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Periprosthetic joint infection caused by *Haemophilus parainfluenzae*. Case report and literature review

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Sir,

Haemophilus parainfluenzae is a pathogen that has been implicated in a broad spectrum of infectious diseases. It is a small, pleomorphic, Gram-negative coccobacillus with fastidious growth requirements mostly found as a commensal bacterium in human upper respiratory tract and oral cavity [1]. It can also be isolated from other mucosal surfaces such as the gut, urethra and vagina [2]. It often causes respiratory and musculoskeletal infections in immunocompromised patients but is not commonly found in osteoarticular infections [2–5].

Moreover, periprosthetic joint infection (PJI) is a disastrous complication that occurs in 1% to 2% of primary and in 4% of revision arthroplasties. In addition, PJI can complicate up to 20% of revision arthroplasties. Most of these infections are caused by Gram-positive microorganisms, where the *Staphylococcus* genus tops the list, and with *Staphylococcus aureus* and *S. epidermidis* being the leaders [6].

In this clinical case we present an infection of a left total knee prosthesis by this extremely unusual bacterium in an immunocompetent patient caused by this microorganism. This study was approved by the ERC of the institution (reference E0053-21_FJD).

The patient was a 67-year-old man with a personal history of hypertension and diabetes mellitus type 2. He was attended in 2009 because pain and blockages of the left knee joint, which seems to have been resolved after 6 months by treatment with chondrosulphuric acid infiltration. In 2015 he again reported pain in his left knee, and again underwent infiltration without success, so in May 2016 it was decided to perform a cemented total knee arthroplasty.

A year later, in May 2017, he came back again because

of progressive pain, and a possible loosening of the prosthesis was observed on radiographs. C-reactive protein (CRP) was 3 mg/dL and erythrocyte sedimentation rate (ESR) of 42 mm/h in addition to abundant joint effusion. An arthrocentesis for culture and study of the joint fluid was performed. Cell count was 6,280 cells/mm³ (85% polymorphonuclears), with glucose 177.0 mg/dl and CRP 6.84 mg/dl. This sample was inoculated in the following culture media: Tryptic soy sheep blood agar (TSS), chocolate agar (CHA), Shadler-5% sheep blood agar (SCS), MacConkey agar (McC), and part of the fluid was also inoculated in a blood culture bottle (BactAlert), all from Biomérieux Marcy l'Etoile, France). TSS, CHA and McC were incubated at 37°C in a 5% CO₂ atmosphere. SCS was incubated in an anaerobic atmosphere at 37°C. All media were incubated for 15 days.

Following these results, a revision surgery was performed in October 2017. During the surgery, the 9 samples were obtained: 1 from histopathology, and 8 for culture: 4 periprosthetic tissue biopsies, 3 components of the prosthesis and 1 synovial fluid.

Histopathology of the biopsy showed no polymorphonuclear cells; only hyperplasia of synoviocytes was observed together with hyalinized tissue. A one-stage revision, using a rotational hinge was performed (Figure 1).

One month later, the patient came to the emergency room with progressive pain and swelling in the right knee and a fever of 38.8 °C. The X-ray of the right knee showed no loosening and a white blood cell count of 12,000 cells/mL with 83% PMN cells, and a CRP of 1.3 mg/liter. At the same time, it was decided to perform a second arthrocentesis to extract the joint fluid and proceed to its analysis and microbiological culture. This analysis showed a blood fluid count of 35,850 leukocytes/mL (92% polymorphonuclear) and 38,000 red blood cells/mL. In addition, this liquid was inoculated in a blood culture bottle and incubated at 37 °C, being positive after 19.7 hours incubation. A subculture was performed in the usual media for bac-

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Figure 1A



Figure 1B



Figure 1 Knee X-rays: frontal view of the left and right knees (Figure 1A), lateral view of the left knee (Figure 1B).

teria and, after 24 h of incubation, growth of small translucent colonies was observed in the chocolate agar. They were identified as *Haemophilus parainfluenzae* colonies by MALDI-TOF technique (VitekMS, BioMérieux, Marcy l'Etoile, France). Its susceptibility was tested by disc diffusion technique according to EUCAST criteria (*Haemophilus* test medium: $35^{\circ}\text{C} \pm 2^{\circ}\text{C}$ in 5% CO_2 for 16–18 hours), so our microorganism showed susceptibility to ciprofloxacin, chloramphenicol, tetracycline, cefuroxime, amoxicillin-clavulanic acid, ceftriaxone, cotrimoxazole and meropenem, being resistant to ampicillin and clarithromycin. Subsequently, a debridement, antibiotics and implant retention (DAIR) procedure was performed including polyethylene replacement. Several samples were collected for microbiological culture: joint fluid, polyethylene and 5 tissue samples.

All tissue samples were inoculated in TSS, CHA, SCS, McC and Sabouraud chloramphenicol agar slants (SC). The joint fluid was inoculated in TSS, CHA, McC and SCS. Polyethylene sample was sonicated according to the previously described protocol [7]. All media were incubated for 15 days.

After 2 days of incubation, small colonies were detected in 2 of 5 tissue samples and the joint fluid. Finally, *H. parainfluenzae* was identified again with the same antibiotic susceptibility. The patient was treated with ceftriaxone 2 g/24 h and ciprofloxacin 400 mg/12 h intravenously for 7 days and then was switched to ciprofloxacin 500 mg/12 h and cotrimoxazole

800/160 mg/8 h orally for a total of 6 months. The patient gradually improved, with a decrease in CRP in blood tests (1.55 mg/dl 1 month after surgery) and the other inflammatory markers, in addition to and improvement in his mobility. Finally, the patient was considered cured after 3 years of follow-up.

This microorganism is part of the normal microbiota of the mouth and upper respiratory tract, and it can be responsible for a broad spectrum of serious infections such as endocarditis, bacteremia, and pneumonia [8]. However, PJI due to *H. parainfluenzae* is an extremely rare entity, with only 4 case patients reported in the medical literature, 3 of them occurred after procedures in the oral cavity (Table 1) [2–5].

In most cases, *H. parainfluenzae* infection is usually preceded by an invasive procedure, including those in the oral cavity [1,3–5,8]. In our case, the age of our patient (67 years) is very close to the average age of the cases already published in the literature (76 years) [9]. He also has a history of diagnosed diabetes mellitus type II hypertension, a septoplasty performed in 2006 and a radical prostatectomy performed in 2012. A few months before the first left total knee replacement, he also underwent a successful shoulder operation.

The source of our patient's infection is unclear, but we can contemplate the possibility that it was this shoulder surgery the patient underwent due to the proximity between this extremity and the respiratory tract. In addition, like other cases

Table 1 Cases of prosthetic *H. parainfluenzae* infection reported in the literature

	Age/sex	Prosthetic joint	Comorbidities	Positive samples	Surgical intervention	Therapy	Length of therapy	Outcome
Present case	67 / M	TKP	Type 2 DM Hypertension Shoulder operation Left knee arthroplasty	Joint fluid Two periprosthetic tissue	DAIR. Replacement of polyethylene.	Ceftriaxone 2 g/24 h and ciprofloxacin 400 mg/12 h IV (7 days) → oral ciprofloxacin 500 mg/12 h and oral cotrimoxazole 800/160 mg/8 h	6 months	Cure
Jellicoe et al. [3]	78 / F	THP	Arthroplasty complication Dental extraction	Joint fluid	Two-stage replacement	After washout: Gentamicin beads and cement spacer Flucloxacillin/ ampicillin (500/500 mg)	10 months	Cure
Manian et al. [4]	72 / M	TKP	Root-canal procedure	Joint drainage	Surgery refused	Oral cephalixin (6 months) → IV ceftriaxone (2 months) → oral ciprofloxacin	> 2 years	Chronic infection
Pravda et al. [5]	78 / F	TKP	Arthroplasty complication Root-canal procedure	Joint fluid	Arthroscopic irrigation and debridement	IV ampicillin (1 month) → oral amoxicillin (2 months)	3 months	Cure
Bailey et al. [2]	75 / M	TKP	Chronic lymphoid leukemia Arthroplasty complication	Joint fluid One peripros- thetic tissue	two-stage replacement	Only flucloxacillin and rifampicin (6 weeks) without success (before surgery) → cement spacer with 1g of gentamicin and 2g of vancomycin (after first stage) → 3 dosis of oral cefuroxime (750 mg)	No reported	Cure

DAIR: Debridement, antibiotics, and implant retention; DM: Diabetes mellitus; F: female, IV: intravenous, M: male; THP: total hip prosthesis; TKP: total knee prosthesis.

published in the literature with an extended asymptomatic period between surgery and the onset of symptoms, it establishes the hematogenous route as the most likely cause of infection. [3,4,10–12].

Antibiotic resistance in this organism is more diverse and widespread than is commonly appreciated. It may show resistance to penicillins such as ampicillin and amoxicillin, including amoxicillin-clavulanic acid and some cephalosporins due to the presence of beta-lactamases. They remain in most cases susceptible to carbapenems and quinolones, while the rate of resistance to clarithromycin in Spain exceeds 22.5% [9,13,14]. In our case, *H. parainfluenzae* was resistant to clarithromycin and ampicillin, remaining susceptible to the other antibiotics tested. Our patient was successfully cured after intravenous treatment with a cephalosporin followed by de-escalation to oral cotrimoxazole and ciprofloxacin for 6 months. In most of

the cases described this is the time and treatment indicated, but it can be as long as 2 years [4,14,15].

In summary, despite the high prevalence of *H. parainfluenzae* in the normal oral microbiota, its low pathogenic power makes it a very rare microorganism in this pathology. To our knowledge, only 4 cases of PJI with this bacterium have been reported. In addition, most PJI are due to Gram-positive microorganisms such as coagulase-negative *staphylococci* and *S. aureus*, as well as some Gram-negative bacilli, such as *Escherichia coli*, while *H. parainfluenzae* is a very rare microorganism. Therefore, correct and early microbiological diagnosis is essential for a good outcome of these infections.

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CONFLICT OF INTEREST

Authors declare have no conflict of interest

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