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Short communication

Emerging presence of urethritis and balanitis by *Pasteurella bettyae*

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ABSTRACT

Background: Humans can also be infrequent infected by *Pasteurella bettyae*. We report the first association of *P. bettyae* with urethritis and balanitis in men who have sex with men practicing unprotected intercourse.
Patients and methods: The standard culture for bacteria and fungi in genital samples, and a PCR study for *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Trichomonas vaginalis*, *Mycoplasma* spp. and *Ureaplasma* spp, were performed. Cultured microorganisms were identified by Maldi-Tof mass spectrometry and the susceptibility of the isolates were evaluated with the gradient test.
Results: P. bettyae were isolated and were found to be susceptible to penicillin, amoxicillin-clavulanic acid, trimethoprim-sulfamethoxazole, ciprofloxacin, and doxycycline.
Conclusion: This novel finding highlights the need for complete microbiological screening in adequate samples to detect possible infectious agents in these cases, not limited to conventional agents. These rare microorganisms can be detected by the application of Maldi-Tof in colonies grown in culture media.

1. Introduction

Pasteurella is a genus of small, Gram-negative, nonmotile coccobacilli that form part of the nasopharyngeal and gastrointestinal mucosal microbiota of dogs and cats, among other animals. *Pasteurella multocida* is the species most frequently responsible for infections [1], being associated with skin and soft tissue infections commonly acquired through animal bites or scratches. In rare cases, it has been identified in clinical samples of the respiratory tract infections, meningitis, bacteremia, endocarditis, peritonitis, secondary osteoarticular disease, and urinary tract infections [1,2].

Humans can also be infected by *Pasteurella bettyae*, another species in this genus that has been detected in genitourinary samples from infected patients, suggesting the possibility of its sexual transmission [3,4]. We report the first two published cases of infection (urethritis and balanitis) caused by *P. bettyae,* detected in men who have sex with men (MSM) and had practiced unprotected intercourse.

2. Case presentation

2.1. Case 1

A 53-year-old MSM was referred to the Infectious Diseases Unit of our hospital after experiencing urethral discomfort for a few days, with no purulent secretion, fever, or rectal tenesmus. He reported recent unprotected intercourse. He had been HIV-positive since 2004 and was currently under antiretroviral treatment (dolutegravir and lamivudine) with an undetectable viral load. He had a history of hepatitis C virus, treated and was cured in 2018; syphilis reinfection, treated in 2018; and an episode of gonococcal urethritis in 2017. Inguinal exanthema and lymphadenopathy were ruled out by physical examination; pharyngeal, rectal, and urethral exudates were obtained; and a syphilis serology was ordered. Prophylactic treatment was administered with a single dose of 400 mg cefixime and 1 g azithromycin. Following standard protocols, pharyngeal exudates were cultured on Thayer-Martin agar and rectal and urethral exudates on both chocolate agar and Thayer-Martin agar (Becton Dickinson, Sparks, MD) in CO_2-rich atmosphere for 48 h. A PCR study was performed using the BD MAX™ system (Becton Dickinson) for *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, and *Trichomonas vaginalis* (BD MAX CT/GC/TV), and for *Mycoplasma genitalium*, *Mycoplasma hominis*, *Ureaplasma parvum*, and *Ureaplasma urealyticum* (BD MAX System,

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BioGX DNA, 350–011-A-MAX) [5]. PCR was only positive for *M. hominis* in the rectal exudate sample. The syphilis serology RPR titer was 1:2. Numerous homogeneous colonies appeared on chocolate agar inoculated with the urethral exudate after incubation for 48 h, and these were identified as *P. bettyae* by matrix-assisted laser desorption/ionization – time of flight mass spectrometry (MALDI-TOF MS) (Bruker Biotyper, Billerica, MA); (score 2.203). A phenotypic panel was not used for the identification.

E-test results (MIC Test Strip Liofilchem®, Roseto degli Abruzzi, Italy) were susceptible interpreted using CLSI M45 criteria (2015), obtaining the following MIC values: 0.125 μg/ml for ampicillin, 0.125 μg/ml for amoxicillin-clavulanic acid, 0.032 μg/ml for trimethoprim/sulfamethoxazole, 0.004 μg/ml for ciprofloxacin, and 0.25 μg/ml for doxycycline. The final diagnosis was *P. bettyae*-induced urethritis accompanied by asymptomatic proctitis due to *M. hominis*. The patient was prescribed 100 mg doxycycline every 12 h for three weeks. 10 days after the end of this treatment, PCR tests and pharyngeal, rectal and urethral exudate cultures were repeated and all were negative.

2.2. Case 2

A 47-year-old MSM was referred to the unit after a few days with fever (38.7 °C) accompanied by the appearance of an erythematous macular lesion on the left side of the glans and the appearance of a right inguinal tumor-like formation that was painful to palpation, suggesting a lymphadenopathy. He reported unprotected sexual intercourse during the previous few weeks. He had been diagnosed with HIV in 2013 and was under antiretroviral treatment (dolutegravir and lamivudine), with an undetectable viral load. He had a history of successfully treated syphilis. Blood analyses revealed 108 mg/L C-reactive protein (normal range: 0–5 mg/L) and 540 mg/dl fibrinogen. Urethral and rectal exudates were collected, and syphilis serology was performed. He was treated empirically with a single dose of ceftriaxone followed by 100 mg doxycycline every 12 h for four weeks. RPR results and PCR results for exudates (*C. trachomatis*, *N. gonorrhoeae*, *M. genitalium*, *M. hominis*, *U. urealyticum* and *U. parvum*) were all negative. Abundant homogeneous colonies grew on the cultured urethral sample exudate and were subsequently identified by MALDI-TOF MS as *P. bettyae* (score of 2.105). E-test results revealed susceptibility to penicillin (MIC of 0.38 μg/ml), amoxicillin-clavulanic acid (0.5 μg/ml), trimethoprim-sulfamethoxazole (0.094 μg/ml), ciprofloxacin (0.06 μg/ml), and doxycycline (MIC 0.5 μg/ml). On completion of the empirical treatment, the clinical manifestations and genital and inguinal lesions had disappeared.

3. Discussion

The genus *Pasteurella* comprises facultative aerobic-anaerobic bacteria that are able to grow without inducing hemolysis on chocolate and blood agars but not on MacConkey agar. Their growth is favored in a CO_2-enriched atmosphere and at an optimal temperature of 37 °C. *P. multocida* is identified as the causal agent in most patients with skin or soft tissue infections, usually related to contact with animals, as noted above, although other etiologies have been described [2,6].

P. multocida rarely produces urinary tract infections, whereas *P. bettyae* is responsible for 1% of all *Pasteurella*-induced infections and has been identified in genital ulcer, vaginal, cervical, urethral, Bartholin's cyst, and scrotal abscess exudates and urine samples [3,4,7–9]. It has also been isolated in amniotic fluid, placenta, and newborn blood, indicating possible maternal-fetal transmission during labor [9,10]. A study in Rwanda reported that *P. bettyae* was responsible for 3.6% of urethral infections, suggesting its sexual transmission [11]. In the present study, it was the sole microorganism observed in samples from the two patients and it disappeared after antibiotic therapy. This microorganism can only be detected when standard protocols are rigorously followed, including culture on artificial media. We highlight the value of MALDI-TOF technology to detect these microorganisms, which have low metabolic activity and cannot be definitively identified with biochemical tests, which may be responsible for an infradiagnosis of this microorganism.

The first-line treatment of *P. bettyae* is penicillin, to which it is generally susceptible, as in the present patients, However, cases of resistance have been described, with 29% of the clinical isolates in Rwanda being beta-lactamase producers [11]. An alternative option is to prescribe second- or third- generation cephalosporins, fluoroquinolones, and/or tetracycline [2].

Epidemiological changes appear to be taking place in the etiology and localization of urethritis and/or balanitis, indicating the need for more comprehensive diagnostic procedures and wider microbiological analyses, adapting the direct microbiological testing resources available for clinical needs [12–14]. In genital diseases cases, especially among MSM, analysis of samples should be considered whether or not a lesion is present, although the cost-effectiveness of this approach has yet to be evaluated in our health setting. It should be borne in mind that there are frequently no pathognomonic lesions for sexually transmitted diseases. Tests should include cultures for bacterial agents that are difficult to grow; PCR for the detection of simple herpes virus, *N. gonorrhoeae and C. trachomatis;* and, when possible, serotyping. One limitation of this study was that exudate samples were not stained, which could have revealed the presence of leukocytes; and don't provide the demonstration of sexual transmission, as there is no sample in partners.

4. Conclusion

In conclusion, this report of infections caused by *P. bettyae* in two MSM patients with a history of unprotected sexual intercourse highlights the need for further research on the pathogenicity of this microorganism as a potential infective agent of the genital tract and on its capacity for urethritis and balanitis. These findings underscore the importance of targeted treatment based on the culture of clinical samples, avoiding the administration of unnecessarily broad empirical treatments.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the 1964 Helsinki declaration and its later amendments

Disclosure of interest

The authors declare that they have no competing interest.

Authors' contributions

1. Conception and design of the manuscript: JGF, ARC.
2. Data collection: JGF, ARC.
3. Analysis and interpretation of the data: plus ARC.
4. Writing, review, approval of the submitted manuscript: plus ARC, CCHT.

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