Blood Culture-Negative Infective Endocarditis by *Mycoplasma hominis*

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Mycoplasma hominis is a habitual colonizing microorganism of the lower genital tract but can exceptionally be the causal agent of blood culture-negative infective endocarditis (IE).

Keywords: Mycoplasma hominis ; endocarditis ; pacemaker lead

1. Introduction

The *Mycoplasma* genus belongs to the *Mycoplasmataceae* family in the *Mollicutes* class. It includes a group of slow-growing bacteria species with no cell wall, characterized by a small genome and limited biosynthetic capacity. They are beta-lactam-resistant due to the absence of a cell wall, and their high nutritional demand makes them difficult to culture [1][2], although this problem has recently been solved by applying molecular techniques. They are often found as colonizers of mucosae, mainly respiratory and genitourinary [3][4]. *Mycoplasma hominis* was the first of various human pathogen species to be isolated. It colonizes the human genital tract and is transmitted by sexual contact [1]. It is not a pathogen in the adult vagina, being present in the vaginal/cervical secretions of around 50% of adult women [5]. However, it has increasingly been attributed to pathogenic action mechanisms at different levels and can be the cause of joint (periprosthetic, septic arthritis) [6], nervous system (drainage-related ventriculitis, neonatal meningitis) [7], respiratory [8], mediastinal [9], genitourinary (pyelonephritis, urethritis, bacterial vaginosis) [10], and even endovascular [11] infection. Reported pathogenicity mechanisms include enhanced adherence to eukaryotic cells (P50, P100), cell dissemination via certain proteins (e.g., Vaa), and local toxicity. Polymerase chain reaction (PCR) is frequently utilized for the microbiological identification of *M. hominis*, which is commonly susceptible to doxycycline and moxifloxacin [12].

2. Mechanism of Endocarditis by *M. hominis*

The underlying pathogenic mechanism of endocarditis by *M. hominis* appears to be nosocomial, possibly secondary to bacteremia caused by the instrumentalization of colonized areas before, during, or after surgery. The median time interval between heart surgery and symptom onset was six months (range, 1–12 months).

The most frequent clinical signs/symptoms in the published cases were fever and valve insufficiency [13][14][15][16][17][18][19][20][21][22][23]. Serial blood cultures were negative in all 11 patients. *M. hominis* was identified by culture in six cases (in combination with molecular analysis in three of these) and by molecular analysis (16 s ribosomal DNA PCR) of the explanted valve in the remaining five [13][14][15][16][17][18][19][20][21][22][23].

Blood culture plays an essential role in the diagnosis and treatment of IE, and a major diagnostic challenge is therefore posed by blood culture-negative infective endocarditis (BCNIE) [24], reported to represent between 2.5 and 70% of all endocarditis cases in different countries and series [25]. It is essential to consider other causes in patients with IE and negative blood cultures after ruling out an infectious etiology [26]. Besides serology for the detection of fastidious agents such as *Coxiella burnetii* and *Bartonella* spp. [26], valve biopsy is the most useful diagnostic approach, especially with the application of histologic and broad-range PCR techniques, when available [27].

Mycoplasma hominis does not Gram stain, it has limited biosynthetic capacity, and it is difficult to isolate in culture medium1. In addition, the characteristic “fried egg” (0.3–0.6 nm) appearance of colonies in culture hampers their ready visualization [25]. Currently, PCR is successfully used to study the extracted valve, offering elevated specificity and sensitivity values [27]. In the present case, the study of blood cultures with real-time multiplex PCR (Septifast) yielded a diagnosis only a few hours after establishing clinical suspicion, allowing the early administration of targeted antibiotic therapy.

After blood samples had been drawn for culture, all patients received empirical antibiotic treatment. Seven (63.6%) were prescribed combined antibiotic treatment with three drugs, most frequently associating a glycopeptide or lipopeptide with beta-lactam and aminoglycoside [13][16][17][18][21][22][23]. The other four received a combination of glycopeptide with aminoglycoside, beta-lactam with aminoglycoside, glycopeptide with beta-lactam, or glycopeptide with lipopeptide [14][16][19][20]. The present patient was treated with a combination of beta-lactam, lipopeptide, and macrolide.

After the detection of *M. hominis*, nine of the eleven patients (81.8%) [13][14][15][17][18][19][20][21] were prescribed targeted antibiotic treatment, one died during the immediate postoperative period, and the remaining patient was lost to the follow-up [16][22]. Only one of the empirical treatments initially received by the patients was active against *M. hominis* [16]. The antibiotics most frequently administered in targeted therapy were doxycycline (7/9 cases, 77.8%) [13][15][17][18][19][20][21], quinolones (6/9 cases, 66.7%) [16][17][19][20][21][23], and clindamycin (4/9 cases, 44.4%) [13][16][18][20]. All patients were treated with a combination of antibiotics except for one prescribed monotherapy with doxycycline15.

The duration of treatment ranged between 4 and 10 weeks (median of 8 weeks, mean of 9.5 weeks). Eight patients (72.7%) had a favorable outcome, including two who required heart transplantation [13][23], two patients (18.2%) died [14][16], and one was lost to the follow-up [22].

The intrinsic structural characteristics of *M. hominis* render it resistant to the antibiotics usually administered against IE, including macrolides, aminoglycosides, beta-lactams, and cotrimoxazole. The treatment of choice is doxycycline (100 mg/12 h), quinolones (moxifloxacin [400 mg/day], levofloxacin [500 mg/day]), or clindamycin (300 mg/8 h) [12]. The optimal antibiotic regimen for endocarditis by *M. hominis* has not been established, although most authors recommend a single antibiotic therapy cycle of 6–8 weeks alongside valve replacement [13][14][15][16][17][18][19][20][21][22][23]. One patient who received doxycycline for 8 weeks required heart transplantation for acute heart failure due to recurrent perivalvular insufficiency [13].

In conclusion, *M. hominis* is rarely the cause of IE but should be contemplated in cases of BCNIE, especially in individuals with a recent history of cardiac surgery or device implantation. Although the clinical manifestations are non-specific, this entity should be considered in such patients in the presence of fever, clinical bacteremia, and/or signs/symptoms of heart failure not previously experienced. Clinical suspicion is also strengthened by the presence of elevated acute phase reactants (C-reactive protein, procalcitonin, leukocytosis) early after cardiac surgery with no evident focus of infection, especially when blood cultures are negative [19].

A more rapid diagnosis permits the earlier administration of targeted treatment, with doxycycline and quinolones as the drugs of choice. This has important prognostic implications, given the intrinsic resistance of *M. hominis* to the antibiotics habitually prescribed against IE produced by staphylococci and streptococci [14].

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