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Letter to the editor

Prosthetic joint infection with pseudo-tumoral aspect due to *Mycobacterium bovis* infection after Bacillus-Calmette-Guerin therapy

Dear Editor

We report here a rare and particular case of hip arthroplasty infection due to *Mycobacterium bovis* with an initial pseudo-tumor aspect after Bacillus-Calmette-Guerin (BCG) therapy in a context of bladder cancer. This type of infection is infrequent, but clinicians should be aware of the diagnosis because of serious functional consequences.

A 70-year-old man was referred to our rheumatology department in September 2015 because of total functional disability of the left lower limb. In 2003, he had undergone un-cemented left total hip arthroplasty with a metal-on-polyethylene femoral head to treat osteoarthritis. Up to September 2014, he had not complained about his hip. Bladder papillary urothelial carcinoma had been treated with BCG from April to May 2013, without transurethral bladder resection. Since then, the cancer was considered in remission. The patient had also undergone radiofrequency ablation of hepatocellular carcinoma, with success.

Activity-related pain in the lower limp had progressively intensified since September 2014. First, the patient had to use a wheelchair, and then he could not move his leg and had to stay in bed. He had no fever, weight loss, night sweats or other constitutional symptoms. Medical examination revealed an isolated, painless, supra-centimetric mass in the inguinal fold. Laboratory tests showed only elevated C-reactive protein level (40 mg/L, normally 0–5 mg/L). Initial radiography revealed a large trochanteric bone defect and a medial femoral cortex osteolysis with a loosening of the prosthesis hardware (Fig. 1). CT scan revealed an abnormal, large, rounded, clearly outlined mass of 7×9 cm between the acetabulum and the femoral neurovascular bundle (Fig. 2). Ultrasound-guided puncture of the mass yielded a haematic and purulent material. Aerobic and anaerobic bacterial cultures were negative. Histology revealed classical chronic inflammation with no worn-out prosthetic bodies. On day 14 of specific mycobacterial culture, a BCG *M. bovis* strain appeared.

The treatment was an association of 4 antibiotics, namely rifampicin, ethambutol, moxifloxacin and isoniazid. Then, encephalopathy developed, due to moxifloxacin, which was stopped after only 30 days of treatment. Two months later, radiography revealed external femoral cortex osteolysis at the tip of the femoral implant (Fig. 3). Surgical excision of the mass resulted in complete pain disappearance. The patient was under the antibiotic treatment for 1 year, with total hip arthroplasty replacement after 6 months of treatment (Fig. 4). During the surgery, a femoral fracture occurred and osteosynthesis was performed. The procedure consisted of removing the prosthetic implants with excision of all clinically suspect tissues, followed by extensive washing with antiseptic and physiologic serum with a high-pressure washer. After implantation of the new arthroplasty, the same washing procedure was performed before suturing. Intraoperative bacteriological and mycobacterial cultures were negative and histology did not reveal any inflammatory cells or neutrophils.

Loosening of total joint replacement is a frequent complication, particularly after total hip arthroplasty (2% to 14% after a 20-year follow-up) [1]. Polyethylene wear-induced osteolysis is the most well known aseptic etiology and is sometimes associated with a soft-tissue mass corresponding to a granuloma [2]. However, septic osteolysis should always be looked for, and with a pseudo-tumoral mass, neoplasia should be eliminated.

Tuberculosis vaccine, an attenuated strain of *M. bovis*, discovered by Calmette and Guerin, has been used for treatment since 1921 [3]. Because of its immune-modulating effect, it is the most effective intravesical immunotherapy for superficial urothelial bladder carcinoma. Most patients experience irritating voiding, such as urinary urgency, dysuria, urinary frequency and occasionally hematuria. Flu-like symptoms may occur, including low-grade fever and malaise for less than 24 to 48 hr after instillation, and are resolved with symptomatic treatment. Osteoarticular complications are rare and could result from the implantation of living bacteria in the bladder or from a strong immune response with reactive arthritis in 0.5% to 1% of patients [4]. No effective method is available to prevent BCG toxicity [5]. However, it is recommended not to start the instillations within the first 14 days after resection for bladder cancer or when there is still macroscopic

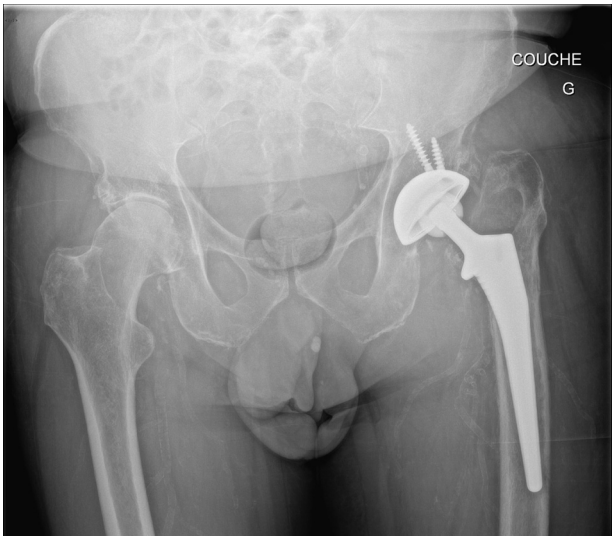

Fig. 1. September 2015 radiography of the pelvis of a 70-year-old man who had undergone total hip arthroplasty in 2003, showing trochanteric bone defect and medial femoral cortex osteolysis with a loosening of prosthesis hardware.

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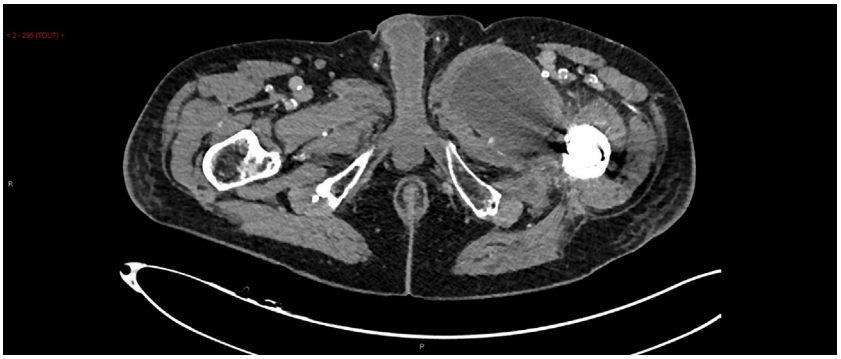

Fig. 2. CT scan showing a pseudo-tumoral aspect of a large mass in contact with the left pelvic muscles.

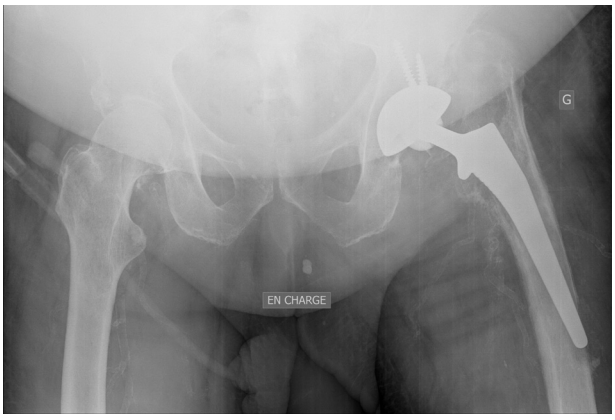

Fig. 3. Radiography of the pelvis 2 months later showing a worsening of the loosening with an external femoral cortex osteolysis at the tip of the femoral implant.

hematuria because of a theoretical risk of hematogen contamination. Only 8 cases of prosthetic infections due to *M. bovis* have been reported (6 after total hip arthroplasty and 2 after total knee arthroplasty) [6–13].

We have no predictive factor to help identify patients at risk for BCG infection [14]. Most patients present sub-acute or chronic joint pain, so the diagnosis is difficult and delayed, particularly because symptoms are not acute and BCG complications can occur soon or long after treatment. Indeed, BCG bacillus can persist in the urinary tract for half a month after treatment [15]. Only 2 published cases did not lead to removal of the prosthesis; these patients received treatment for at least 1 year [8,11].

For our case, 1-stage arthroplasty exchange seemed to be the most appropriate strategy. The patient's general condition had greatly improved with rehabilitation and allowed for proposing surgery. Because the patient had many comorbidities, 1-stage surgery seemed preferable, especially since it was a difficult surgical procedure. In the literature, 3 patients had undergone 2-stage arthroplasty replacement (one patient died due to an underlying condition), 2 patients had undergone 1-stage arthroplasty replacement and 2 others debridement, antibiotics and prosthesis conservation [6–13]. For our patient, the risk of osteolysis prevented the conservation solution. All patients received antibiotics for 1 year with a long pre-surgical period to substantially reduce bacterial inoculum.

With lack of guidelines for this type of infection, different therapeutics are possible, but the final decision regarding surgical management and antibiotics must respect the patient's health and occur after expert consultation. We consulted the French National Council of Reference for Mycobacteria at every step of the management.

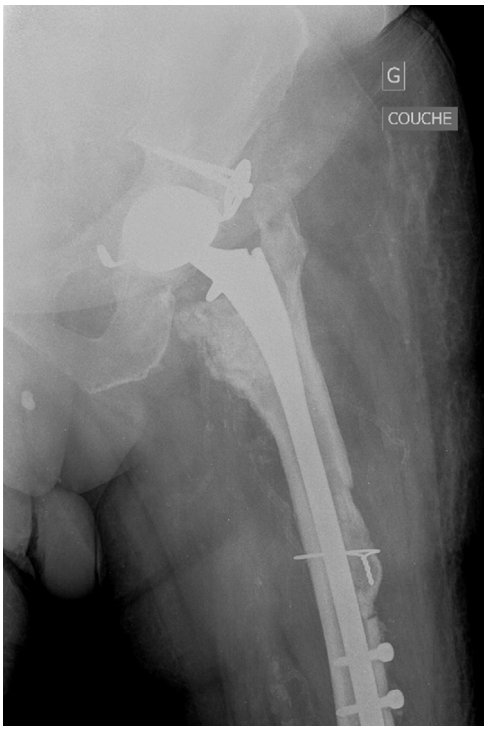

Fig. 4. Radiography of the hip after prosthesis replacement.

In our case, the pseudo-tumoral aspect associated with the loosening of the total hip arthroplasty was tricky. Its aspect showed many similarities with polyethylene wear-induced osteolysis with classical inflammatory granuloma. Considering the medical history of the patient, peri-prosthetic malignancy was also suspected. Acid-fast staining, cultures, and PCR testing are generally often negative, so a needle biopsy of the mass was crucial for our patient. In our university hospital, we systematically perform mycobacterial cultures for every articular puncture to avoid misdiagnosis in case of chronic infection. This point is specific to our referral center for osteoarticular infections and is justified by the fact that more than 10% of extra-pulmonary tuberculosis infections concern bone and joints [16]. All mycobacterial samples are cultured for 42 days [17]. A regimen of antituberculous drugs was essential along with removal of the mass. The need for prolonged therapy shows the difficulty in treating this type of infection. Pyrazinamide could not be used because of the intrinsic resistance of *M. bovis* [18]. Recommendations for antimicrobial therapy include at least isoniazid, ethambutol and rifampicin. Despite no guidelines for *M. bovis* treatment, moxifloxacin is well absorbed orally and highly active

against it [19]. Thus, we added moxifloxacin to obtain a 4-drug regimen and increase the chance of success of the treatment.

Peri-prosthetic infection due to *M. bovis* is clearly a very rare complication of BCG therapy, but clinicians should be able to evoke this diagnosis when confronted with peri-prosthetic pseudo-tumoral lesions after BCG instillation, especially with the high risk of serious articular destruction.

Disclosure of interest

The authors declare that they have no competing interest.

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