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Clinical significance of *Sphingomonas* species in urethritis - Case series in 6 patients

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Abstract

The role of *Sphingomonas* spp. as aetiological agents in patients with urethritis is unclear. Therefore, we conducted an observational, retrospective study in six male patients, who presented with complaints of acute urethritis between January 2023 and July 2023 in our outpatient urological medical office. Microbiological cultures from urethral swabs were carried out on different culture media and *Sphingomonas* spp. were isolated in these patients. Ciprofloxacin treatment (750 mg twice daily for five days) was initiated in two of the six patients, while four patients received no antibiotics. Of these untreated patients three were asymptomatic and one patient had significant clinical improvement at reevaluation after a median time of three weeks. We conclude, that antibiotic treatment is not mandatory when *Sphingomonas* spp. are detected in urethral swabs. Watchful waiting and assessing the clinical symptoms in a follow-up contact seems to offer a good alternative.

Keywords: Sphingomonas; Urethritis; Clinical significance; Therapeutic management.

Abbreviations: NCNGU: Nonchlamydial Nongonococcal Urethritis; EUCAST: European Committee on Antimicrobial Susceptibility Testing; Ssp: Species

Introduction

Sphingomonas species are a group of Gram-negative, rod-shaped bacteria, which occur as environmental germs but are also occasionally detected in human specimens. In some publications, these bacteria were detected in urethritis patients by using sophisticated PCR and sequencing methods [1-3]. However, in these studies the prevalence rates of *Sphingomonas* spp. were comparable between patients with and without urethritis. Therefore, the clinical significance of this genus for this disease entity remained unclear. To our knowledge there are no clinical data for the role of *Sphingomonas* spp. in urethritis to date. For this reason, we evaluated the further course of patients with a positive culture of *Sphingomonas* spp. in urethral swabs.

Patients and methods

We retrospectively assessed six male patients between January 2023 and July 2023, who presented with symptoms of acute urethritis. The physical examinations were inconspicuous, there was no discharge from the urethra and the urine sediment was without any abnormal findings in all men. Consequently, the decision was made to have a urethral swab.

Urethral swabs (Nerbeplus, Winsen/Luhe, Germany) were taken under sterile conditions after disinfection of the orificium urethrae externum and the glans with 2% chlorhexidine solution. Then, the specimens were transported to the laboratory, plated onto Columbia blood-, McConkey-, Schaedler-, Schaedler

gonococci-, anaerobia-agar and a thioglykolat bouillon, and incubated for 48 hours. Additionally, a Gram stain was performed. Cultured bacterial colonies were differentiated using MALDI-TOF mass spectrometry. Antibiotic resistance testing was carried out in four of the six isolates according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) specifications using *Pseudomonas* breakpoints [4].

To check the chlorhexidine solution for sterility, we inoculated 1 ml and 100 µl of the disinfectant in 10 ml tryptone-soya broth (Oxoid, Wesel, Germany), respectively.

Results

A total of 36 urethral swabs from different patients were investigated during the study period. In six (17%) male patients (median age 55 years, Table 1) *Sphingomonas* spp. were isolated. This surprisingly high incidence prompted us to conduct a retrospective study of these individual cases.

S. paucimobilis was isolated in two cases, four isolates were not typable on species level and were most likely other species out of the *Sphingomonas* genus (Table 1). Coculturable organisms were coagulase-negative staphylococci in two cases and *Candida albicans* and *Streptococcus agalactiae* in one case, respectively. Cultures for gonococci all remained negative. All *Sphingomonas* isolates which were tested for antibiotic resistance (n=4), were susceptible to meropenem, susceptible for increased exposure for ceftazidime, and resistant to piperacillin/tazobactam. For ciprofloxacin, three isolates were susceptible for increased exposure and one isolate was resistant. According to EUCAST, there are no breakpoint values for other orally available antibiotics [4].

All patients were informed in detail about the benefits and potential side effects of ciprofloxacin therapy, especially with regard to an official warning against the use of ciprofloxacin in Germany [5] and the unclear role of *Sphingomonas* spp. as the pathogen responsible for their symptoms. Four of the six patients were reticent about antibiotic treatment, therefore antibiotics were not started, but a follow-up appointment was arranged. All four men were symptom-free or had significantly improved clinically even without antibiotics at the second visit (Table 1). Two patients were treated with ciprofloxacin 750 mg twice daily for five days because of their urgent individual request. Both patients were also clinically asymptomatic during follow-up.

To exclude secondary contamination, we carried out a sterility test of the disinfectant solution used. After a 72 h incubation period, all broths were sterile.

Discussion

Determining the cause of Nonchlamydial, Nongonococcal Urethritis (NCNGU) is still a major challenge. Although other microorganisms like *Mycoplasma genitalium*, *Mycoplasma hominis*, *Trichomonas vaginalis* or *Ureaplasma* spp. occur as significant pathogens, the microbiological etiology of urethritis remains undetected in 30-50% of cases [2]. Even highly sensitive test methods such as PCR have not led to any clear results about new emerging pathogens that could be responsible for urethritis [1-3], although one study [1] suggested a possible role of *Pseudomonas*-like bacterial species in NCNGU. To our

Table 1: Laboratory findings and clinical course of patients suffering from urethritis.

Age	Microscopy: Leukocytes	<i>Sphingomonas</i> species	Coculture	Treatment	Follow-up
61	(+)	<i>Sphingomonas</i> spp.*	CnS**	yes***	Symptom-free after 4 weeks
39	none	<i>S. paucimobilis</i>	CnS**	no	Symptom-free after 3 weeks
61	+	<i>Sphingomonas</i> spp.*	<i>C. albicans</i>	no	Significant improvement after 4 weeks
49	none	<i>S. paucimobilis</i>	<i>S. agalactiae</i>	no	Symptom-free after 2 weeks
62	none	<i>Sphingomonas</i> spp.*	-	no	Symptom-free after 3 weeks
45	none	<i>Sphingomonas</i> spp.*	-	yes***	Symptom-free after 4 weeks

*Not typable on species level using MALDI-TOF mass spectrometry. **CnS: Coagulase-negative Staphylococci. ***Ciprofloxacin 2x750 mg for 5 days. All samples were negative for *N. gonorrhoeae*.

knowledge, there are currently no study results regarding the etiological and clinical significance of *Sphingomonas* spp. in the development of urethritis.

We identified six patients in whom *Sphingomonas* spp. were detected as the sole pathogen or in combination with other pathogens. None of the patients had urethral discharge. No antibiotic therapy was started in four patients and all of them were symptom-free or had significant clinical improvement at the follow-up appointment. This indicates that the pathogenic significance of *Sphingomonas* spp. was very questionable in these cases. Under special circumstances like nosocomial urinary tract infection [6,7] or nephrolithiasis [8], *Sphingomonas* may play a significant role. Considering the results of our study in an outpatient setting of urethritis patients, these bacteria are more likely to represent colonization rather than causal infectious agents. This particularly applies to patients with no discharge and normal urine sediment findings.

The etiology of the symptoms in the four patients who had clinical improvement even without antibiotic therapy remains unclear. It should be kept in mind that there are also non-infectious causes of urethritis that have a self-limiting course. In a study by Hsu YT et al. [9] 142 of 365 male patients with urethritis-like symptoms had a diagnosis of noninfectious disease. In this subcohort, it was not clear whether the improvement in symptoms could be attributed to the empirical therapy or whether the course was self-limiting. Since *Sphingomonas* spp. are environmental germs, secondary contamination with these bacteria may be another explanation for their detection in clinical samples [7]. However, we took the samples under strictly sterile conditions and processed all swabs in a sterile laminar airflow workbench. Additionally, we examined the solution for disinfecting the urethral orifice before swabbing for potential contaminants, which turned out to be sterile. Therefore, secondary contamination seems unlikely, but cannot be completely ruled out. Nonetheless, our results suggest that *Sphingomo-*

nas spp. tend not to play a significant role in the development of urethritis.

Conclusion

In case of detection of *Sphingomonas spp.* in urethral swabs of patients with NCNGU it seems advisable to wait and see rather than to initiate an immediate antibiotic therapy. However, it is absolutely necessary to arrange a second appointment in order to assess the clinical course. Studies in larger case series should be conducted to support this approach.

Declarations

Conflict of interest: Nothing to declare.

Consent: The work was performed retrospectively after routine clinical operations. Informed consent was guaranteed as part of the clinical treatment.

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Ethical approval: Due to the retrospective character of the study, an ethics vote by the North Rhine Medical Association was not necessary.

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