Failure in syndromic management due to drug-resistant *Mycoplasma genitalium* in Florianópolis, South Brazil

Falha no manejo sindrômico devido a Mycoplasma genitalium *resistente em Florianópolis, Sul do Brasil*

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ABSTRACT

Introduction: *Mycoplasma genitalium* is a bacterium associated with sexually transmitted infections that can cause urethritis in men and complications in women, including preterm birth. Increasing macrolide resistance in *M. genitalium* poses challenges to treatment efficacy. **Objective:** To present a case of treatment failure of urethritis caused by macrolide-resistant *M. genitalium*. **Case report:** This case report describes a 20-year-old man with persistent urethral symptoms despite azithromycin treatment, wherein *M. genitalium* harbored the A2058G mutation in the 23S rRNA. Subsequent treatment with moxifloxacin resolved symptoms and cleared *M. genitalium*. **Conclusion:** The study highlights the importance of resistance testing to guide antimicrobial therapy and emphasizes the need for updated treatment guidelines in Brazil.

Keywords: Sexually transmitted diseases. Macrolides. Quinolones. Polymorphism, single nucleotide. Urethritis.

RESUMO

Introdução: *Mycoplasma genitalium* é uma bactéria associada a infecções sexualmente transmissíveis, que pode causar uretrite em homens e complicações em mulheres, incluindo nascimento prematuro. O aumento da resistência aos macrolídeos em *M. genitalium* coloca desafios à eficácia do tratamento. **Objetivo:** Apresentar um caso de falha terapêutica de uretrite causada por *M. genitalium* resistente aos macrolídeos. **Relato de caso:** Este relato de caso descreve um homem de 20 anos com sintomas uretrais persistentes, apesar do tratamento com azitromicina, em que *M. genitalium* possuía a mutação A2058G no rRNA 23S. O tratamento subsequente com moxifloxacino resolveu os sintomas e eliminou *M. genitalium*. **Conclusão:** O estudo destacou a importância dos testes de resistência para orientar a terapia antimicrobiana e enfatizou a necessidade de atualizar as diretrizes de tratamento no Brasil.

Palavras-chave: Infecções sexualmente transmissíveis. Macrolídeos. Quinolonas. Polimorfismo de nucleotídeo único. Uretrite.

INTRODUCTION

First isolated in 1980, *Mycoplasma genitalium* (MG) is a bacterium associated with sexually transmitted infections (STIs) that can cause acute, and chronic, urethritis in men, and is also associated with cervicitis, preterm birth, and spontaneous abortion in women[1–3]. Similar to the European guideline on MG infection management[4], the 2022 Brazilian clinical protocol and therapeutic guidelines[5] recommend the use of azithromycin as the first-line treatment for urethritis caused by MG; however, there is a lack of second-line options when therapeutic failure or macrolide resistance is observed. Cases of macrolide-resistant MG are increasing internationally[6] due to single nucleotide polymorphisms at nucleotide positions 2058 and 2059 (*Escherichia coli* numbering) in the 23S ribosomal ribonucleic acid (rRNA) subunit[7,8]. At the time of publication of this manuscript, a study regarding MG resistance was in progress in Brazil but has not yet been published.

OBJECTIVE

This case report aimed to describe a macrolide treatment failure in male urethritis caused by MG and how resistance testing, when available, can assist antimicrobial therapy.

CASE REPORT

A 20-year-old man-who-has-sex-with-man (MSM) reached out to the Molecular Biology, Microbiology, and Serology Laboratory at the Health Sciences Center of the Universidade Federal de Santa Catarina (Brazilian Reference Laboratory for Gonococcal Antimicrobial Surveillance Program) with urethral irritation and burning sensation, as well as rectal discharge. He claimed to have had urethral and oropharyngeal symptoms post-sexual relations two months prior, but syndromic treatment was administered and resolved the previous-mentioned symptoms. The patient then declared having a permanent sexual partner, enrolling in receptive rectal sex, and active and passive oral sex. His partner claimed to have no symptoms but was also invited to collect a sample. Genital (urethral swab) and extra-genital (oropharynx swab and rectal swab) samplings were

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carried out for both individuals, utilizing flocked swab (Sun Trine®, China) and universal transport medium (Copan® UTM-RT, Italy) for storage. Sample deoxyribonucleic acid (DNA) extraction was performed with ReliaPrep™ Blood gDNA Miniprep System kit (Promega®, USA), followed by a real-time polymerase chain reaction (qPCR) performed using Allplex™ CT/NG/MG/TV Assay kit (Seegene®, South Korea), both following the manufacturer's instructions. In the patient's samples, *Neisseria gonorrhoeae* (NG) was found in his oropharynx and rectal swab, while MG was detected in the urethral sample. As for the partner, both NG and MG were found in the rectal swab, NG was detected in the oropharynx sample, and *Chlamydia trachomatis* (CT) in the urethral swab (**Table 1**).

After the first sampling, both the patient and his partner were treated with 500 mg intramuscular ceftriaxone and a single dose of 1 g oral azithromycin, following Brazilian therapeutic guidelines[5]. Seven days later, the patient persisted with symptoms such as itching and a burning sensation in his urethra. Additional samples were collected from the same anatomical sites, followed by DNA extraction and qPCR as previously described. NG and CT were no longer detected, while MG remained present in urethral (patient) and rectal (partner) samples (**Table 2**).

Extracted DNA from the first sampling round was used to perform a qPCR using Allplex™ MG & AziR Assay kit (Seegene®, South Korea) and Allplex™ MG & MoxiR Assay kit (Seegene®, South Korea) to possibly detect six mutations responsible for azithromycin resistance (A2058G, A2058C, A2058T, A2059G, A2059C, and A2059T in the subunit 23S rRNA) and six mutations responsible for moxifloxacin resistance (A247C, G248A, G248T, G259C, G259T, and G259A in the *parC* gene). In both samples, the A2058G mutation was detected in 23S rRNA, and no mutations were observed in the *parC* gene. Upon medical recommendation, both patients received moxifloxacin 400 mg orally once a day for seven days. After completing the treatment, the patient declared he no longer had urethral symptoms. Another urethral sampling was carried out ten days after the beginning of moxifloxacin treatment and showed a negative result for MG. We did not have the opportunity to sample the rectal sample after moxifloxacin treatment.

Table 1 – Real-time polymerase chain reaction results at the time of diagnosis.

Sample origin	qPCR outcome	
	Patient	Partner
Urethra	MG	CT
Oropharynx	NG	NG
Rectal	NG	NG, MG

MG*: Mycoplasma genitalium*; NG: *Neisseria gonorrhoeae*; CT: *Chlamydia trachomatis*; qPCR: real-time polymerase chain reaction.

Table 2 – Real-time polymerase chain reaction results after syndromic management protocol treatment.

Sample origin	qPCR outcome	
	Patient	Partner
Urethra	MG	-
Oropharynx	-	-
Rectal	-	MG

MG: *Mycoplasma genitalium*; qPCR: real-time polymerase chain reaction.

DISCUSSION

In this study, we reported a case of macrolide-resistant MG with a successful outcome after quinolone treatment. The patient and his partner were diagnosed with different pathogens in genital and extragenital anatomical sites for which empirical treatment was effective, except for MG. After moxifloxacin retreatment, the patient's symptoms were resolved, and MG was not detected in the urethral sample.

The treatment of MG infections has become a challenge mainly due to macrolide-resistant cases, which reach more than 50% prevalence in the United States, Canada, Germany, United Kingdom, Norway, Australia, New Zealand, and Greenland territory[6]. In some countries where the rate of macrolide resistance is already known, such as the United States[9] and Australia[10], other treatment regimens are recommended, such as the use of doxycycline 100 mg orally two times a day for seven days, followed by moxifloxacin 400 mg orally once a day for seven days. In these countries, and in the European guidelines, resistance testing is recommended when available, since it is essential to guide antimicrobial treatment[4,9,10].

MG was also detected in the rectal swab of the sexual partner, who was asymptomatic. Studies on MSM report MG positivity of around 5.4% in rectal samples[11], which can reach more than 40% when screening sexual partners of men with urethritis caused by MG[12]. These results suggest that the rectal is an important anatomical reservoir of this bacteria. Corroborating a previous case report[13], the present study showed that testing before treating and the cure control for STI, including sexual partnerships, must be done whenever possible, even in asymptomatic cases, in order to interrupt the transmission chain and for better antimicrobial stewardship[5].

Besides, MG, NG, and CT were also detected, and at least one of the pathogens was identified in each sampling site of both patients. Also, only one of the individuals reported symptoms in the urethral and rectal sites. The percentage of asymptomatic STIs varies according to the anatomical site, and population studied[14]. For NG, most of the time, male urogenital infections present with symptoms; in a multicentric study that evaluated approximately 11,000 participants, 86.8% of them reported symptoms[15]; while for CT, asymptomatic cases can reach 80% in male urogenital infections and 90% in extragenital cases[14,16]. In the present case report, the patient's sexual partner was contacted and an STI screening in genital and extragenital sites was performed, detecting an asymptomatic case. The patient and his sexual partner were treated, possibly interrupting the transmission chain.

Strengths and limitations

This case describes a clinical report of treatment failure for an STI attributed to *M. genitalium* that demonstrated resistance. MG is a poorly studied bacterium in Brazil, and there is a lack of data on its antimicrobial resistance profile regarding treatments used in the country. This report details the treatment follow-up of a patient, from the ineffectiveness of the initial approach to the correct diagnosis of the etiological agent, made possible only by molecular testing availability. The absence of bacterial culture and genome sequencing are limitations of this study as they could enrich and provide additional genomic data about the bacterium. Furthermore, it was not possible to perform a new collection of the patient's sexual partnership after treatment with moxifloxacin.

CONCLUSION

The authors consider that cases like this are very frequent but not observed because screening for MG in exposed populations is not performed and resistance to MG is not yet evaluated in Brazil. These findings reinforce the importance of STI testing, especially in cases where symptoms do not resolve. A second-line treatment option should be discussed to update The Brazilian Clinical Protocol and Therapeutic Guidelines for STI Treatment, regarding *Mycoplasma genitalium*.

Approval by the Human Research Ethics Committee

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Participation of each author

FHB: Conceptualization, Data curation, Formal Analysis, Writing - review & editing. MAS: Conceptualization, Sample Collection, Data curation, Formal Analysis, Writing - review & editing. JAR: Conceptualization, Sample Collection, Data curation, Formal Analysis, Writing - review. HBSG: Conceptualization, Data curation, Formal Analysis, Writing - review. JMM: Conceptualization, Data curation, Formal Analysis, Writing - review. JKW: Conceptualization, Data curation, Formal Analysis, Writing - review & editing. PAV: Patient care and management. MLB: Conceptualization, Data curation, Formal Analysis, Writing - review & editing.

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Conflict of interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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