Prosthetic Hip Infection Caused by *Tropheryma whippiei*[▽]

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We report a case of prosthetic hip infection due to *Tropheryma whippiei* in a 74-year-old man not previously known to have Whipple's disease. Diagnosis was based on systematic 16S rRNA gene amplification and sequencing of samples obtained during revision hip arthroplasty.

CASE REPORT

A 74-year-old retired man was admitted to the Orthopedic Surgery Department (Hôpital Ambroise Paré, Boulogne-Billancourt, France) in June 2006 with suspected prosthetic joint infection (PJI), pain, and local signs of inflammation of the left hip. This patient had undergone total left hip replacement at our hospital 3 years earlier and had shown no signs of prosthesis dysfunction since surgery.

This patient had undergone multiple surgical interventions for bilateral hip dysplasia (varisation osteotomy [left hip] in 1977, partial hip replacement [left hip] in 1982, total hip replacement [right hip in 1982 and left hip in 1992 and 2002], replacement of right hip prosthesis due to fracture in 1997 and 2002, and replacement of left hip prosthesis due to loosening in 2003). The patient was diagnosed with severe chondropathy of the right knee in 1994, and the internal meniscus was removed by arthroscopy. In 2001, corticosteroid treatment was initiated for an intermittent, seronegative joint disease involving the knees, ankles, and wrists. The patient displayed only partial improvement and was still receiving corticosteroids (prednisone, 15 mg/day) at the time of admission in June 2006. The patient had suffered from demyelinating polyneuropathy since 1994, confirmed by electromyography and thought to be related to chronic alcoholism.

On the day of his admission, the patient underwent a short surgical intervention for left hip joint puncture. The joint fluid was cloudy, and microscopy after Gram staining showed many polymorphonuclear neutrophils but no bacteria. Cultures on solid and liquid media remained negative. The laboratory parameters were as follows: C-reactive protein concentration, 25 mg/liter; hemoglobin concentration, 10 g/dl; white blood cell count, 7.9×10^9 /liter (polymorphonuclear neutrophil count, 6.52×10^9 /liter); and no antinuclear antibodies detected. The left hip prosthesis was replaced in a single step in late June. Five perioperative specimens were taken and sent for microbiological examination. Gram staining showed white blood cells, which were rare to numerous, depending on the sample,

but no bacteria. All cultures remained sterile after 10 days of incubation on solid media and 15 days in liquid media.

We then checked for the presence of bacterial DNA in the five perioperative samples. PCR was carried out, using AmpliTaq Gold polymerase (Applied Biosystems, Courtaboeuf, France) to amplify the 16S rRNA gene, with the 91E (5'-TC AAA(G/T)GAATTGACGGGGGC-3') and 13BS (5'-GCCC GGGAACGTATTTCAC-3') primers (13); the beta-globin gene (268 bp) was amplified as a control (7). A 16S rRNA gene fragment of the expected size (470 bp) was amplified from all five specimens, together with the beta-globin gene. Dideoxy sequencing of the amplified 16S rRNA gene fragments was carried out on both strands with a BigDye Terminator cycle sequencing kit (Applied Biosystems, Courtaboeuf, France), using the same primers as for amplification. Sequencing products were purified by gel filtration, using Bio-gel P100 (Bio-Rad, Marnes-la-Coquette, France), and run on a 3700 DNA analyzer (Applied Biosystems). Similarity searches (GenBank database) showed the amplified sequences to be 100% identical to the 16S rRNA gene sequence from the *Tropheryma whippiei* reference strain (12).

Clinical examination of the patient revealed no other signs of Whipple's disease. Duodenal biopsy samples were taken for histological examination and molecular detection of *T. whippiei*. Duodenal sections were examined under a light microscope and were found to contain normal tissue, without infiltration, with periodic acid Schiff (PAS)-positive macrophages. Molecular tests for *T. whippiei* gave negative results for duodenal, saliva, and serum samples (Didier Raoult, Unité des Rickettsies, Marseille, France). Lumbar puncture yielded clear cerebrospinal fluid containing no cells, but with slightly high protein levels (0.69 g/liter; normal values, 0.10 to 0.45 g/liter). Stored histological samples obtained during surgery on the right hip in 1997 were reanalyzed and found to contain PAS-positive mononuclear cells. However, *T. whippiei* DNA was not amplified (positive beta-globin gene control) from these samples in PCR, carried out after paraffin removal.

Trimethoprim-sulfamethoxazole (160 mg and 800 mg, twice daily) treatment was initiated in July 2006 and maintained until April 2007. Polyarthritides completely resolved following antibiotic therapy, and corticosteroid therapy was discontinued in April 2007. At the time of the patient's last examination, in August 2007, the patient showed no sign of left hip prosthesis

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dysfunction and no further signs of chronic joint disease. However, his polyneuropathy remained unchanged.

Discussion. Whipple's disease is a rare systemic infectious disorder that preferentially affects middle-aged white men and is caused by *Tropheryma whippelii*, a slow-growing, facultative intracellular bacterium (11, 13). The main symptoms of the disease are weight loss, arthralgia, diarrhea, and abdominal pain. Joint involvement is common, but only one case of PJI due to *T. whippelii* has been described (6). This reported case was that of a 58-year-old woman with known Whipple's disease who presented with isolated knee PJI 2 years after the end of a 20-month course of treatment with trimethoprim-sulfamethoxazole. *T. whippelii* knee infection was demonstrated by specific molecular detection from joint fluid and was cured by restarting antibiotic treatment for *T. whippelii* infection (6).

We report here a second case of PJI caused by *T. whippelii*—the first shown to involve a hip prosthesis—in a patient free of gastrointestinal symptoms and not diagnosed before the molecular detection of *T. whippelii* in his hip.

To our knowledge, this is the first reported case of PJI due to *T. whippelii* presenting as an apparently primary infection in a patient not previously diagnosed with Whipple's disease. Diagnosis was particularly difficult in this case due to the patient's extensive history of surgery, with multiple interventions for both hips and symptoms centered on an apparently banal PJI which we expected to be due to staphylococci. Our laboratory has a policy of routinely carrying out universal PCR, by amplifying the 16S rRNA gene, in all cases of culture-negative PJI, and it was this procedure that eventually led to diagnosis. Several teams have reported their experience with the use of universal PCR for the molecular diagnosis of PJI (2, 5). For the time being, we feel that this approach should be reserved, as in our case, for cases of surgically demonstrated PJI for which perioperative cultures remain negative.

Whipple's disease is a systemic disease affecting multiple organs, including the intestine, joints, central nervous system, eyes, heart, and lungs (3, 14). The most suggestive signs are weight loss and diarrhea. However, in many cases, as here, the disease begins insidiously with arthropathy, without clinical or histological signs of gastrointestinal involvement, and with no evidence of weight loss. Several cases of isolated Whipple's arthritis (i.e., with no other organs or tissues affected) have been reported since the introduction of molecular methods for the diagnosis of infectious diseases caused by fastidious organisms (4). This confirms that joints may be affected specifically, in the absence of any other apparent sign of the disease.

Retrospectively, we were able to link the chronic polyarthritis of our patient to Whipple's disease. Antibiotic treatment had a spectacular effect on polyarthritis in this patient, whereas corticosteroid treatment for a number of years had been unsuccessful. By contrast, the patient's polyneuropathy was unaffected by antibiotic treatment, consistent with the idea that this disease is not specifically due to *T. whippelii*, particularly as the neurological manifestations of Whipple's disease are essentially central or affect the cranial nerves (8). It is possible that the long-term treatment of our patient with corticosteroids favored colonization of the prosthesis by *T. whippelii* or

the development of this bacterium within the joint. Immunosuppressive therapy for Whipple's arthropathy has been associated with the early appearance of gastrointestinal manifestations, suggesting that this treatment may increase the replication of *T. whippelii* (9). Corticosteroids may thus have increased the bacterial load of *T. whippelii* in our patient.

PCR-based detection of *T. whippelii* DNA has been shown to be more sensitive than PAS staining and is currently the fastest and simplest way to diagnose Whipple's disease (4). *T. whippelii* can now be cultured on cells or on an axenic medium (1, 11), making it possible to isolate this bacterium from blood, duodenum and muscle biopsy samples, cardiac valves, synovial fluid and tissue, cerebrospinal fluid, lymph nodes, aqueous humor, and stools (3, 10). This approach has also made it possible to determine the antibiotic susceptibility of *T. whippelii* under controlled conditions (1). Nevertheless, *T. whippelii* can be cultured in specialized laboratories only and remains difficult to detect, as it grows slowly and there is a risk of false-negative cultures due to prior antibiotic administration.

This report emphasizes the utility of applying universal PCR for the diagnosis and treatment of culture-negative infections. It also suggests that "orthopedic" manifestations of Whipple's disease may be underestimated in aged patients.

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