Septic arthritis caused by *Bacteroides thetaiotaomicron*: A case report and review

Sir,

The septic arthritis is an uncommon infection with an incidence of 4 to 12/100,000 person-years. This complication is characterized by the rapid destruction of the joint with loss of function, because of hematogenous spread or direct inoculation of bacteria into the joint [1]. Septic arthritis of the knee is the most frequent location, with catastrophic sequelae and significant associated morbidity and mortality. Arthroscopic surgery and intra-articular injections represent two associated risk factors [2,3]. Polymicrobial etiology is uncommon, with the presence of coagulase-negative staphylococci (CNS) and *Staphylococcus aureus*, as the main microorganisms involved [4]. In turn, anaerobic bacteria are less common and are related to septic arthritis located in small joints, such as the wrist [5]. Most of the anaerobic microorganisms that cause arthritis are located in the intestinal tract and the origin of the infection is usually by hematogenous spread [6].

We describe the first case of anaerobic septic knee arthritis associated to *Bacteroides thetaiotaomicron* in a patient after arthroscopic surgery and periodic knee infiltrations.

A 33-year-old male patient, who underwent reconstruction of the anterior cruciate ligament (ACL) of his left knee in 2015 in Italy. Since then, he has received hyaluronic acid injections every 6 months until the end of 2019. Since mid-February 2020, he had marked inflammation and recurrent joint effusion, requiring 2 evacuating arthrocentesis per week. On March 25, 2020, he came to our center with a fever and persistent effusion in the joint. A magnetic resonance imaging (MRI) was performed where abundant global synovitis and posterior extra-articular edema were observed. Synovial fluid was obtained for analysis and cultivation by arthrocentesis. The joint fluid analysis showed 41,627 leukocytes/mL, 93.6% neutrophils and without the presence of crystals. No bacterial growth was observed after 5 days of incubation. The patient’s general biochemistry revealed an erythrocyte sedimentation rate (ESR) of 37 mm/h and a C-reactive protein (CRP) of 3 mg/dl. The following day, arthroscopic intervention for debridement and cleaning was decided, and empiric antimicrobial therapy was started with vancomycin 1g/12h and ceftazidime 2g/8h intravenous. Four samples of synovial exudate extracted during the surgical intervention were sent to culture. Two samples were incubated in conventional plate culture, without microbial growth after five days.

Two subcultures were performed for aerobic and anaerobic organisms from a liquid medium and incubated at 35°C in an environment containing 5% CO₂ and anaerobic chamber, respectively. The incubation system was Bact/Alert® (BioMérieux) for five days. in one of the anaerobic samples, the system detected microbial growth after 16 hours of incubation. The anaerobic sample was seeded in medium Schaedler agar (SCS) observing microbial growth, under anaerobic conditions.

*B. thetaiotaomicron* was identified using the matrix-assisted laser desorption ionization time of flight mass spec-

| Antimicrobial         | MIC (mg/L) | Susceptibility |
|-----------------------|------------|----------------|
| Amoxicillin-clavulanic| 0.25       | S              |
| Clindamycin           | >256       | R              |
| Imipenem              | 0.12       | S              |
| Metronidazole         | 0.25       | S              |
| Cefoxitin             | -          | R              |
| Chloramphenicol       | -          | R              |
| Piperacillin-tazobactam| -        | S              |

MIC: minimum inhibitory concentration, R: resistant, S: susceptible
| Year/author | Age/Sex | Underlying condition | Type of infection | Antibiogram of Bacteroides thetaiotaomicron | Antimicrobial treatment | Evolution |
|------------|---------|----------------------|-------------------|---------------------------------------------|-------------------------|-----------|
| 1990 Patey [11] | 51/Female | Surgery for a genital and rectal prolapse 3 months before | Polymicrobial meningitis | - | Thiophenicol and metronidazole | Recovery |
| 1996 Funada [12] | 42/Female | Acute lymphocytic leukemia (neutropenic enterocolitis) | Polymicrobial sepsis | Imipenem | Gentamicin and ceftazidime | Imipenem Exitus (massive GIB) |
| 2003 Matsukawa [13] | 68/Male | Hepatitis C, alcohol abuser with hepatic cirrhosis | Polymicrobial sepsis | - | Imipenem | Clinic improvement |
| 2005 Feuillet [14] | 45/Male | Hearing loss and otorrhea for many years. | Cholesteatoma and meningitis | Amoxicillin-clavulanic, imipenem, metronidazole and clindamycin | Penicillin G, cefotetan and vancomycin | Amoxicillin-clavulanic and metronidazole Negative CSF culture and clinic improvement |
| 2006 Miragliotta [15] | 44/Female | Uterine fibromyoma | Post-surgical infection | Amoxicillin-clavulanic, imipenem, metronidazole and moxifloxacin | Amoxicillin, piperacillin-tazobactam and cefoxitin. | Teicoplanin, imipenem and metronidazole Clinic improvement |
| 2012 Faur [16] | 46/Male | Peritoneal dialysis due to kidney failure secondary to cystic kidney disease | Peritonitis | - | Amikacin, vancomycin and metronidazole oral | Negative peritoneal dialysis fluid culture and clinical improvement |
| 2013 Chao [17] | 86/Male | Peritoneal dialysis | Peritonitis | Chloramphenicol and metronidazole | Clindamycin and penicillin | Metronidazole Recovered completely |
| 2013 Toprak Ülger [18] | 62/Male | Head pancreas adenocarcinoma | Post-surgical bacteremia | Carbenapems and ampicillin-sulbactam | Metronidazole | Ampicillin-sulbactam Clinic improvement |
| 2014 Agarwal [19] | 56/Male | Disseminated multiple myeloma | Posterior spinal wound infection | - | Daptomycin, piperacillin-tazobactam and metronidazole | Cure |
| 2014 Kim [20] | 60/Male | Diabetes mellitus | Polymicrobial myotic aneurism | - | Metronidazole | - |
| 2015 Sadarangani [21] | 43/Male | Sigmoid diverticulitis | Post-surgical intra-abdominal collection | Tigecycline | Clindamycin, piperacillin-tazobactam, ertapenem, meropenem and metronidazole | Tigecycline Clinic improvement |
| 2016 Nkamga [22] | 41/Male | None | Chronic paravertebral muscle abscess | - | Metronidazole | Cure |
| 2019 Kalay [23] | 16/Male | None | Polymicrobial meningitis | - | Metronidazole and meropenem | Negative CSF culture and clinic improvement |
| 2020 Kanaujia [24] | 15/Male | None | Recurrent otitis media | Metronidazole, piperacillin-tazobactam, chloramphenicol and imipenem | Clindamycin and cefoxitin | Metronidazole Clinic improvement and cure |

GIB: gastrointestinal bleeding, CSF: cerebrospinal fluid
trometry system (MALDI-TOF MS, VITEK MS®, BioMérieux). The susceptibility test was performed with the VITEK 2XL® system (BioMérieux). Antibiogram for *B. thetaiotaomicron* is shown in table 1. Antimicrobial treatment was modified to piperacillin-tazobactam 4.5g/8h. After 2 weeks of intravenous antimicrobial treatment, the patient was completely afebrile, with a normalized PCR (0.5 mg/dl) and ESR (18 mm/h), with a flexion of the joint of 110°, without effusion, with moderate residual synovitis, mild bone edema and no intra-articular collections on MRI. Hospital discharge was decided with sequential antimicrobial therapy with metronidazole 500 mg/8h, for 2 weeks. A follow-up MRI was performed in July, showing complete resolution of the synovitis and edema. The patient returns to professional activity in October fully recovered.

Anaerobic etiology in septic arthritis of the native joints is infrequent. Despite everything, cases of knee infection caused by *Bacteroides fragilis* group have been documented [7,8]. To our knowledge, this is the first case septic arthritis with isolation of *B. thetaiotaomicron*. It is an anaerobic, aerotolerant, gram negative, non-sporeulated bacillus that is part of the human commensal flora, present in the gastrointestinal and genitourinary tract [9,10]. *B. thetaiotaomicron* has been described as a pathogen in infections mainly of abdominal origin, postsurgical, meningitis and otitis. It is a very rare anaerobic, all cases reported in the literature are shown in table 2 [11-24]. The presence of concomitant chronic pathologies in more than half of the collected patients may suggest an opportunistic behavior of *B. thetaiotaomicron*. About the susceptibility profile, an increase in antimicrobial resistance has been reported in the *Bacteroides fragilis* group in the last two decades [25]. Clindamycin was classically considered the treatment of choice for infections caused by anaerobes. However, the degree of resistance to clindamycin in a study carried out in 13 European countries with 824 clinical isolates has risen to 28–60% in the *Bacteroides fragilis* group and specifically to 41% in *B. thetaiotaomicron* [26]. Therefore, clindamycin should not be recommended as empirical treatment in infections caused by *B. fragilis* group. In respect of the family of beta-lactams and carbapenems, the emergence of resistance to piperacillin-tazobactam and to a lesser extent to meropenem and imipenem implies the need to routinely identify and perform susceptibility tests on anaerobic bacteria such as *B. fragilis* group for adequate treatment.

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None to declare

**CONFLICTS OF INTEREST**

The authors declare no conflict of interest.

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8. In conclusion, septic knee arthritis is an infectious complication that can lead serious consequences. Our patient being the first described case of anaerobic septic arthritis associated with *B. thetaiotaomicron*. The emerging resistance of *B. thetaiotaomicron* to carbapenems and metronidazole implies the need to routinely identify and perform susceptibility tests on anaerobic bacteria such as *B. fragilis* group for adequate treatment.
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