facilitates transmission and acquisition of STIs, including human immunodeficiency virus (HIV) [2]. Given that STIs are often asymptomatic, regular testing and timely treatment remains the cornerstone for optimal prevention of spread of these infections in the population. Hence, the Centers for Disease Control and Prevention (USA) recommends that all men who have sex with men (MSM) should be screened annually (or every 3–6 months, if at ‘increased risk’) for genital and extragenital infections with STI agents (HIV; syphilis; urethral, rectal and pharyngeal gonorrhoeae; and urethral and rectal Chlamydia) [3].

Management strategies, including investigations to address extra-genital Chlamydia trachomatis and Neisseria gonorrhoeae in both sexes, exist. Recommendations for screening of STIs at pharyngeal sites are there only for gonorrhoea. However, the same are lacking for other STIs, including genital mycoplasmas [3]. Many studies have reported the prevalence of pharyngeal C. trachomatis, usually asymptomatic with unclear implications [4]. Genital mycoplasmas have only rarely been isolated from pharyngeal sites in people, even in the presence of genital infections [5].

In addition to the ‘classical’ sexually transmitted pathogens, recent studies have also demonstrated a strong association between abnormal urogenital findings and the detection of Ureaplasma urealyticum. It is an important cause of non-gonococcal urethritis, accounting for nearly 5–26% of all cases [6]. Though two species of Ureaplasma cause human infection, Ureaplasma parvum (biovar 1) and U. urealyticum (biovar 2), U. urealyticum is more significantly associated with symptomatic urogenital infections [7]. Here, we report a case of a HIV-positive bisexual male with oropharyngeal and urethral U. urealyticum infection, co-infected with human papilloma virus (HPV) and Treponema pallidum.
**CASE REPORT**

A 35-year-old male presented to the STI clinic at the All India Institute of Medical Sciences, New Delhi, India, for evaluation of urogenital discharge and generalized lymphadenopathy involving the cervical, axillary and inguinal groups of lymph nodes. He had undergone surgical excision of ano-genital warts (AGWs) previously. He was bisexual, with multiple homosexual and heterosexual casual partners, with a history of unprotected receptive and insertive oral and anal sex. There was no history of past blood transfusion or intravenous drug abuse. He reported never being tested for HIV nor any other STIs. His medical history did not reveal any significant systemic abnormalities. On examination, he had scanty mucoid urethral discharge and multiple AGWs, with no lesions nor inflammation in the oropharynx and rectum. A Gram-stained smear of the urethral discharge under an oil-immersion objective of a microscope revealed 4–5 white blood cells, but no Gram-negative intra-cellular diplococci were seen. Microscopic examination of the urethral discharge was negative for any motile trophozoites, yeast cells and pseudohyphae. The patient was diagnosed clinically as a case of recurrent HPV infection with urethritis.

On investigation, his venereal disease research laboratory (VDRL) test was reactive (titre of 1 : 16) and his T. pallidum haemagglutination assay (TPHA) was positive. The patient was tested for HIV as per National AIDS Control Organisation (NACO) guidelines strategy 2B, in which three rapid tests were done for confirmation of diagnosis. CD4$^+$ counts were estimated on a FACS Count microbead-based system, as recommended by the National Guidelines on the Enumeration of CD4 Lymphocytes [8]. The patient was HIV-1 positive, with a CD4$^+$ lymphocyte count of 123 cells µl$^{-1}$. He was seronegative for both hepatitis B surface antigen and anti-hepatitis C antibodies. Clinician collected urethral, rectal and oropharyngeal swabs were sent for detection of N. gonorrhoeae, C. trachomatis and genital mycoplasmas. Culture of the discharge for N. gonorrhoeae was negative on gonococcal agar with vancomycin, colistin, nystatin and trimethoprim sulfate, and so was the PCR assay for C. trachomatis targeting cryptic plasmid at genital, rectal and oropharyngeal sites. PCRs for Mycoplasma hominis and Mycoplasma genitalium were negative. Culture for Ureaplasma spp. was carried out in pleuro-pneumonia-like organism (PPLO) broth containing urea (Fig. 1a) and PCR was based on amplification of the urease gene (Fig. 1b) [9]. The isolate of Ureaplasma was further biotyped in a second PCR targeting the multiple banded antigen (MBA) gene. Species identification is based on an amplicon size of 408 bp for U. parvum (biovar 1) and an amplicon size of 448 bp for U. urealyticum (biovar 2) [10]. Ureaplasma was positive by culture and PCR in samples taken from the urethra and oropharynx, but negative in the rectal sample.

Histopathology of the warty lesion confirmed the diagnosis of AGWs. The patient was diagnosed to have oropharyngeal and urethral U. urealyticum infection, co-infected with HIV, T. pallidum and HPV. Contact tracing was attempted, but the patient refused to share any information about his partners.

The patient was treated with doxycycline, 100 mg twice daily for 7 days, and a weekly dose of 2.4 million IU benzathine penicillin for 3 weeks, for Ureaplasma infection and syphilis, respectively, as per Centers for Disease Control and Prevention guidelines for STI, 2015 [3]. Azithromycin and doxycycline have been recommended for non-gonococcal urethritis; however, considering the better response to doxycycline for extragenital Chlamydia, this was given. Penicillin remains the drug of choice for syphilis, with no resistance reported to date. The AGWs were treated with 10–20 % podophyllin resin, applied once a week for 8 weeks, and the patient was referred to an anti-retroviral therapy (ART) centre for management of the HIV infection. On evaluation at 6 weeks, he reported a cessation of the urethral discharge with healing of the warty lesions. A post-treatment, oropharyngeal swab and first-void urine sample of the patient were negative for Ureaplasma spp. both by culture and PCR. The patient was counselled for safe sex practices and advised to have regular follow-ups.

**DISCUSSION**

Extragenital Ureaplasma infections have been rarely reported and, to the best of our knowledge, this is the first report of oropharyngeal Ureaplasma infection from India. There has been one recent report of rectal Ureaplasma infection found in a culture from an MSM individual [11]. Globally, there are few studies of pharyngeal infection with Ureaplasma spp. Isolation from the pharynx of both men and women seeking treatment at several clinics in the USA yielded Ureaplasma prevalence rates of 14.8 %, including U. parvum (biovar1) and U. urealyticum (biovar 2), which were not distinguishable at that time [5]. In a study from Japan, the prevalence of U. parvum and U. urealyticum in the pharynx of Japanese female sex workers practicing fellatio on their clients was 0.2 and 0.7 %, respectively, whereas the prevalence in the genitals was 40.4 and 10.2 %, respectively. Though presence in the pharynx was not significantly associated with presence in the genitals, a history of performing fellatio was significantly associated with U. urealyticum pharyngeal infection [12]. Even though the significance of isolation of U. urealyticum from the oropharynx is not established, it may serve as an extragenital reservoir. It has been established that the risk of retroviral transmission is increased in the presence of co-infections with organisms that breach the epithelial barrier [13]. Since Ureaplasma infections are potentially mucosa disrupting, they may similarly increase the risk of HIV transmission, and detection may be important even if the patient is asymptomatic. However, the low CD4$^+$ count in our patient, which suggests a long-term HIV infection, could be responsible for the various infections acquired. The generalized lymphadenopathy in the patient could possibly be a manifestation of HIV infection. There were no symptoms of any primary or
secondary syphilis, so diagnosis of latent syphilis was made, and the patient was treated accordingly.

Barbee and colleagues have previously observed that nearly a third of all cases of symptomatic gonococcal and non-gonococcal, non-chlamydial urethritis (NGNCU) among MSM attending an STI clinic was probably acquired through oral sex [14]. A limitation of their study was their inability to identify the aetiological agents of NGNCU, as these agents were not tested for routinely in their clinic. In our patient, the same organism, *U. urealyticum* (biovar 2), was isolated from the urethra as well as the oropharynx, supporting acquisition through orogenital contact. However, this might be two independent transmissions as well. The proximity of the oropharynx to the lungs is of concern, as evident in recent reports, in which disseminated *Ureaplasma* resulting in hyperammonaemia caused fatal consequences in immunocompromised patients [15, 16].

Screening of all patients who present to the STI clinic for multiple STIs is now recommended and this case highlights the importance of screening all patients with high-risk behaviour for multiple co-pathogens infecting the genital tract. Early detection and treatment of sexually transmitted pathogens in HIV-infected patients would prove prudent to control retroviral transmission. However, commercially available nucleic acid amplification tests (NAATs) have not been validated for samples from extragenital sites. New standard use of commercial NAATs for *N. gonorrhoeae* and *C. trachomatis* alone may be missing out on infections that culture methods or expanded NAATs would otherwise identify. A multiplex NAAT does not include testing for *Mycoplasma* or *Ureaplasma* spp. and, thus, these infections will not be detected. Expansion of the STI test panel in commercial systems and additional specimen source sampling within a comprehensive programme will increase identification of STI carriers. Addressing currently hidden genital mycoplasmas by extragenital testing of more persons would reveal many more reservoirs of infections. There is little evidence on the specificity or sensitivity of NAATs for *U. urealyticum* at extragenital sites. However, our patient tested positive for *U. urealyticum* by both culture and PCR at both the sites, thereby ruling out the possibility of false-positive results. An arbitrary choice of 6 weeks was made as there are no published data or guidelines on the ideal timing for a *U. urealyticum* test of cure at an extragenital site.

This report is suggestive of the idea that failure to identify and eradicate *Ureaplasma* spp. from the oropharynx may play a critical role in its transmission in MSM. Considering the role of disseminated *Ureaplasma* in immunocompromised patients, they are of great concern. Furthermore, this report should add momentum to the efforts to promote widespread pharyngeal screening for other pathogens. It is also important to conduct investigations to define the yet unidentified organisms causing infections of the oropharynx that may be responsible for a significant proportion of cases of NGNCU.

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**Ethical statement**
The subject of this paper gave informed consent to the work.

**References**
1. Arif N, Juyal D, Sebastian S, Khanna N, Dhawan B. Analysis of laboratory testing results for *Chlamydia trachomatis* infection in an STI clinic in India: need for extragenital screening. *Int J Infect Dis* 2017;57:1–2.
2. Ghys PD, Fransen K, Diarlo MO, Ettienne-Traoré V, Coulibaly IM et al. The associations between cervicovaginal HIV shedding, sexually transmitted diseases and immunosuppression in female sex workers in Abidjan, Côte d’Ivoire. *AIDS* 1997;11:F85–F93.
3. Workowski KA, Bolan GA, Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep 2015;64:1–137.

4. Loomba P, Knight V, McNulty A. What would be missed if we didn’t screen men who have sex with men for oral Chlamydia trachomatis? A cross-sectional study. Sex Health 2016;13:196–198.

5. Sackel SG, Alpert S, Fiormara NJ, Donner A, Laughlin CA et al. Orogenital contact and the isolation of Neisseria gonorrhoeae, Mycoplasma hominis, and Ureaplasma urealyticum from the pharynx. Sex Transm Dis 1979;6:64–68.

6. Moi H, Horner PJ. 2016 European guideline on the management of non-gonococcal urethritis published. Euro Surveill 2016;21:928–937.

7. de Francesco MA, Negrini R, Pinsi G, Peroni L, Manca N. Detection of Ureaplasma biovars and polymerase chain reaction-based subtyping of Ureaplasma parvum in women with or without symptoms of genital infections. Eur J Clin Microbiol Infect Dis 2009;28:641–646.

8. National AIDS Control Organisation (NACO). National Guidelines for HIV Testing. New Delhi: National AIDS Control Organisation (NACO), Ministry of Health and Family Welfare, Government of India; 2015. www.naco.gov.in/sites/default/files/National_Guidelines_for_HIV_Testing_21Apr2016.pdf.

9. Stellrecht KA, Woron AM, Mishrik NG, Venezia RA. Comparison of multiplex PCR assay with culture for detection of genital mycoplasmas. J Clin Microbiol 2004;42:1528–1533.

10. Knox CL, Timms P. Comparison of PCR, nested PCR, and random amplified polymorphic DNA PCR for detection and typing of Ureaplasma urealyticum in specimens from pregnant women. J Clin Microbiol 1998;36:3032–3039.

11. Abbott CE, Greene RE, Kapadia F, Halkitis PN. A case of rectal ureaplasma infection and implications for testing in young men who have sex with men: the P18 cohort study. LGBT Health 2017;4:161–163.

12. Deguchi T, Yasuda M, Yokoi S, Nakano M, Ito S et al. Failure to detect Mycoplasma genitalium in the pharynges of female sex workers in Japan. J Infect Chemother 2009;15:410–413.

13. Mbulawa ZZ, Marais DJ, Johnson LF, Boule A, Coetzee D et al. Influence of human immunodeficiency virus and CD4 count on the prevalence of human papillomavirus in heterosexual couples. J Gen Virol 2010;91:3023–3031.

14. Barbee LA, Khosropour CM, Dombrowski JC, Manhart LE, Golden MR et al. An estimate of the proportion of symptomatic gonococcal, chlamydial and non-gonococcal non-chlamydial urethritis attributable to oral sex among men who have sex with men: a case-control study. Sex Transm Infect 2016;92:155–160.

15. Fernandez R, Ratliff A, Crabb D, Waites KB, Bharat A. Ureaplasma transmitted from donor lungs is pathogenic after lung transplantation. Ann Thorac Surg 2017;103:670–671.

16. Bharat A, Cunningham SA, Budinger GRS, Kreisel D, Dewet CJ et al. Disseminated Ureaplasma infection as a cause of fatal hyperammonemia in humans. Sci Transl Med 2015;7:284re3.

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