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Letter to the Editor

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Domingo Fernández Vecilla[1,3]
Julia Aragón Díez[1,3]
María Carmen Nieto Toboso[1,3]
Jaume Rosselló Soria[2,3]
José Luis Díaz de Tuesta del Arco[1,3]

Could *Mycoplasma genitalium* be involved in chronic granulomatous orchiepididymits? Case report and literature review

[1]Clinical Microbiology and Parasitology Service. Basurto University Hospital. Bilbao (Vizcaya). Spain
[2]Pathological Anatomy Service. Basurto University Hospital. Bilbao (Vizcaya). Spain
[3]Biocruces Bizkaia Health Research Institute. Barakaldo (Vizcaya). Spain.

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Sir,

Mycoplasma genitalium is the smallest known self-replicating bacterium, presenting a slow and fastidious growth. It was first isolated from urethral swabs of two symptomatic men with urethritis in 1980 [1]. It lacks a cell wall and therefore cannot be detected by Gram staining. *M. genitalium* is predominantly found in the genitourinary tract of both sexes. It establishes infection intracellularly, which together with the antigenic and phase variation of the proteins expressed on its surface manages to evade the adaptive immune system [2].

A 33-year-old male patient presented to his physician for left testicular pain of more than one year's duration, related to certain movements. The patient had no external data of inflammation, urethral discharge, dysuria, hemospermia or pain on ejaculation. As medical history, the patient had suffered an episode three years earlier of left epididymitis with an unidentified cause diagnosed by ultrasound (enlarged epididymis, with marked vascularization in the color doppler study, while the testicle showed normal structure and vascularization) and for which he received analgesic treatment, but no antibiotics. On examination of the left testicle, the lower pole was palpated with a mass of approximately 1-2 cm hard and painless. Ultrasound showed a 1.2 cm hypoechogenic solid mass with slight peripheral vascular enhancement (Figure 1), so the study was complemented with a computed tomography (CT) and blood tests with tumor markers. In the blood test, both chorionic gonadotropin beta subunit and alpha 1 fetoprotein were in normal ranges, while the CT scan of the chest, abdomen and pelvis ruled out tumor dissemination.

After evaluation of the case, left radical orchiectomy via inguinal route was conducted. The surgical sample was sent to anatomic pathology for study and a 1.6 x 1.1 cm lesion of yellowish-white coloration and necrotic-purulent appearance was observed. Microscopically (Figure 2), a necrotizing, impaling and exudative granulomatous lesion was observed, while in the rest of the epididymis chronic inflammatory changes with suppurative flare-up and images of spermatogenic granuloma of long evolution were observed. Grocott, Ziehl and Warthin-Starry techniques (which can detect fungi, mycobacteria and *Helicobacter pylori* or spirochetes, respectively), together with immunohistochemical markers for germinal lesion (OCT-4 and SALL-4), as well as PLAP, D2-40 and CK AE1-AE3, were negative.

DNA eluate was obtained using the Cobas© DNA Sample Preparation Kit panel (Roche Diagnostics, Basel, Switzerland) from the lesion to perform PCR of *Mycobacterium tuberculosis* using the GenoType Mycobacteria Direct panel (Hain Lifescience, Nehren, Germany), which allows us, by amplification of 23S rRNA, the detection of *M. tuberculosis Complex*, *Mycobacterium avium, Mycobacterium intracellulare, Mycobacterium kansasii and Mycobacterium malamoense*, with negative results. The STI Essential Assay AllpexTM panel (Seegene, Seoul, South Korea) that detects 7 pathogens related to sexually transmitted infections (*Chlamydia trachomatis, Mycoplasma genitalium, Mycoplasma hominis, Neisseria gonorrhoeae, Trichomonas vaginalis, Ureaplasma parvum* and *Ureaplasma urealyticum*) was also performed, detecting *M. genitalium* with Ct (cycle threshold) values of 21. A semen sample was sent 1 month after this study and the STI Essntial Assay Allplex© panel again detected *M. genitalium*, but this time with Ct values of 33. In addition, the ResistancePlus© MG FleXible panel was performed on the GeneXpert system (Cepheid, California, USA), which detects both *M. genitalium* and macrolide resistance mediated by mutations in the 23S rRNA gene, with detection of the microorganism, but without detection of the mutation.

Following this result, the patient was treated with 100 mg/12 h of doxycycline for 7 days, followed by 1 g of azithromycin on the 8th day and 500 mg the next two days. The

Correspondence:
Domingo Fernández Vecilla
Clinical Microbiology and Parasitology. Hospital Universitario de Basurto.
Avenida Montevideo nº18, Gurtubay pavilion, 3rd floor. Postal code: 48013, Bilbao (Basque country). Spain.
E-mail: domingofvec@gmail.com

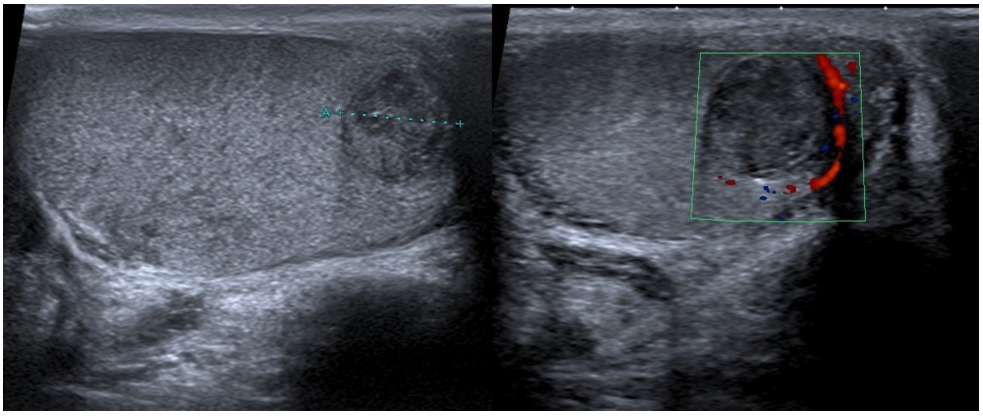

Figure 1 | **A hypoechogenic solid mass of rounded morphology measuring 12 mm with slight peripheral vascular enhancement is visualized.**

patient was evaluated again 5 weeks later and was found to be asymptomatic.

Granulomatous orchitis is a pathologic syndrome attributed to different etiologic factors, with a common histologic feature in all of them, granulomatous inflammation in the testis. Because granulomatous inflammation of the testis can be seen in many conditions, the diagnosis is one of exclusion. Because the clinical presentation and sonographic findings are often suspicious for malignancy, the specimen for pathologic examination is usually an orchiectomy specimen. Significant associated medical history includes testicular trauma or surgical procedure, history of tuberculosis, urinary tract infections, and epididymitis, among others [3,4].

Enterobacteriaceae such as *Escherichia coli* or *Salmonella enteritidis, Actinomyces israeli* or sexually transmitted microorganisms such as *N. gonorrhoeae* or *C. trachomatis* are some of the possible causative agents of epididymitis, orchitis or non-granulomatous orchiepididimitis [5-7]. Within granulomatous orchioepididymitis, the infectious cause is one of the possible differential diagnoses along with idiopathic, tumor or autoimmune causes [4,7]. Making a differential diagnosis is fundamental and *M. tuberculosis, Treponema pallidum, Mycobacterium leprae,* brucellosis or rarer infectious etiologies such as fungal (blastomycosis, coccidiomycosis, histoplasmosis or cryptococcosis) or parasitic (filariasis or *Schistosoma* spp.) should be considered when patients live in or travel from endemic areas [7-10]. Following the increase in people migrating from countries with a high incidence of tuberculosis disease and the increase in the population of immunocompromised patients, *M. tuberculosis* has to be taken into account. Genitourinary tuberculosis is one of the most frequent extrapulmonary presentations after lymphatic tuberculosis. Although epididymal involvement is frequent, very few cases occur in the form of orchitis [7,9].

M. genitalium has emerged in recent decades as a sexually transmitted pathogen, in fact, it is estimated to account for 10-35% of non-gonococcal urethritis [11,12] Due to its fastidious growth, culture is limited to research laboratories and reference centers and clinical diagnosis is usually performed by molecular methods. In a 2018 meta-analysis, its prevalence was observed to vary from 1.3% in developed countries to 3.9% in developing countries, although this data could be biased, as the detection of asymptomatic infections would be more common in patients who frequent centers or consultations specializing in sexually transmitted infections [13,14]. In this same meta-analysis, the prevalence by risk groups was estimated at 0.9% in pregnant women, 3.2% in men who have sex with men and 15.9% in sex workers. As *M. genitalium* infection is not a notifiable disease in Spain, the epidemiological data available are based on case series published at different times and in different areas, ranging from 2.4% to 9% in men and from 0.96% to 13% in women [14-16].

In many cases, detection of *M. genitalium* does not correlate with symptoms or signs of genital tract infection such as urethritis, abnormal vaginal discharge, or pelvic pain, suggesting that asymptomatic infection may not be pathogenic. Further studies should be done to determine whether asymptomatic infection could cause long-term complications. Previously, this microorganism has been associated with acute or chronic urethritis, proctitis or even epididymitis, while its association with prostatitis is still unclear [12,17]. This is the first time that *M. genitalium* is implicated in a case of orchiepididymitis, although we cannot discriminate whether this microorganism was the cause of epididymitis at first and chronified causing the granulomatous lesion or was responsible for the suppurative flare-up of the pre-existing lesion.

Granulomatous inflammation of the testis can be seen in many pathologies, so a thorough differential diagnosis is essential. The advance of molecular techniques in recent years has changed microbiology with rapid identification of multiple pathogens, improving the screening of various infections. The relevance of *M. genitalium* as a sexually transmitted pathogen has increased in the last decades being demonstrated its impli-

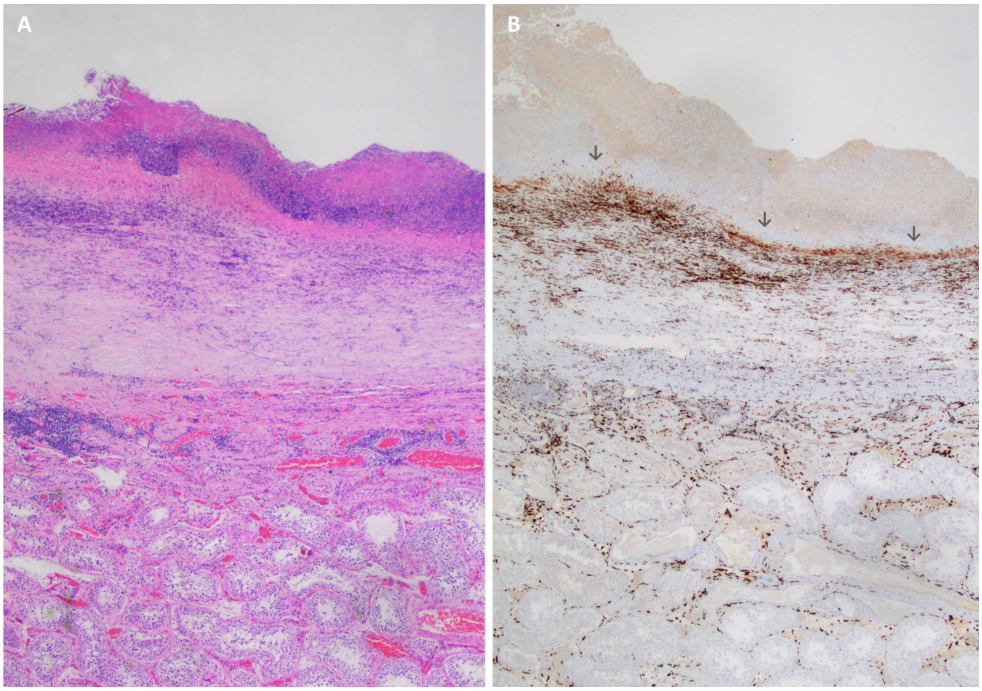

Figure 2 **A: Hematoxylin-Eosin stain. 2x. Histological slides showing testicular parenchima composed by seminiferous tubules. Contiguous to the parenchima, a thick well defined fibrotic layer with mixed inflamation, containing an exudative necrotic granuloma.**
B: Immunohistochemistry. 2x – Histiocytic palisade (↓) of the granulomatous wall is observed by CD163 positive staining.

cation in urethritis, proctitis or epididymitis. More studies and reports are needed to demonstrate its possible pathogenicity as a cause of other different conditions.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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