CASE REPORT
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Periprosthetic Hip Joint Infection with *Flavonifractor plautii*: A Literature Review and Case Report

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The purpose of this case report and review of the literature is to provide documentation on periprosthetic hip joint infection with *Flavonifractor plautii* (formerly known as *Eubacterium plautii*), a strictly anaerobic bacterium, and to report on a successful pathway for management including staged surgical revisions and extended antibiotic therapy. A systematic review of the literature was conducted, which identified this case as only the fifth documented case of human infection with this organism; as a result, conduct of further research is warranted, based on the paucity of reports in the literature addressing anaerobic periprosthetic joint infection.

Key Words: Hip joint, Prosthesis-related infections, Anaerobic bacteria, Clostridium, Total hip arthroplasty

A low incidence of periprosthetic joint infection (PJI) after elective primary total hip replacement, 2%, has been reported[1,2]. PJI with the onset of clinical features >12 months post-implantation most commonly occurs as a result of haematogenous seeding to the joint. The rates of PJI may be higher for metal on metal bearing implants; however, the responsible organisms are similar[3,4]. The majority of infective organisms are gram-positive organisms, such as *Staphylococcus aureus* and *Staphylococcus epidermidis*[5]. The reported incidence of atypical anaerobic PJI is higher in hip arthroplasty compared with knee arthroplasty[6] and is increasing[7].

Anaerobic bacteria have been implicated in only 3-6% of PJI cases[8]. Of these, isolation of *Cutibacterium acnes*, which represents the majority, commonly occurs 3-12 months post-implantation from direct inoculation at the time of surgery. The literature includes only a few reports addressing management of PJI with *Clostridia* species, which is closely related to *Flavonifractor plautii*, and publications are limited to only case reports[9-18]. *F. plautii* (formerly known as *Eubacterium plautii* or *Fusobacterium plautii*) is a strictly anaerobic, non-spore forming, non-motile, rod-shaped bacterium; understanding of its biological and pathologic properties is limited[19]. Regarding genomic sequencing, the organism shares a 99% similarity to *Clostridium orbiscindens*[20]. To the best of our knowledge, we report on the first documented case of PJI with this organism and the only reported study of human infection in an immunocompetent individual. The purpose of this case report and review of the lit-

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erature is to provide documentation of PJI with this rare pathogen and to report on a successful pathway for management including staged surgical revisions and extended antibiotic therapy.

CASE REPORT

Our patient was a 62-year-old male non-smoker who presented to the emergency department with a complaint of worsening pain in the left groin and subjective fevers for approximately four weeks. His second dose of the ChAdOx1 nCoV-19 (Oxford–AstraZeneca) vaccine was administered two weeks prior to presentation and he experienced one episode of diarrhoea 10 days prior to presentation. He had no recent history of taking antibiotics.

The patient had undergone a total replacement of the left hip 15 years prior for treatment of arthrosis secondary to hip dysplasia. Until this current episode, no complication had been reported in association with the implant except for minor asymptomatic osteolysis secondary to metal-on-metal wear. His medical history included hypertension and paroxysmal atrial fibrillation for which he took rivaroxaban. He was admitted to a hospital six years prior with diarrhoea, haematochezia, and *Bacteroides vulgatus* bacteremia, which was treated successfully with antibiotics. No significant gastrointestinal abnormality was observed by inpatient gastroscopy and colonoscopy performed at that time and the patient made a full recovery. The patient had no additional medical history and no risk factors for immunocompromise.

Upon arrival in the emergency department, the patient was afebrile and mild tachycardia was detected with a heart rate of 100-110 bpm in atrial fibrillation and he was hypotensive with a blood pressure of 80/40 mmHg. His respiratory rate was 19 breaths per minute and his S_pO_2 was 99% on room air. The left hip joint showed irritability to passive movements. Findings from cardiovascular, gastrointestinal, and respiratory examinations were otherwise unremarkable.

The results of blood analysis indicated elevated levels of inflammatory markers (Fig. 1). The levels of blood metal ion were normal. The pelvic x-ray showed no new changes to the prosthesis, which showed longstanding, unchanged features of femoral osteolysis secondary to metal wear (Fig. 2). Aspiration of the hip performed in the emergency department yielded 20 mL of haemoserous fluid, returning 250,200 white blood cell count (WBC)/μL; gram-negative and positive bacilli were detected on microscopy (Fig. 3).

The patient was started on empirical intravenous antibiotic therapy (cefazolin) and transferred to the intensive care unit for further resuscitation. On day 2, light growth of tiny, grey, translucent colonies was isolated on an anaerobic agar plate inoculated with the joint aspirate (Fig. 4).

On day 4, these colonies were identified as *F. plautii* by matrix-assisted laser desorption/ionisation-time-of-flight mass spectroscopy (MALDI-TOF MS, MALDI Biotyper®; Bruker, Billerica, MA, USA) with a confidence score of 1.96. Growth of the same organism was observed in a peripheral blood culture anaerobic bottle. According to recommenda-

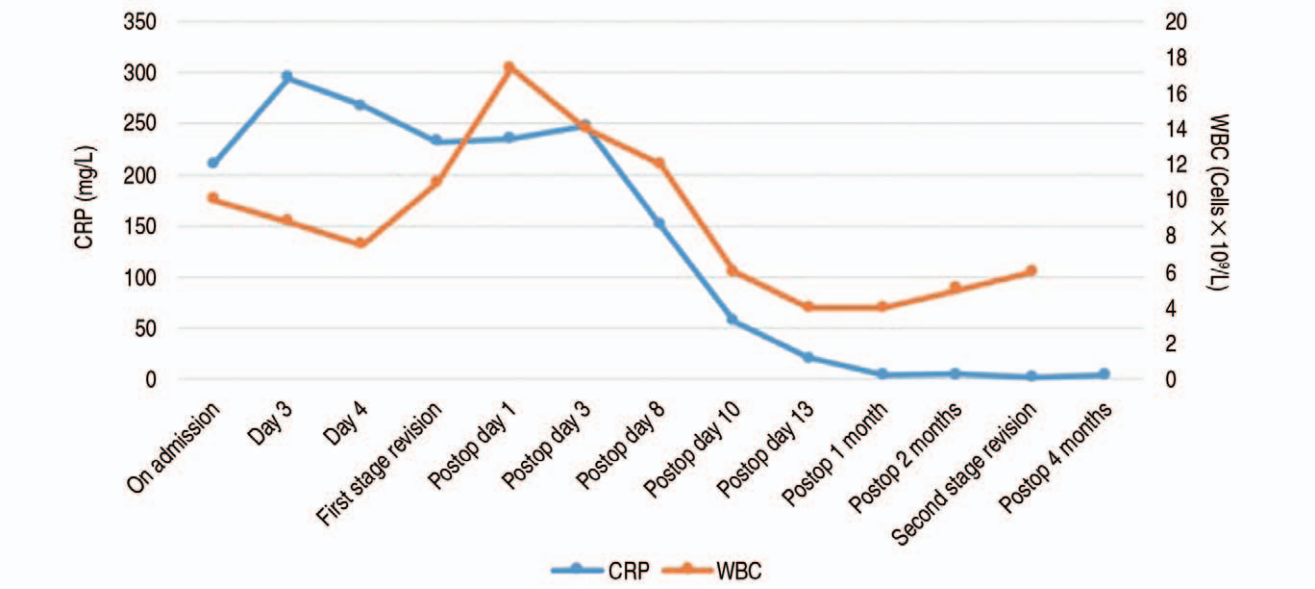

Fig. 1. Serum inflammatory markers during admission. C-reactive protein (CRP) (mg/L) on left y-axis (blue line); white blood cell count (WBC) (cells × 10^9/L) on right y-axis (orange line). Postop: postoperative.

tion by the infectious disease team, the antibiotic regimen was changed to include amoxycillin-clavulanate, gentamicin, metronidazole, and vancomycin. Antibiotic susceptibility was determined on day 4 and therapy was adjusted accordingly (Table 1).

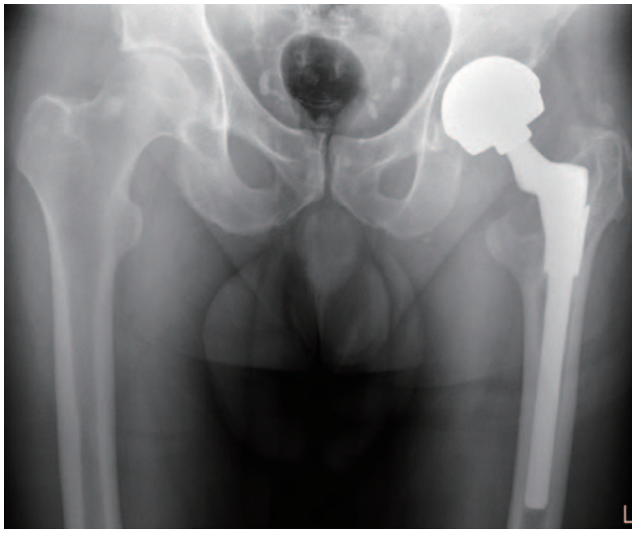

Fig. 2. Anteroposterior pelvis x-ray at time of acute presentation with hip pain and sepsis. S-ROM femoral components (DePuy Orthopaedics, Warsaw, IN, USA) with metal on metal bearing. The proximal femoral erosion around the lesser trochanter was longstanding and unchanged in size over many years.

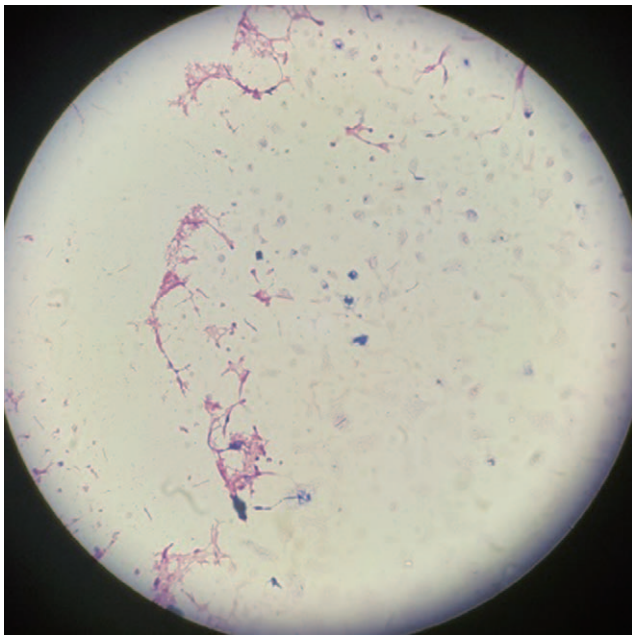

Fig. 3. Gram-positive and negative bacilli on gram stain microscopy (20× magnification) of left hip joint synovial fluid aspirate.

Surgical intervention was delayed due to limited access to operating theatres during the coronavirus disease 2019 (COVID-19) pandemic, thus, the patient underwent medical stabilisation in the intensive care unit. On day 7, the patient underwent a first-stage revision hip arthroplasty. Exploration of the hip was performed using the posterior approach, resulting in detection of extensive abscess formation and destruction of soft tissue deep to the fascia. No gross evidence of metalosis was observed. No loosening of the stem was observed and the use of a fine oscillating saw around the implant/bone interface was required in order to facilitate its removal. Good fixation of the acetabular component was observed and use of the Explant® acetabular cup removal system (Zimmer Biomet, Warsaw, IN, USA) was required. Debridement of extensive erosion of pericapsular soft tissue was performed. Pulse lavage and intermittent irrigation with hydrogen peroxide were performed for irrigation of the field with 6 L of normal saline. Reaming of the canal was performed using a 14 mm flexible reamer, followed by thorough washing with a canal brush. Extraction of all hardware was followed by implantation of an antibiotic cement articulating spacer containing a mixture of gentamycin and vancomycin (Fig. 5). No organisms were isolated on culture from intraoperative specimens or subsequent postoperative blood cultures.

A thickened ascending colon was observed on a postoperative computed tomography of the abdomen, and a sub-

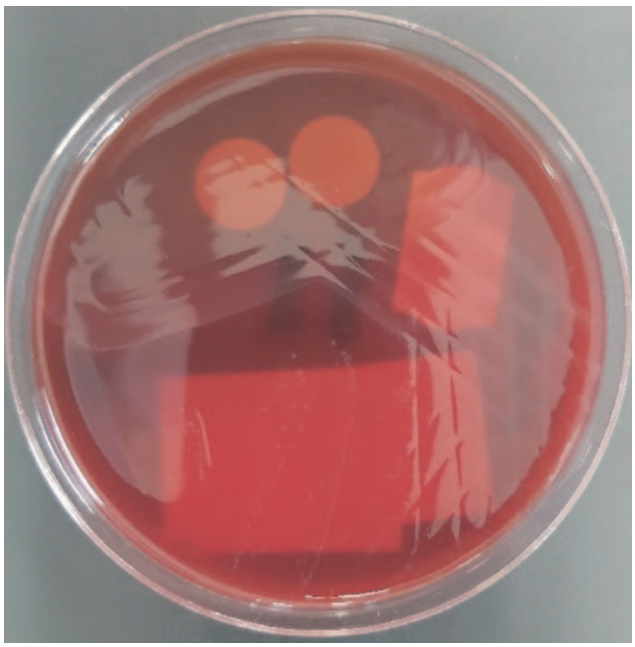

Fig. 4. *Flavonifractor plautii* colonies isolated on anaerobic blood agar.

sequent colonoscopic biopsy showed a single sigmoid tubular polyp and diverticular disease. Conservative management was administered. Findings from a chest x-ray, uranalysis, and cardiac echocardiogram performed during admission were normal.

The patient received 24-hour intravenous administration of ceftriaxone 2 g for six weeks via a central line followed by oral amoxicillin/clavulanic acid and metronidazole for six weeks. Normalisation of the C-reactive protein occurred during this period (Fig. 1). After completion of oral antibiotics, a further aspiration of the hip was performed, which yielded 832 WBC/μL, 20% polymorphonuclear cells and negative cultures after incubation for two weeks.

Second stage revision arthroplasty was performed three months after the first stage. A posterior approach was used for exposure of the hip. Extraction of the antibiotic cement and all spacer implants was performed. No macroscopic evidence of infection or bone necrosis was observed. Multiple swabs and tissue cultures sent from both acetabular and femoral sites showed no growth on extended culture. Administration of routine intraoperative surgical antibiotic prophylaxis was subsequently performed (cefazolin and vancomycin). Preparation of acetabular and femoral sides was performed with implantation of uncemented components (Fig. 6). The patient was discharged on day 7 and his recovery was uncomplicated. At 12-month follow-up the patient remains in good health without ongoing infective issues. He remains off antibiotics. Normal, pain free gait with near normal hip range of movement has been observed by physical examination.

Table 1. Antibiotic Susceptibility Testing of the *Flavonifractor plautii* Blood Culture Isolate Performed via Gradient Diffusion*

Antibiotics	Susceptibility	MIC (mg/L)
Amoxicillin-clavulanate	Sensitive	0.125
Ceftriaxone	Sensitive	0.38
Clindamycin	Sensitive	0.38
Metronidazole	Sensitive	0.016
Moxifloxacin	Sensitive	0.38
Penicillin	Intermediate	0.38
Vancomycin	Resistant	3

MIC: minimum inhibitory concentration.
* Etest®; bioMérieux, Marcy-l'Étoile, France.

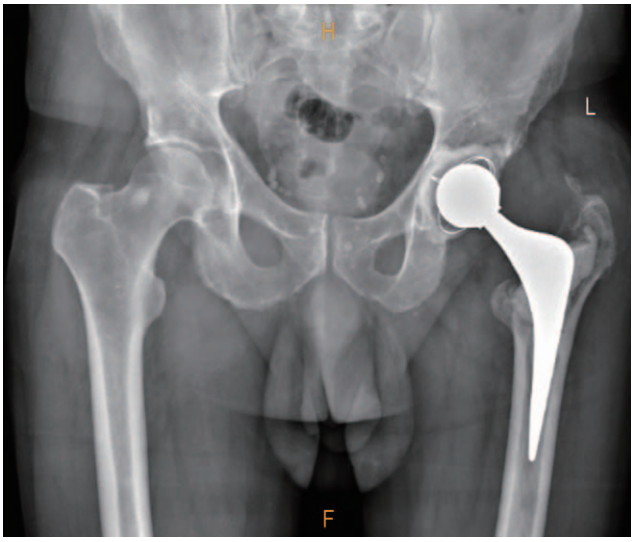

Fig. 5. X-ray pelvis after first stage revision with antibiotic cemented articulating spacer.

DISCUSSION

A PubMed search for the terms: '*Flavonifractor plautii*' OR '*Eubacterium plautii*' was conducted, resulting in identification of 51 articles; all abstracts were read. Abstracts that failed to provide a discussion of either organism in the context of pathological human infection were excluded (Fig. 7). Discussion of human infection with either organism was included in four abstracts[21-24] (Table 2). After these papers were read, data extraction was performed, including patient age, sex, concurrent pathology, immunosuppression, time to culture, and culture technique.

The results of our systematic search of the literature indi-

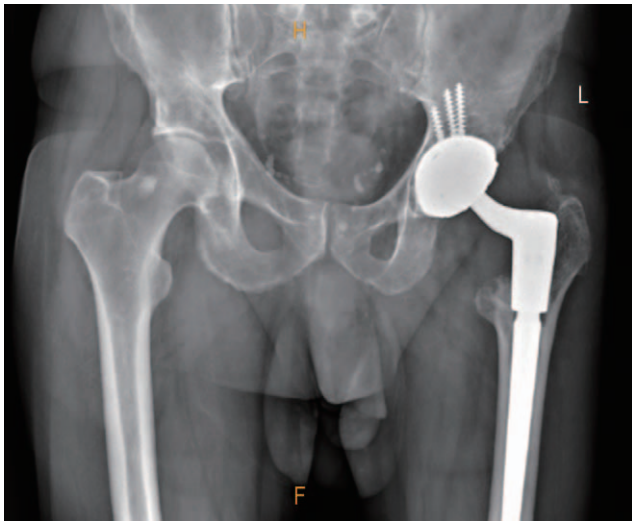

Fig. 6. Anteroposterior pelvis x-ray at 1-year follow-up. The definitive implants include Stryker Trident® Tritanium® shell with 3 screws, Restoration® MDM® X3® polyethelene insert, Restoration® Modular Hip System femoral components, Biolox® delta 28 mm ceramic head.

cated that most studies of *F. plautii* have been in relation to its role in the gut microbiome[25,26] with potential associations with colorectal cancer[27], altered immune function[28], and inflammatory bowel disease[29]. In all four documented cases, human infection occurred in the setting of immunosuppression and diagnosis was delayed. The slow growth rate of the bacterium, the requirement for use of enriched media, and the need for strictly anaerobic incubation complicate identification of *F. plautii*. Identification is further complicated by its inconsistent appearance with use of conventional gram staining processes[30]. Accurate identification of the organism as gram-positive on initial staining was reported in only one previous study[21].

Identification of anaerobic bacteria, including *C. acnes*, occurs more frequently in hip PJI than in knee PJI[8]. In general, there is a paucity of evidence for use in guiding diagnosis and management of anaerobic PJI, and the revised criteria established by the Musculoskeletal Infection Society (MSIS) limit discussion to *C. acnes* only[31]. Clostridium PJI is most frequently observed in the setting of polymicrobial infection, usually in patients who have a history of gastrointestinal disease[32]. Isolation of *C. difficile* has been reported in protheses of the hip[12,14], knee[15], and shoulder[9]. PJI with this organism can be catastrophic; amputation was reported in two of the five recorded cases[33].

We believe that gut translocation and haematogenous seeding to the prosthesis following a recent diarrhoeal illness in our patient was the most plausible mechanism of infection. Although the patient's history of previous diarrhoeal illness and *B. vulgatus* bacteremia was suspicious, extensive investigation for assessment of intestinal pathology showed no troublesome findings. Recent administration of the ChAdOx1 nCoV-19 (Oxford–AstraZeneca) vaccine may have been a factor in development of his newly diagnosed diarrheal illness; one large study reported that the incidence of this side effect was 2.2%[34].

Selection of our strategy of administering high-dose intravenous antibiotics and performing 2-stage revision arthroplasty, which was based on the apparent infection chronicity (~4 weeks), adhered to accepted practice for management of established PJI[35]. Ideally, the first operative intervention should have been performed prior to day 7 and sam-

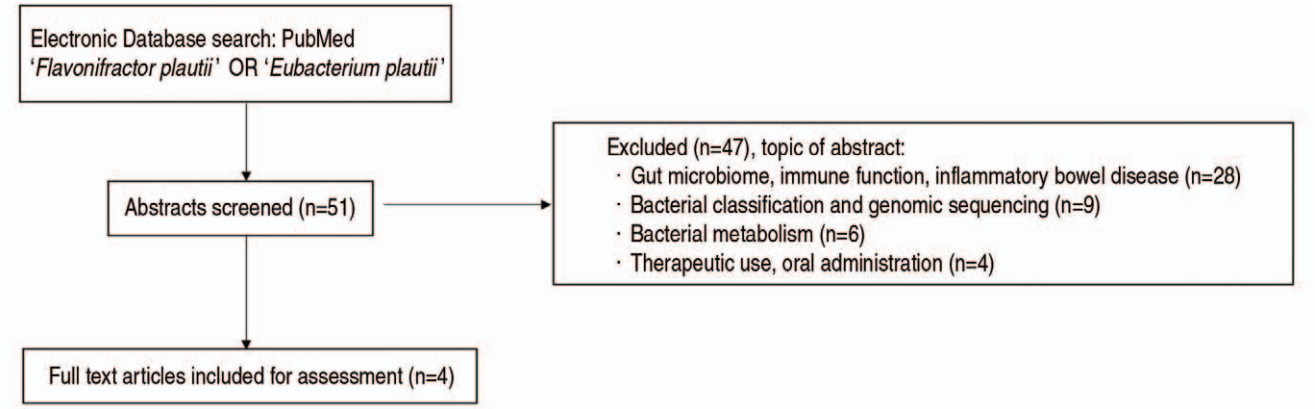

Fig. 7. Flow chart for the literature review.

Table 2. Summary of Previously Documented Human Infections with *Flavonifractor plautii*

Study	Age (yr)/sex	Pathology	Immuno-suppression	Site (s) cultured	Time to culture	Gram stain
Garre et al.[23] (1991)	45/M	Dog bite	Asplenic	Blood CSF	After patient discharged	Negative
Orlando et al.[24] (2008)	33/M	Laparotomy for perforated ileum	Renal transplant graft rejection	Blood Pleural fluid	Day 4	Irregular
Berger et al.[21] (2018)	69/M	Necrotising cholecystitis	Chemotherapy	Blood	Day 4	Positive
Costescu et al.[22] (2022)	45/M	Severe burns	Burns	Blood	Day 3	Negative

M: male.

pling of intraoperative tissue should have been performed prior to the start of antibiotic therapy; however, access to operating theatres was limited by the impact of the COVID-19 pandemic and urgent antibiotic therapy was required for treatment of the patient's clinically septic condition. This was likely the reason that subsequent intraoperative specimens remained culture negative. Accurate diagnosis may be compromised by administration of preoperative antibiotics, which has been implicated in cases of culture negative PJI[36-38]. Nonetheless, the patient fulfilled the definition for PJI that was established by the 2018 validated International Consensus Meeting (ICM), and elevated serum and synovial markers met the minor criteria for diagnosis[31].

Sampling of multiple hip aspirate cultures was also performed prior to the second stage for augmentation of the standard PJI protocol. Catastrophic outcomes related to antibiotic resistance and high virulence of organisms have been reported in multiple case reports of clostridium PJI; therefore, these negative cultures were obtained in order to ensure confidence in the eradication of the atypical organism[10,15].

This study describes only a single patient infected with a rare organism, thus, it is limited in its utility for use in guiding the management of anaerobic PJI. With increasing rates of arthroplasty and PJI, conduct of further research for stratification of patient risk and for better understanding of the implications of atypical anaerobic infections will be required.

The case described in this report highlights a successful pathway for management of treatment for atypical anaerobic PJI and the results of a review of the literature confirmed the organism as novel. The pathway included staged surgical revisions with explantation of the prosthesis and use of a temporary antimicrobial-impregnated cement spacer. Effective eradication of the organism was achieved by administration of extended therapy with ceftriaxone, amoxicillin/clavulanic acid, and metronidazole. Secondary definitive arthroplasty was performed safely following fine needle aspiration in order to confirm eradication of the organism.

CONFLICT OF INTEREST

The authors declare that there is no potential conflict of interest relevant to this article.

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