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

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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/mcl, 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-

Table 1 Antibiogram of *Bacteroides thetaiotaomicron*

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

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Table 2 Literature review of *Bacteroides thetaiotaomicron* cases.

Year/author	Age/Sex	Underlying condition	Type of infection	Antibiogram of <i>Bacteroides thetaiotaomicron</i>		Antimicrobial treatment	Evolution
				Susceptible	Resistant		
1990 Patey [11]	51/Female	Surgery for a genital and rectal prolapse 3 months before	Polymicrobial meningitis		-	Thiopenicol and metronidazole	Recovery
1996 Funada [12]	42/Female	Acute lymphocytic leukemia	Polymicrobial sepsis (neutropenic enterocolitis)	Imipenem	Gentamicin and ceftazidime	Imipenem	Exitus (massive GIB)
2003 Matsukawa [13]	68/Male	Hepatitis C, alcohol abuser whit 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 ceftazidime.	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	Carbapenems 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 mycotic 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 ceftazidime	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-sporulated 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, post-surgical, 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 has also been described [26, 27]. metronidazole, resistance is extremely rare, with only two cases reported in the literature for *B. thetaiotaomicron*. It is associated with the acquisition of *Nim D* genes located on chromosomes or plasmids. Resistance rates in the *B. fragilis* group are less than 1% in studies with multiple clinical isolates [18,21,26]. This reduction in the antimicrobial susceptibility confirms the need to always perform susceptibility tests on isolates of *Bacteroides fragilis* group, since it cannot be assumed that beta-lactams, carbapenems, and metronidazole will always be valid options.

Knee arthroscopy is a common and relatively safe procedure, with an infection rate that varies depending on the series from 0.0009 to 0.4% [28]. Age <50 years, male sex, diabetes, tobacco, complex interventions, and morbid obesity were identified as risk factors related to post-intervention knee infection [29]. Our patient underwent arthroscopic surgery in 2016;

therefore, it seems little to proclaim that his septic arthritis is a direct consequence of the intervention. On the other hand, periodic infiltrations may be the main cause of infection. The association between septic arthritis of the knee and the intra-articular administration of corticosteroids is well demonstrated, whereas the injection of hyaluronic acid has not yet been, even though there are cases described in the literature [3, 30]. The treatment of septic arthritis consists of immobilizing the joint, draining the infected synovial fluid to obtain good control of the infection, and carrying out appropriate antimicrobial treatment with the appropriate duration [31].

In conclusion, septic knee arthritis is an infectious complication that can leave 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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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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