Primary Syphilis in the Male Urethra: A Case Report

Laura C. Chambers,^{1,a} Sujatha Srinivasan,^{2,a} Sheila A. Lukehart,^{3,4} Negesse Ocbamichael,⁵ Jennifer L. Morgan,⁵ M. Sylvan Lowens,⁵ David N. Fredricks,^{2,3} Matthew R. Golden,^{3,5} and Lisa E. Manhart¹

¹Department of Epidemiology, University of Washington, ²Fred Hutchinson Cancer Research Center, ³Department of Medicine and ⁴Department of Global Health, University of Washington, and ⁵Public Health—Seattle & King County HIV/STD Program, Washington

We documented urethral *Treponema pallidum* infection in a man with nongonococcal urethritis and a negative syphilis serology using broad-range bacterial polymerase chain reaction (PCR) and sequencing, targeted PCR, and immunofluorescence microscopy. He subsequently seroconverted for syphilis. Early syphilis may present as urethritis. Urethral *T. pallidum* shedding can occur before seroconversion.

Keywords. 16S rRNA gene PCR; nongonococcal urethritis; primary syphilis; *Treponema pallidum*.

The incidence of syphilis has increased markedly among men who have sex with men (MSM) in many urban areas of high-income nations. In 2015, the incidence of primary and secondary syphilis among MSM in the United States was approximately 309 cases per 100 000 persons [1]. In King County, Washington, the incidence among MSM doubled from 450 to 901 cases per 100 000 persons between 2005 and 2015 [2].

With increases in syphilis cases, clinicians may see rare presentations more frequently. This report describes a case of nongonococcal urethritis (NGU) in which *Treponema pallidum* was the only known pathogen noted. The patient had enrolled in a cross-sectional study on the etiology of NGU that utilized broad-range 16S ribosomal RNA (rRNA) gene polymerase chain reaction (PCR) with sequencing to characterize the male urethral microbiota. Detection of *T. pallidum* by PCR and sequencing alerted us to this case.

CLINICAL NARRATIVE

A 28-year-old, non-Hispanic, White, human immunodeficiency virus (HIV)-negative, circumcised MSM presented to the Public

Health—Seattle and King County Sexually Transmitted Disease Clinic seeking evaluation of a 4-day history of urethral irritation. He reported 5 sex partners (4 new) in the past 2 months, condomless insertive oral and anal sex at his last sexual episode, and recent contact with HIV. He did not report urethral discharge or dysuria, but acknowledged a 9-month history of “jock itch.” The clinician noted scant urethral discharge; erythema of the meatus and distal urethra; a dry, itchy, macular rash with well-demarcated borders on the inner thighs and groin crease; and normal inguinal lymph nodes. First-void urine, 2 urethral swab specimens, and a serum specimen were collected. On a Gram-stained slide of urethral exudates, the clinician observed no Gram-negative intracellular diplococci (GNID), but >20 polymorphonuclear leukocytes (PMNs) per high-power field (HPF). The patient was diagnosed with NGU and tinea cruris, provided azithromycin (1g) for the NGU, and advised to use an over-the-counter antifungal for the tinea cruris. Nucleic acid amplification tests (NAATs) for urethral *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, and *Mycoplasma genitalium* were performed on the urine sample (Aptima; Hologic, Inc.; San Diego). A rapid plasma reagin (RPR) test to screen for syphilis was performed on the serum specimen (Macro-Vue, Becton, Dickson, and Company, Franklin Lakes). All tests were negative. The remaining urine and a dry urethral swab specimen were frozen for future testing.

Although the study consisted of a single visit, the patient returned for 4 additional non-study visits due to continued urethral symptoms (12, 15, and 25 days after the initial NGU diagnosis) and non-urethral complaints (54 days after the initial NGU diagnosis). On day 12, he reported that his urethral symptoms had resolved within 1 week of azithromycin therapy but had returned 2 days earlier (day 10) and worsened to include urethral irritation, urethral itch, and dysuria. His partner had been treated as a contact to NGU (antibiotic and partner[s] unknown), and he had resumed sporadic sexual activity on day 7 (condomless penile and oral exposures). The clinician noted scant, clear urethral discharge; a very red and inflamed urethra; a red glans penis; a dry, macular groin rash; and bilaterally-enlarged inguinal lymph nodes. A urethral Gram stain revealed >20 PMNs/HPF, but no GNID. The patient was diagnosed with recurrent NGU and prescribed a 14-day course of moxifloxacin. NAATs of urethral specimens for the herpes simplex virus 1 and 2 (Solana HSV 1 + 2/VZV, Quidel, San Diego) and an adenovirus culture were negative.

On day 15, the patient returned with gastrointestinal discomfort and persistent urethral symptoms, including urethral discharge. He had discontinued moxifloxacin after 2 days due to gastrointestinal symptoms and requested azithromycin. The

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^aL. C. C. and S. S. contributed equally to this manuscript.

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Correspondence: L. C. Chambers, Department of Epidemiology, University of Washington, 325 Ninth Avenue, HMC #359931, Seattle, WA 98104 (lauracc@uw.edu).

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clinician noted scant, clear urethral discharge; a persistent rash consistent with tinea cruris; and bilaterally-enlarged inguinal lymph nodes. A urethral Gram stain had 11 PMNs/HPF and no GNID. The patient was diagnosed with persistent NGU and provided azithromycin (1 g).

On day 25, the patient returned with worsening urethral symptoms and a 3-day history of painful penile swelling. The clinician noted a moderate amount of clear urethral discharge, a swollen distal penis shaft, dorsal vein and urethral induration, and a firm left inguinal lymph node. No genital or oral lesions were noted. An on-site RPR test was reactive for syphilis. Motile spirochetes were observed in a drop of urethral discharge by darkfield microscopy in the clinic. The patient was diagnosed with primary syphilis in the urethra and treated with intramuscular benzathine penicillin G (single dose; 2.4 million units). The RPR titer was 1:16; a *T. pallidum* particle agglutination assay (Serodia, Fujirebio, Inc., Tokyo) was reactive;

and an enzyme immunoassay (CAPTIA Syphilis IgG, Bio-Rad Laboratories, Inc., Hercules) was non-reactive. On day 54, the patient returned with non-urethral complaints. He did not report urethral symptoms and did not have visible urethral discharge. A repeat RPR titer was 1:8; a *T. pallidum* particle agglutination assay was reactive; and an enzyme immunoassay was equivocal.

RETROSPECTIVE LABORATORY WORK

As part of the NGU study, we applied broad-range 16S rRNA gene PCR targeting the V3-V4 region, with deep sequencing [3], to the urine specimen from the initial NGU visit. We detected 3989 *T. pallidum* sequence reads at 6% relative abundance (Figure 1). No other known pathogens were noted. The majority of sequences represent skin commensal bacteria, including *Corynebacterium* and *Dermabacter* species. Amplification of

Figure 1. Evidence of urethral *Treponema pallidum* infection in specimens collected at the initial nongonococcal urethritis visit. *A*, Composition of the urethral microbiota (relative abundances) in a first-void urine specimen. *B*, *Treponemes* visualized with fluorescence microscopy of a smear prepared from a urethral swab specimen.

2 *T. pallidum* gene targets, *tp0548* and the 47-kDa lipoprotein (*tp0574*) [4], confirmed the presence of the *T. pallidum* subspecies *pallidum*. A restriction digestion analysis targeting both 23S ribosomal DNA alleles [5] revealed an A2058G mutation, which confers azithromycin resistance. Finally, indirect immunofluorescence microscopy, using pooled *T. pallidum*-infected rabbit sera [6] on a smear prepared from the urethral swab from the initial NGU visit, revealed numerous treponemes (Figure 1).

DISCUSSION

This patient, diagnosed with NGU, had a negative syphilis serology but evidence of urethral *T. pallidum* infection by broad-range 16S rRNA gene PCR and sequencing, *T. pallidum*-specific PCR, and immunofluorescence microscopy, highlighting the urethra as the site of an active, clinically-significant early syphilis infection and a potential source of transmission, even in a seronegative man. Persistent, worsening urethritis-like symptoms in this patient despite receiving azithromycin therapy are likely explained by the presence of a macrolide-resistant mutation in his *T. pallidum* strain. This patient's NGU resolved after the receipt of intramuscular benzathine penicillin G, further supporting *T. pallidum* as the cause of his urethral symptoms.

The presence of *T. pallidum* in the patient's urethral exudates could have resulted from a urethral chancre that was not visible on clinical examination or could have been a consequence of mucosal shedding of the infection. An estimated 1% of primary syphilis chancres develop at the urethral meatus [7], though, to our knowledge, primary syphilis presenting as NGU in the absence of a visible chancre has not been reported. In a report from 1891, a few cases of intra-urethral primary chancre of the fossa navicularis (dilated portion of the urethra within the glans penis) were described [8], but we did not identify any subsequent reports of this clinical presentation.

A recent report suggested that mucosal surfaces may shed *T. pallidum* DNA in the absence of a visible primary chancre or secondary lesions [9]. However, detection of *T. pallidum* DNA at these sites by PCR alone is not equivalent to demonstrating the presence of viable, infectious organisms. Nevertheless, our patient had clearly-identifiable, motile *T. pallidum* organisms in his urethral discharge, indicating viable bacteria were present. Direct mucosal shedding of *T. pallidum* may be possible in some cases, and this would have implications for our understanding of the natural history and transmission of syphilis. Sexual transmission is generally thought to require direct contact between a primary chancre or secondary lesion and a partner's mucosal surface or skin site with microabrasions.

Serological testing remains the most common method of syphilis diagnosis. However, RPR is only 70–80% sensitive in primary syphilis [10, 11], *T. pallidum*-specific serological tests are variably sensitive in early infection [11], and increasing evidence suggests that *T. pallidum* nucleic acids can be detected

using PCR during primary syphilis, in some cases prior to seroconversion [12]. PCR testing is typically conducted on swabs obtained from primary chancres or moist secondary lesions. However, limited evidence of mucosal *T. pallidum* shedding in the absence of positive serological tests suggests that there may be a role for targeted NAAT of mucosal swab specimens from persons at very high risk of syphilis. This requires further study.

Our report has limitations. The patient had only 1 research visit. Specimens from subsequent visits were not available to determine the ongoing presence of *T. pallidum* nucleic acid in his urethra. Moreover, the patient saw a different clinician at each visit, with potential variations in the descriptions of clinical findings. Finally, the patient reported condomless exposures during this time period. The possibility of re-infection cannot be ruled out.

In conclusion, primary syphilis presenting as NGU may be seen more often as the incidence of syphilis increases. Our data suggest that syphilis may be an occasional cause of urethritis. Future research on the frequency of mucosal *T. pallidum* shedding during early syphilis would inform our understanding of the natural history of syphilis and the potential utility of pairing serological screening with PCR testing to optimize diagnoses and reduce transmission.

Notes

Author contributions. The manuscript concept was developed by L. C. C., S. S., S. A. L., D. N. F., M. R. G., and L. E. M. Clinical data were compiled for the manuscript by L. C. C., J. L. M., and M. S. L. Oversight of the clinical care described in the manuscript was provided by N. O. Laboratory work for the manuscript was conducted by S. S., D. N. F., and S. A. L. The manuscript was drafted by L. C. C. and S. S. The manuscript was critically revised by all authors.

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