Failure of syndromic management due to drug-resistant *Mycoplasma genitalium* infection in South Africa: a case report

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Abstract

We report a case of management failure of male urethritis syndrome due to macrolide resistant *Mycoplasma genitalium* in South Africa. We detected mutations in 23S rRNA and one of the quinolone resistance determining regions. This report confirms that drug-resistant *M. genitalium* infection can undermine effectiveness of syndromic management in Africa.

Keywords Non-gonococcal urethritis, bacterial disease, urethritis (bacterial), bacterial disease, Africa, location, men, other, treatment

Introduction

In South Africa, sexually transmitted infections (STIs) are managed syndromically through algorithms based on the patient's presenting symptoms. Male urethritis syndrome (MUS) is a common clinical presentation at primary healthcare facilities in South Africa; it is usually caused by *Neisseria gonorrhoeae, Chlamydia trachomatis*, *Trichomonas vaginalis* or *Mycoplasma genitalium* infection.[1] *M. genitalium* infection is treated by azithromycin in the syndromic management regimen. However, there have been reports of widespread treatment failure of azithromycin for male urethral infection from across the globe, but not yet from the African continent where syndromic management is used.[2] We present a case of syndromic treatment failure due to drug-resistant urethral *M. genitalium* infection and discuss the implications of this for the management of STIs in resource-constraint settings.

Case report

A 25-year-old male, HIV-negative, presented at a community health centre (CHC) in Soweto, South Africa, with symptoms suggestive of MUS. He complained of dysuria and penile discharge for the last 14 days. The patient reported one stable female sexual partner that did not have symptoms. He was treated syndromically for MUS with 250 mg ceftriaxone intramuscular injection and 1 g azithromycin as per the current South African STI management guidelines.[3] In addition, a partner notification slip was issued to allow him to notify his sexual partner.

Four weeks later, the patient returned to the same CHC complaining of persistent dysuria and penile discharge. The symptoms remained unchanged following initial syndromic treatment and he was unwilling to disclose and notify his sexual partner. Discharge was confirmed during examination; no other abnormalities were identified. The patient was enrolled in a study addressing the aetiology of persistent symptomatic STIs in men in Johannesburg. After

informed consent was obtained, a sample of urethral discharge and first-void urine (FVU) were obtained for further investigation. In line with the South African STI management guidelines, the patient was treated with an increased dosage of 1 g of ceftriaxone combined with a single dose azithromycin 2 g.

The urethral discharge swab was plated on New York City agar for culture of *N. gonorrhoeae*; no growth was observed after 48 hrs. FVU was used for molecular detection of *C. trachomatis*, *N. gonorrhoeae*, and *T. vaginalis* using the PrestoPlus CT-NG-TV assay (Microbiome Ltd, Houten, the Netherlands)[4]; all reactions were negative. *M. genitalium* infection, however, was detected from the urine sample using a validated in-house *M. genitalium* PCR assay.[5] *M. genitalium* DNA was tested for macrolide drug resistance-associated mutations in the 23S rRNA gene using real-time PCR coupled with melting curve analysis.[6] Melting curve analysis of the DNA showed a peak (63.7°C) differing from the wild type strain (68.3°C). Sequence analysis of the 23S rRNA gene confirmed a mutation at position A2071G, associated with macrolide resistance (Table 1).[6, 7] A quinolone resistance-associated mutation was detected by sequencing of quinolone-resistance determining regions of the *parC* and *gyrA* genes.[8] The patient was contacted telephonically to discuss his results and was advised to return to the clinic for retreatment. Unfortunately, the patient did not return for further treatment and could no longer be reached telephonically.

Table 1. Mutations associated with macrolide and quinolone resistance in *Mycoplasma genitalium* infection in a patient failing management of male urethritis syndrome in South Africa

Drug resistance associated alterations in *Mycoplasma genitalium*		
23S rRNA gene[a]	***par*C gene**[a]	***gyr*A gene**
A2071G	C234T (Pro-62→Ser)[b]	Wild type

[a] Nucleotide positions according to *M. genitalium* numbering according to G37 reference genome (NC_000908).
[b] Numbering of amino acids according to *M. genitalium* gene sequences

Discussion

We present a case of failure of syndromic management of male urethritis due to macrolide-resistant *M. genitalium* infection in South Africa. In addition, a mutation associated with quinolone resistance was identified that has been reported from various countries across the globe.[7] To our knowledge, a case of male urethritis by multi-drug resistant *M. genitalium* infection has not been reported from the African continent before. In the absence of routine diagnostics, resistance data of *M. genitalium* in Africa are scarce and limited to small series of asymptomatic infections in women.[9, 10]

The case that we report highlights a potential limitation of syndromic management in the context of macrolide-resistant *M. genitalium* infection. As per guidelines, our patient was treated twice with azithromycin and ceftriaxone, but without success. Moxifloxacin is not included in the current algorithm nor is it routinely available in public care in South Africa, although its effectiveness in this case is uncertain. Diagnostics are not routinely available in the public healthcare system in South Africa and, if done, usually only focus on the cultivation of *N. gonorrhoeae*. As such, it is highly unlikely that our patient would have received adequate antimicrobial treatment.

The widespread use of azithromycin in the syndromic management of STIs has significantly enhanced the spread of macrolide-resistant *M. genitalium* infections.[11] As debated by others, and confirmed by us through this case report, drug-resistant *M. genitalium* infection has the potential to undermine the effectiveness of syndromic management of STIs.[11,12] Epidemiological data on the prevalence and distribution of macrolide-resistance in the African context are urgently warranted to inform syndromic management guidelines. Important considerations in that regard are the implementation of aetiological testing that should include *M. genitalium* and potential drug resistance, as well as the establishment of a strengthened second-line algorithm for those that fail initial syndromic management.

Ethical approval

The study was approved by the Research Ethics committee, Faculty of Health Sciences, University of Pretoria (Ref 253/2017).

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Declaration of Conflicting Interests

The Authors declare that there is no conflict of interest.

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