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SHORT COMMUNICATION

Spontaneous Regression of Untreatable *Mycoplasma genitalium* Urethritis

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Mycoplasma genitalium is a sexually transmissible pathogen that causes non-gonococcal urethritis (NGU), cervicitis, and has been shown to cause rectal infections in men who have sex with men (1–3). The prevalence in men with symptomatic urethritis varies from 15% to 25% (4). Increasing rates of treatment failures with azithromycin have been reported, and the widespread use of azithromycin 1 g single-dose treatment for NGU is thought to trigger the selection of 23S rRNA gene mutations, causing macrolide resistance (4). An extended azithromycin 1.5 g regimen (500 mg on day 1, followed by 250 mg on days 2–5), was more effective than a single dose in one study (5). In case of treatment failure after a single dose azithromycin, an extended 5-day treatment is not effective (6). Moxifloxacin has been shown to be 100% effective after azithromycin treatment failure (6). However, a few reports of moxifloxacin treatment failure have been published (7). In spite of *in vitro* susceptibility to doxycycline, clinical trials have shown a low clinical cure rate using tetracyclines (5, 8). Without treatment, it is not known how long *M. genitalium* infection persists.

CASE REPORT

A Caucasian, uncircumcised male in his early 60s presented in November 2009 to the Olafia Drop-in Clinic (Department of Venereology, Oslo University Hospital, Norway) with dysuria. A urethral smear stained with methylene blue showed >30 polymorphonuclear leucocytes (PMNL) per high-power field (HPF). He had a female partner in East Asia, but no partner in Norway. He was treated with doxycycline 200 mg on day 1, 100 mg on days 2–7 as per clinic protocol. First-void urine (FVU) was positive for *Chlamydia trachomatis* and *M. genitalium*, negative for *Neisseria gonorrhoeae*, all by nucleic acid amplification tests (NAATs). Because of the positive *M. genitalium* NAAT, one week later he was prescribed azithromycin 500 mg on day 1, and 250 mg on days 2–5, in addition to the 1-week doxycycline treatment (Table SI[1]).

The patient presented for a test of cure 6 weeks later and was asymptomatic. Urethral smear was not performed. NAAT from FVU for *C. trachomatis* was negative, but NAAT for *M. genitalium* was still positive. He denied any sexual contact after the initial treatment. He was prescribed moxifloxacin 400 mg once daily for 7 days. One month later, he was still asymptomatic, no urethral smear was taken, but a NAAT from FVU was positive for *M. genitalium*. He denied any sexual contact. A control FVU for NAAT 2 weeks later was still positive for *M. genitalium*. A urethral smear taken at this occasion showed no signs of urethritis. When specifically asked, he reported occasional discomfort from the urethra. A prolonged doxycycline treatment, 100 mg 2 times daily for 15 days was prescribed. A urethral sample for culture of *M. genitalium* was taken and sent to the Mycoplasma laboratory in Copenhagen. After nearly 6 months of culture, a strain of *M. genitalium* was isolated after inoculating Vero cells with the urethral swab sample, as previously described (9).

Five months after the initial treatment (April 2010), the patient returned for the fourth test of cure. A urethral smear showed a moderate urethritis. He admitted protected sexual contact with his steady partner in East Asia after the last test. His partner had no access to mycoplasma testing, and had not been treated. NAAT from FVU was positive for *M. genitalium*, negative for *C. trachomatis*.

He agreed to consistent condom use, and to returning after 6 months for a new test.

He returned in October 2010, 11 months after the initial positive NAAT for *M. genitalium*. Two weeks prior to the visit, he had taken a 3-day treatment in East Asia with an unknown antibiotic drug for gastrointestinal complaints. After this treatment, he felt drier in the preputium than before. A urethral smear showed no urethritis. NAAT for *M. genitalium* from FVU was still positive, and one week later, a prolonged moxifloxacin treatment 400 mg once daily for 10 days was prescribed.

The *in vitro* susceptibility to azithromycin and moxifloxacin of the *M. genitalium* isolate obtained from the specimen taken 3 months and 3 weeks after the first visit (strain M6714) (10), was determined and showed minimal inhibitory concentrations (MICs) to azithromycin >16 mg/l (resistant), moxifloxacin 4 mg/l (resistant), and doxycycline 1 mg/l (susceptible).

In month 14 a FVU sample taken at home was still positive for *M. genitalium*. Another urethral swab for culture was taken one month later and sent to Copenhagen, but isolation of *M. genitalium* failed. He was aware of the risk of transmitting the infection by unprotected sex. He assured that he had been adherent to all treatment regimens. He had a new steady female sexual partner in East Asia, with whom he always used a condom. After this visit, he was lost to follow-up for more than 2 years.

In October 2012, 3 years and 11 months after the first visit, he re-attended to the department for a new NAAT from FVU, which was negative for C. *trachomatis, M. genitalium* and *Neisseria gonorrhoeae*. Repeated NAAT for *M. genitalium* from FVU 2 weeks later was still negative. He denied having taken any antibiotics the last 2 years, after the last moxifloxacin treatment given by us.

DISCUSSION

This case of untreatable *M. genitalium* urethritis due to azithromycin and moxifloxacin resistance documented by NAAT, culture and *in vitro* MIC determination demonstrates antibiotic resistance that is likely to be experienced more commonly in the future. The patient had a female sexual partner in East Asia. Antibiotic resistance has often emerged in East Asia (11), probably due to widespread and uncritical use of antibiotics.

[1]https://doi.org/10.2340/00015555-2055

The antibiotics given did not eradicate *M. genitalium* during a follow-up time of 14 months, but may have contributed to the remission, which must have occurred during the next 33 months.

As far as we know, such remission of *M. genitalium* urethritis has not yet been documented in the literature. However, spontaneous clearance of *M. genitalium* has been described in women (12). Whether multidrug resistant strains of *M. genitalium* have a lower fitness and, consequently, are more prone to spontaneous regression cannot be excluded; however, experience from other patients does not suggest that this would be the case. On the other hand, spontaneous clearance may be the explanation for the occasional cure seen after azithromycin treatment of *M. genitalium* strains carrying macrolide resistance mediating mutations (13). Spontaneous remission has been reported for *C. trachomatis* infections (14) and it would be expected to be seen with most infections to some extent.

It is a great concern that *M. genitalium* may become the first untreatable sexually transmitted bacterial infection. Reports of treatment failure with moxifloxacin have increased in recent years, and in Australia, 15% of *M. genitalium*-positive specimens were found to contain strains with mutations in the quinolone resistance determining regions of the *parC* gene (15). Ten percent of the patients carried strains with both macrolide and quinolone resistance mediating mutations. If treatment failure with azithromycin and moxifloxacin is experienced, pristinamycin may be a choice (16), and the new fluoroketolide solithromycin may become an option in the future (10). Sitafloxacin has recently been shown to eradicate strains with fluoroquinolone resistance-associated alterations in *ParC* (17). In the present case, the treatment failed and the urethral infection persisted for more than one year, but subsequently regressed spontaneously. Pristinamycin, solithromycin and sitafloxacin were not tried. Pristinamycin is not registered, but is available, in Norway. The price for a 10-day course 1 g ×4 is 430 Euro (in 2014 year value). In contrast to *C. trachomatis*, Norwegian legislation does not classify *M. genitalium* as a threat to public health. The cost must therefore be borne by the patients themselves, and for many this treatment will not be affordable.

REFERENCES

1. Moi H, Reinton N, Moghaddam A. Mycoplasma genitalium is associated with symptomatic and asymptomatic non-gonococcal urethritis in men. Sex Transm Infect 2009; 85: 15–18.
2. Moi H, Reinton N, Moghaddam A. Mycoplasma genitalium in women with lower genital tract inflammation. Sex Transm Infect 2009; 85: 10–14.
3. Reinton N, Moi H, Olsen AO, Zarabyan N, Bjerner J, Tønseth TM, et al. Anatomic distribution of Neisseria gonorrhoeae, Chlamydia trachomatis and Mycoplasma genitalium infections in men who have sex with men. Sex Health 2013; 10: 199–203.
4. Taylor-Robinson D, Jensen JS. Mycoplasma genitalium: from chrysalis to multicolored butterfly. Clin Microbiol Rev. 2011; 24: 498–514.
5. Björnelius E, Anagrius C, Bojs G, Carlberg H, Johannisson G, Johansson E, et al. Antibiotic treatment of symptomatic Mycoplasma genitalium infection in Scandinavia: a controlled clinical trial. Sex Transm Infect 2008; 84: 72–76.
6. Jernberg E, Moghaddam A, Moi H. Azithromycin and moxifloxacin for microbiological cure of Mycoplasma genitalium infection: an open study. Int J STD AIDS 2008; 19: 676–679.
7. Couldwell DL, Tagg KA, Jeoffreys NJ, Gilbert GL. Failure of moxifloxacin treatment in Mycoplasma genitalium infections due to macrolide and fluoroquinolone resistance. Int J STD AIDS 2013; 24: 822–828.
8. Jensen JS, Bradshaw CS, Tabrizi SN, Fairley CK, Hamasuna R. Azithromycin treatment failure in Mycoplasma genitalium-positive patients with nongonococcal urethritis is associated with induced macrolide resistance. Clin Infect Dis 2008; 47: 1546–1553.
9. Jensen JS, Hansen HT, Lind K. Isolation of Mycoplasma genitalium strains from the male urethra. J Clin Microbiol 1996; 34: 286–291.
10. Jensen JS, Fernandes P, Unemo M. In vitro activity of the new fluoroketolide solithromycin (CEM-101) against macrolide-resistant and -susceptible Mycoplasma genitalium strains. Antimicrob Agents Chemother 2014; 58: 3151–3156.
11. Kikuchi M, Ito S, Yasuda M. Remarkable increase in fluoroquinolone-resistant Mycoplasma genitalium in Japan. J Antimicrob Chemother 2014; 69: 2376–2382.
12. Vandepitte J, Weiss HA, Kyakuwa N, Nakubulwa S, Muller E, Buvé A, et al. Natural history of Mycoplasma genitalium infection in a cohort of female sex workers in Kampala, Uganda. Sex Transm Dis 2013; 40: 422–427.
13. Twin J, Jensen JS, Bradshaw CS, Garland SM, Fairley CK, Min LY, et al. Transmission and selection of macrolide resistant Mycoplasma genitalium infections detected by rapid high resolution melt analysis. PLoS ONE 2012; 7: e35593.
14. Geisler WM, Lensing SY, Press CG, Hook EW. Spontaneous resolution of genital Chlamydia trachomatis infection in women and protection from reinfection. J Infect Dis 2013; 207: 1850–1856.
15. Tagg KA, Jeoffreys NJ, Couldwell DL, Donald JA, Gilbert GL. Fluoroquinolone and macrolide resistance-associated mutations in Mycoplasma genitalium. J Clin Microbiol 2013; 5: 2245–2249.
16. Renaudin H, Tully JG, Bebear C. In vitro susceptibilities of Mycoplasma genitalium to antibiotics. Antimicrob Agents Chemother 1992; 36: 870–872.
17. Kikuchi M, Ito S, Yasuda M, Tsuchiya T, Hatazaki K, Takanashi M, et al. Remarkable increase in fluoroquinolone-resistant Mycoplasma genitaliumin Japan. J Antimicrob Chemother 2014; 69: 2376–2382.