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Mycobacterium abscessus as a causative agent of periprosthetic infection

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Abstract

Introduction *Mycobacterium abscessus* species belongs to the group of non-tuberculosis mycobacteria responsible for chronic infections in people with weakened immunity. *M. abscessus* exist in various ecological niches and are able to colonize artificial surfaces, including medical and surgical instruments/devices. Due to the low incidence of *M. abscessus* as a causative agent of orthopedic infection, a rare clinical case of periprosthetic infection caused by *M. abscessus* would interest practitioners. **The aim** is to present a clinical case of periprosthetic infection caused by *M. abscessus*. **Materials and methods** From the medical records and discharge documents, it was known that female patient X. underwent total hip replacement at her residence hospital. Signs of acute infection of the postoperative wound appeared in the early postoperative period. **Results** Three months later, the patient was hospitalized in a specialized institution with a diagnosis of chronic deep periprosthetic infection. During the examination, the mycobacterial etiology of the process was established. During two hospitalizations, the patient underwent 4 consecutive revision surgeries (including muscle plastic surgery and installation of an antimicrobial spacer) and massive parenteral antibiotic therapy for 8 months, including at the outpatient stage, using at least 3 antibacterial agents. After 4 years, the patient does not complain of the infectious process. Postoperative scar is 45 cm. The residual shortening of the right lower limb of 3 cm was compensated by orthopedic shoes. **Discussion** Treatment of infection caused by M. abscessus is challenging due to the natural resistance of the pathogen to a wide range of antibacterial drugs. The literature describes separate cases of orthopedic infections caused by this pathogen. All authors agree that the key to successful treatment is a combination of radical surgical debridement and antibacterial therapy using at least three antimicrobial drugs. **Conclusion** A rare clinical case of periprosthetic infection caused by *Mycobacterium abscessus* after primary hip replacement is presented. This infectious agent is a rare pathogen, for which there is no proven therapeutic algorithm. Long-term aggressive antibiotic therapy in combination with stage-by-stage surgical treatment was successful.

Keywords: orthopedic infection, periprosthetic infection, non-tuberculosis mycobacteria, *Mycobacterium abscessus*, antibacterial therapy

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INTRODUCTION

The species *Mycobacterium abscessus* belongs to the group of non-tuberculous mycobacteria (NTMB) responsible for chronic infections in immunocompromised individuals or cystic fibrosis and includes 3 subspecies: *M. abscessus subsp. abscessus*, *M. abscessus subsp. bolletti* and *M. abscessus subsp. massiliense* [1]. Although *M. abscessus* has traditionally been regarded as an opportunistic pathogen, recent studies show the evolution of the pathogenic potential of *M. abscessus*. The ability of this species to cause the development of pathological processes is due to a significant set of virulence factors, including two groups of factors (mycobacterial and non-mycobacterial), which ensure the interaction of *M. abscessus* with the macroorganism [2].

M. abscessus exist in various ecological niches [1] and are able to colonize artificial surfaces, fomites, medical and surgical instruments/devices [3]. *M. abscessus* can affect the skin, soft tissues, bones, joints, lymph nodes, internal organs [4] and form characteristic granulomas, evading phagosomal defense mechanisms, inducing the production of inflammatory cytokines and recruiting B- and T-lymphocytes to the site of infection [5]. Tendon sheaths, joints, and bones can become infected as a result of various injuries, surgical interventions, invasive procedures, or deep skin puncture [3, 5]. In addition, risk factors for *M. abscessus* infection include prior surgery with implants, use of immunosuppressants, hematologic malignancies, and end-stage renal insufficiency [6].

Only a few confirmed cases of orthopaedic infection caused by *M. abscessus* have been published in the current scientific literature [3]. Due to the low incidence of *M. abscessus* as the causative agent of orthopaedic infection, a rare clinical case of periprosthetic infection caused by *M. abscessus* would be of undoubted interest to practicing physicians (orthopaedic surgeons, traumatologists, infectious disease specialists, therapists). The case to be presented further features complexity and long duration of antibiotic therapy aimed at arresting the infectious process.

Purpose: to present successful management of a clinical case of periprosthetic infection caused by *M. abscessus*.

MATERIALS AND METHODS

From the medical records and discharge documents, it was known that patient H., born in 1957, (180 cm, 68 kg) suffered bilateral idiopathic coxarthrosis in stage 3 and underwent hip replacement in June 2018 at her residence hospital: total cementless arthroplasty of the left hip joint (HJ). The postoperative period was uneventful. In October of the same year, the patient underwent total cementless arthroplasty of the right hip joint in the same hospital. Signs of acute infection of the postoperative wound were detected in the early postoperative period. Signs of inflammation were stopped with conservative measures; the patient was discharged for outpatient treatment.

Three weeks after total arthroplasty of the right hip joint, edema, redness of the area around the postoperative scars of the right thigh developed, and a fistula with abundant purulent hemorrhagic discharge opened. The patient was recommended hospitalization at a purulent surgical department with a diagnosis of phlegmon of the right thigh. In November 2018, debridement was performed, revision of the phlegmon of the right thigh. Bacteriological study of the contents did not reveal any pathogen. During hospitalization she received systemic antibiotic therapy: vancomycin, moxifloxacin, linezolid. At the time of discharge, there was an improvement in the condition, a decrease in the amount of discharge and a change of its nature in serous one. The patient was recommended to contact a specialized institution for further surgical treatment.

This work used clinical, laboratory, instrumental diagnostic methods. The patient signed an informed voluntary consent upon admission to use the results of treatment for educational and scientific purposes.

RESULTS

In mid-January 2019, the patient was hospitalized at the federal medical center. Diagnosis at admission: deep chronic periprosthetic infection of the right HJ, exacerbation, fistulous form (Fig. 1 a). Locally on admission: a granulating wound sized 2 × 3 cm in the upper third of the postoperative scar and two sinuses distal to the scar. The diagnosis was confirmed by fistulography (Fig. 1 b). Concomitant pathology: arterial hypertension in stage 2, risk of cardiovascular complications 3, chronic superficial gastroduodenitis, gastroesophageal reflux disease. She had a history of appendectomy, and three caesarean sections.

Laboratory tests revealed signs of an infectious process: WBC – 8.3 × 10^9/l (toxicogenic granularity of neutrophils ++), ESR – 120 mm/h, CRP – 81 mg/l, hypochromic anemia: Hgb – 74 g/l, RBC – 3.06 × 10^{12}/l, serum iron 3.7 μmol/l. In the dressing room, two tissue biopsies were taken through the fistulous tract from the depth of the wound. To prepare her for surgery, anemia and protein deficiency were corrected.

On January 16, 2019, radical debridement was performed with the installation of a block-shaped spacer (Fig. 2 a) impregnated with vancomycin (10 wt %). Signs of acute cellulitis, a 10 cm fascia defect, fasciitis, myositis, infection pockets posterior and anterior to the femur were revealed intra-operatively. During the removal of the femoral component, a femoral fracture occurred which required osteosynthesis with a cerclage wire. The wound was washed with antiseptic solutions in a volume of 6 liters. The operation was completed by draining the wound according to Redon.

From the day of the surgery, the patient received standard, accepted at the center, empirical antibiotic therapy with vancomycin and cefoperazone/sulbactam (Fig. 3). Having received the preliminary results of the microbiological study of the preoperative material on the 2nd day that detected the growth of *Fusobacterium varium*, the antibacterial drugs were changed to amikacin and levofloxacin. On the fifth day after the operation, the final results of the study were obtained: a pan-resistant strain of *M. abscessus* was isolated from the preoperative material (Table 1). Clarithromycin was added to antibiotic therapy. However, abundant wetting of the dressing with wound discharge was observed and remained significant by post-operative day 7.

The growth of *M. abscessus* was also detected in the intra-operative tissue biopsies and endoprosthesis components on the 12th day after the operation. Moreover, the growth of an unverified strain of *Staphylococcus* sp.

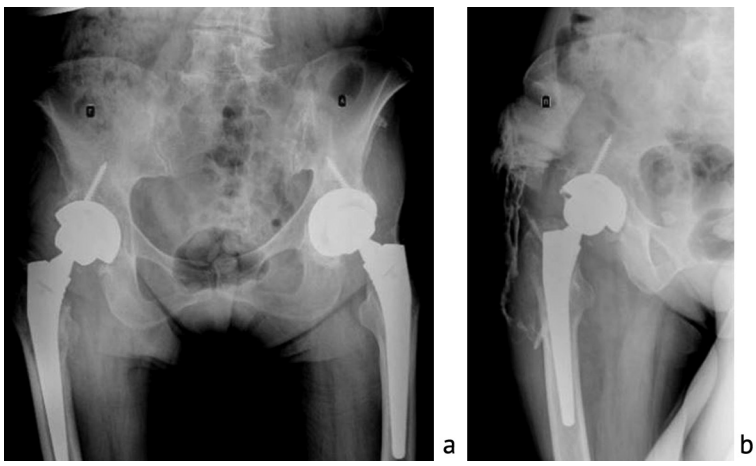

Fig. 1 X-rays of the pelvis upon admission to the federal medical center: *a* X-ray of the pelvis; *b* fistulography of the right hip joint, the spread of a contrast agent into the joint cavity

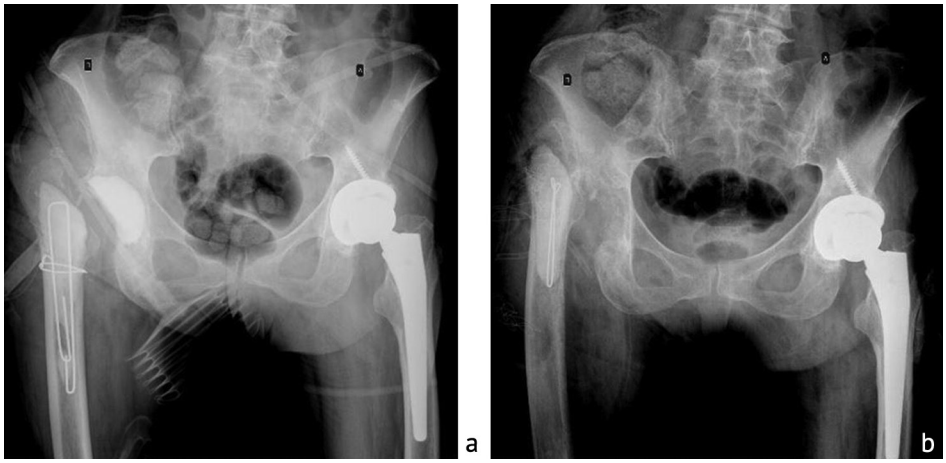

Fig. 2 X-rays of the pelvis after debridement with the installation of an antimicrobial spacer: *a* X-ray after installation of the first spacer into the right hip joint; *b* X-ray after installation of the second spacer into the right HJ

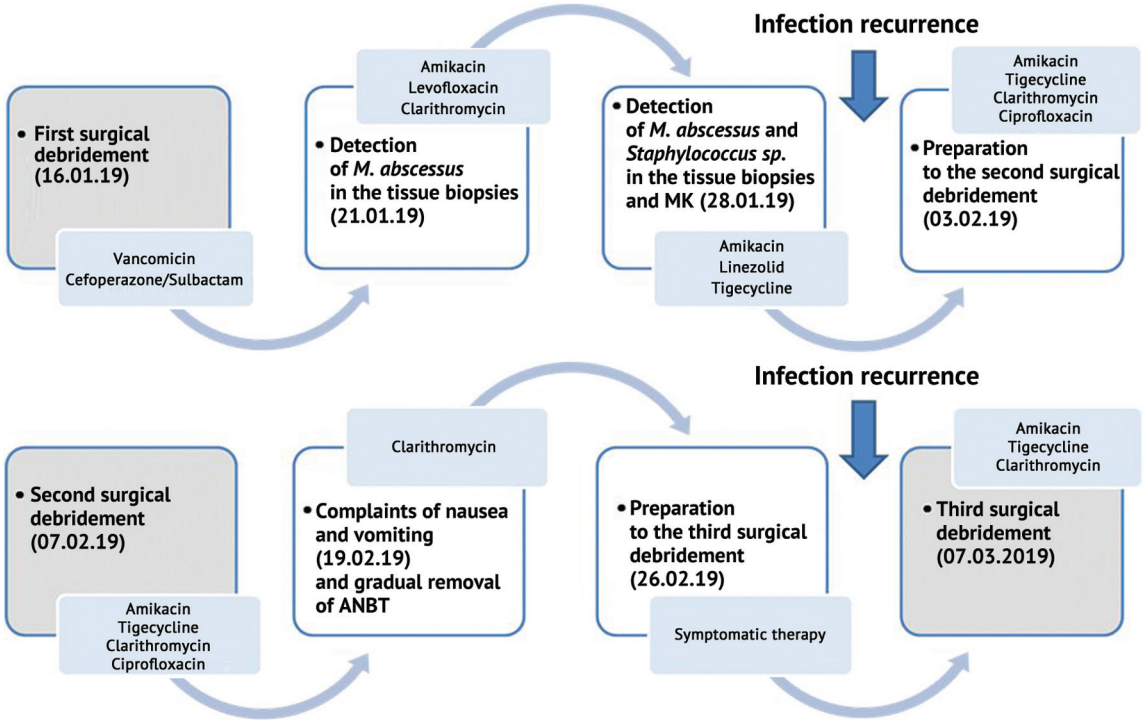

Fig. 3 Correction of the antibacterial therapy during the first hospitalization

Table 1

Sensitivity of the detected *M. abscessus* strain to antibacterial preparations

Mycobacterium abscessus		
Antibioticogram	Sensitivity	МПК
Amoxicillin/Clavulanic Acid	R	> 64/32
Doxycycline	R	> 16
Imipenem	R	> 64
Clarithromycin	R	> 64
Linezolid	R	> 64
Minocycline	R	> 8
Moxifloxacin	R	> 8
Tigecycline	–	4
Tobramycin	R	> 16
Trimethoprim/sulfamethoxazole	R	> 8/152
Cefepime	R	> 3
Cefoxitin	R	> 128
Ceftriaxone	R	> 64
Ciprofloxacin	R	> 16

MSC – minimal suppressive concentration, mg/l.

Due to negative clinical and laboratory dynamics, sutures were removed from the entire depth of the wound, and AB therapy was corrected for amikacin, linezolid, and tigecycline. On the 15th day after the first operation, it was decided to perform a second operation. Due to the final verification of the etiology of the infection caused by *M. abscessus*, the patient was examined by a tuberculosis surgeon. According to his conclusion, the patient was not epidemically dangerous and did not require isolation. It was recommended to continue massive combined antibiotic therapy after repeated sanitation (Fig. 4). On the 19th day after the operation, in order to prepare for surgery and considering the resistance of the isolated strain of *M. abscessus* to all tested antibiotics and the absence of growth of *Staphylococcus* sp., linezolid was discontinued but amikacin, tigecycline were continued, and clarithromycin and ciprofloxacin were additionally prescribed.

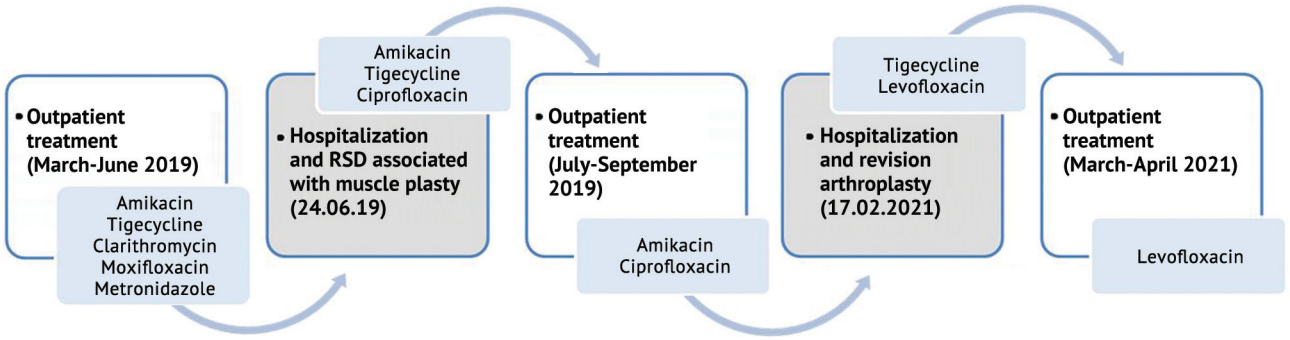

Fig. 4 Correction of antibacterial therapy in the second hospitalization

On February 7, 2019 (day 21 after the first operation), a repeated radical surgical debridement of the infection focus was performed with the reinstallation of a block-shaped antimicrobial spacer impregnated with amikacin (10 wt %) (Fig. 3 b). During the operation, an acute infectious process involving the fascia and muscles was revealed. Before installing a new spacer, the wound was treated with a pulsating stream of saline with the addition of amikacin (2.0 g per 500 ml) with a cavitation effect using the Sonoca 300 apparatus (Söring, Germany). Due to the acute course of the recurrent infectious process, sutures were placed on the fascia and skin.

In the postoperative period, in addition to antibacterial therapy a symptomatic therapy was prescribed: pain relief, correction of anemia and protein deficiency, and vitamin therapy. For the purpose of local ABT, a solution of 0.5 % dioxidine 20 ml was injected through the placed drains once for 5 days. The postoperative wound healed by secondary intention.

On the 12th day after the second operation, the patient began to experience nausea and vomiting associated with the administration of antibiotics. Therefore, antiemetics were prescribed and the number of antibiotics was reduced. First, amikacin and ciprofloxacin were canceled, however, complaints of nausea and vomiting persisted; after three days clarithromycin was canceled, and then tigecycline. The patient was no longer bothered by nausea and vomiting. However, due to the discontinuation of AB therapy, a second recurrence of infection developed and wound dehiscence. On February 26, 2019 (19th day after the second operation), a decision was made to perform a third sanitizing operation. Preparations for surgical intervention were: correction of anemia and protein deficiency. Taking into account previous complaints of AB therapy, amikacin, tigecycline, clarithromycin were prescribed from the day of surgical treatment.

On March 7, 2019, the third sanitizing operation was performed (Fig. 5 a) with repeated reinstallation of the block-shaped antimicrobial spacer, additionally impregnated with meropenem (10 wt %). The postoperative wound was sutured with the formation of a fistula. In the postoperative period, the wound healed throughout, except for the fistula in the lower corner. On March 21, 2019, the patient was discharged for outpatient treatment with a recommendation to continue systemic antibiotic therapy at an outpatient hospital at the place of her residence (Fig. 4).

In the period from March 26, 2019 to June 18, 2019, the patient was on conservative treatment at her residence hospital and received amikacin, tigecycline, moxifloxacin, clarithromycin, metronidazole. Throughout the course of ABT, laboratory monitoring was carried out in order to identify adverse drug reactions. From the moment of discharge and until admission to the federal medical center, she received moxifloxacin, metronidazole, clarithromycin.

On June 24, 2019, the patient was re-admitted to the department of purulent surgery for staged surgical treatment. Diagnosis at admission: chronic recurrent deep periprosthetic infection of the right hip joint, exacerbation, fistulous form; chronic osteomyelitis of the right femur and pelvis, 4 (B), l, exacerbation. Locally on examination: postoperative scar 20 cm in the area of the right hip joint, a functioning fistula in the lower corner with profuse serous purulent discharge.

The laboratory tests were: WBC – 5.4 × 10^9/l, ESR – 48 mm/hour, CRP – 5.1 mg/l, and hypochromic anemia was diagnosed: Hgb – 107 g/l, RBC – 3.42 × 10^{12}/l.

On June 26, 2019, a full-scale operation was performed: radical debridement, removal of the spacer, and replacement of the defect with a non-free muscle flap from the vastus lateralis muscle (LTM) (Fig. 5 b). From the day of surgery, the patient was transferred to parenteral ABT: amikacin, tigecycline, ciprofloxacin.

The wound healed by primary intention, the drains were removed on the 5th day after surgery. In the postoperative period, symptomatic therapy was performed. The growth of microorganisms from intra-operative tissue biopsies and the removed implant was not detected. Antibacterial therapy was continued 14 days post-surgery. On the 15th day after surgery, the patient was discharged for outpatient treatment with a recommendation to continue ABT for 8 weeks with the following drugs: amikacin, ciprofloxacin.

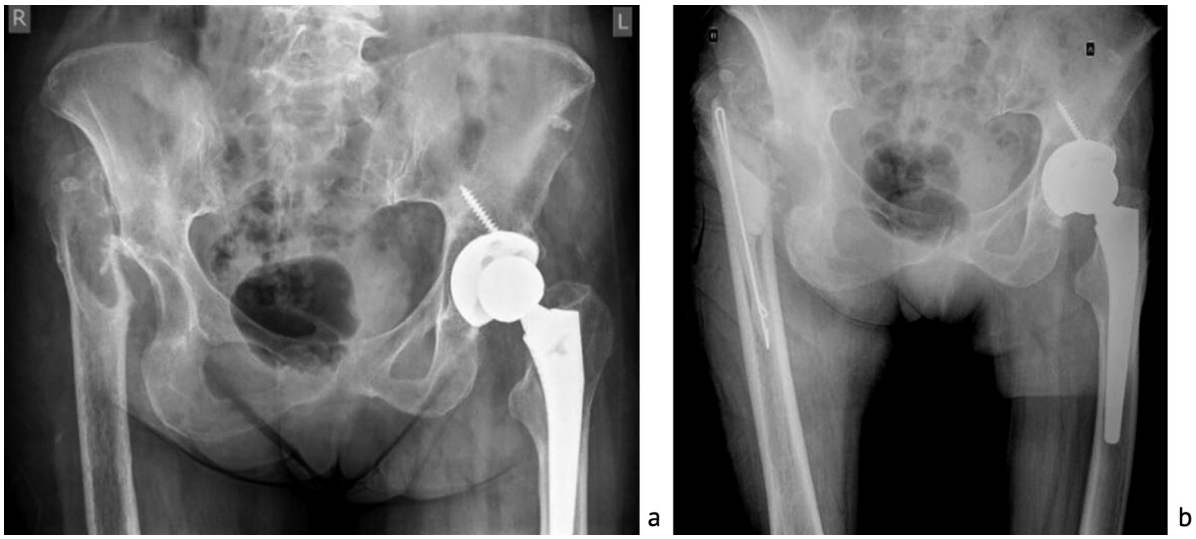

Fig. 5 X-ray of the pelvis after repeated sanitation: *a* X-ray of the pelvis after installation of the third spacer of the right hip joint; *b* X-ray of the pelvis after non-free muscle plasty with vastus lateralis muscle

A year later (17.02.2021), the patient was admitted for revision arthroplasty with a diagnosis of chronic recurrent deep periprosthetic infection of the right hip joint in remission; chronic osteomyelitis of the right femur and pelvic bone, 4 (B), l, remission. No microbial growth was detected in the aspirate from the right hip joint. Status localis: postoperative scar 45 cm in the area of the right thigh without signs of acute inflammation. Shortening of the right lower limb = 5 cm. There were no laboratory signs of exacerbation of the infectious process: WBC – 5.1 × 10^9/l, ESR – 11 mm/hour, CRP – 1.13 mg/l.

Revision arthroplasty of the right hip joint was performed using a cementless fixation of the implant (Zimmer Biomet, USA) (Fig. 6). The postoperative wound healed by primary intention. From the day of surgery, the patient received systemic antibiotics: tigecycline, levofloxacin. On the 7th day, the results of intra-operative cultures were obtained; growth of MSSE was detected in 1 of 5 biopsies. ABT continued 14 days after surgery. At the outpatient stage, the patient was recommended to continue taking levofloxacin 0.5 g twice a day for 1 month.

Being consulted distantly in February 2023, the patient did not complain of the infectious process. The postoperative scar was 45 cm and regular. The residual shortening of the right lower limb of 3 cm was compensated with orthopedic shoes. Laboratory parameters are within normal limits: WBC – 4.09 × 10^9/l, ESR – 15 mm/hour, CRP – 4.9 mg/l, as well as Hgb – 138 g/l, RBC – 4.20 × 1012/l. Checking radiographs show a stable implant components in the right hip joint (Fig. 7).

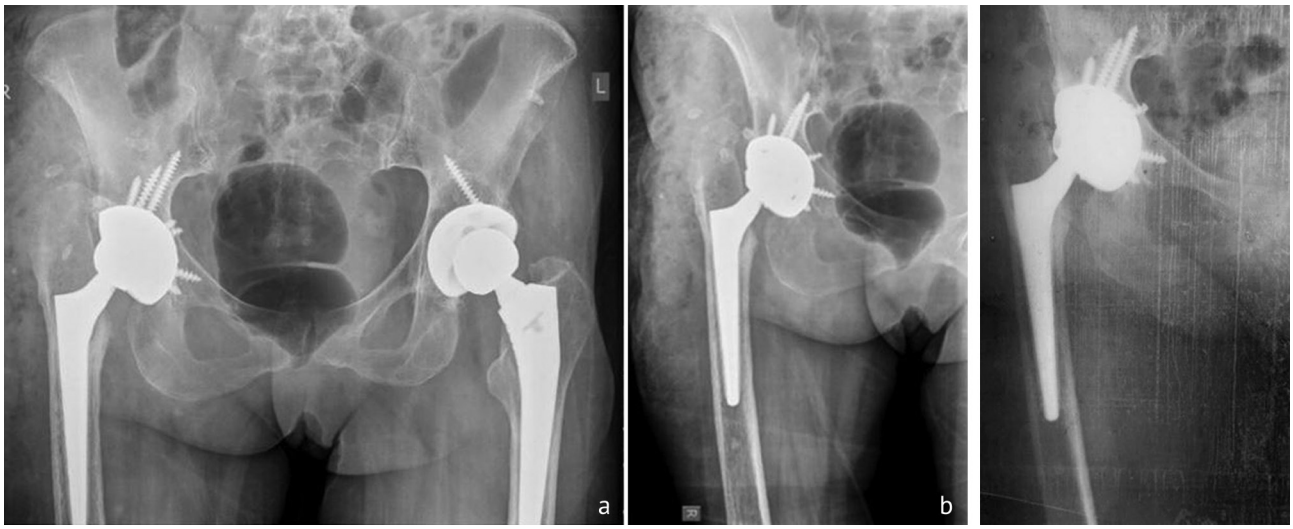

Fig. 6 X-ray of the pelvis after revision arthroplasty of the right hip joint: *a* plain X-ray of the pelvis; *b* X-ray of the right hip joint

Fig. 7 X-ray of the right hip joint at 2-year follow-up

DISCUSSION

Treatment of infection caused by *M. abscessus* is challenging due to the natural resistance of the pathogen to a wide range of antibacterial drugs. As a rule, it is necessary to prescribe at least three antibiotics active against the pathogen [7].

Cases of periprosthetic infection caused by *M. abscessus* are described in the world literature as case reports. One of them was an elderly 78-year old patient who developed an acute bilateral infection 5 weeks after bilateral knee arthroplasty [8]. A course of empirical anti-tuberculosis therapy (rifampicin, isoniazid, pyrazinamide and ethambutol), as well as joint debridement with replacement of modular components, did not lead to success. After the first relapse, bilateral installation of antimicrobial spacers was performed. To treat the second recurrence, arthrodesis of the right knee joint was performed using the Ilizarov apparatus and two-stage revision arthroplasty of the left knee joint using a combination of rifabutin, clarithromycin and amikacin. One-and-a half year treatment and 7 operations resulted in the arrest of the infectious process caused by *M. abscessus*.

There is a known case of multiorgan *M. abscessus* involvement in a patient with chronic back pain with a nodular lesion of the right leg, without fever, chills, rash, shortness of breath or cough. Laboratory data showed moderate leukocytosis. A computed tomography scan of the chest revealed bilateral cavitation nodules. Skin biopsies, sputum, and blood cultures revealed *M. abscessus*, and treatment with meropenem, tigecycline, and amikacin was prescribed. The patient was readmitted to the hospital due to worsened low back pain. Magnetic resonance imaging of the lumbar spine revealed destructive changes in L4 and L5 vertebral bodies and osteomyelitis. Blood culture and bone biopsy again detected *M. abscessus*. An echocardiogram was performed due to persistent bacteremia, which revealed large vegetations on the tricuspid valve and small vegetations on the mitral valve. Therapy was changed to a course of amikacin with cefoxitin for 8 weeks and imipenem for twelve months [9]. In addition, a nosocomial outbreak of septic arthritis caused by NTM following corticosteroid injections has been described [10]. The authors note that clinicians should be aware that mycobacterial infections, including *M. abscessus*, are one of the differential diagnoses in patients with subacute arthritis and soft tissue infection [6]. Despite long-term combined antibiotic therapy, treatment of infections caused by *M. abscessus* frequently fails, leading to progressive disease and ultimately death [7]. Fukui et al reported a fatal case of *M. abscessus* infection in a patient treated with corticosteroids for 17 years. X-ray of the right elbow showed osteolysis, and magnetic resonance imaging revealed fluid in the right elbow. The growth of *M. abscessus* was recorded from joint fluid and blood cultures. The patient received antimicrobial treatment with clarithromycin, amikacin, and imipenem/cilastatin in combination with debridement and, although blood and joint fluid cultures were negative after 1 week, the patient died 6 weeks after initiation of antimicrobial treatment [6]. In our case, the total duration of ABT was 8 months; the patient received, among other drugs, amikacin, tigecycline, ciprofloxacin, and clarithromycin.

Another clinical case was an 84-year-old patient who developed periprosthetic knee infection and sepsis 8 weeks after surgery [3]. Two consecutive revisions involving the replacement of modular components were unsuccessful. During the two-stage treatment, the infectious process was stopped. The antibacterial drugs used were vancomycin, azithromycin, amikacin, tigecycline, cefoxitin, ciprofloxacin and linezolid. The total treatment period was 84 weeks (more than 1.5 years), during which 4 operations on the knee joint were performed.

There are described cases of other locations of orthopedic infection caused by *M. abscessus*. Wong et al described two cases of foot infection following open fracture-dislocations. In one case, the patient was treated with clarithromycin and doxycycline, in the second with cefoxitin, clarithromycin and doxycycline. Ten months after debridement, the infection was arrested [11]. *M. abscessus* can also cause osteomyelitis of the thoracic spine [12-14], rupture of the flexor tendon of the hand [15], and post-injection septic arthritis [16].

In our case of chronic recurrent periprosthetic infection, five surgical interventions, long-term combined antibiotic therapy and two years of complex treatment were required to stop the infectious process caused by *M. abscessus*. Residual shortening of the right lower limb of 3 cm was the result of a long-term infectious process and many surgical interventions, which led to contraction of the thigh muscles with relative preservation of the bones that form the hip joint. Currently, the patient uses orthopedic shoes to compensate for length discrepancy and moves without additional support.

Pprescribing targeted therapy, doctors can only rely on the results of the antibiotic sensitivity of a particular *M. abscessus* isolate; however, due to the peculiarities of the bacteriological diagnosis of NTMB, correct results will be obtained no earlier than 5 days after harvesting the material (for slow-growing mycobacteria – from 7 days). In addition, this type of NTMB is characterized by an extreme antibiotic resistance profile. Within the framework of personalized medicine, it is also possible

to expand the therapeutic approaches of etiotropic therapy through genetically engineered bacteriophages or selected combinations of drugs in accordance with the determination of their senergid antimicrobial activity against a specific isolate. The effectiveness of new beta-lactamase inhibitors, including avibactam, against *M. abscessus* has been experimentally established [17]. Combinations of the antimicrobial agents, vancomycin/clarithromycin and dual beta-lactam therapy, have been shown to have a synergistic effect, suggesting their possible use in multidrug regimens [18, 19]. In addition, bacteriophage therapy has been effective in severe cases of disseminated *M. abscessus* infection [20]. Although many of those experimental therapeutic approaches demonstrate in vitro activity against *M. abscessus*, most do not currently have evidence of their effectiveness in clinical use for the treatment of infections caused by this pathogen.

CONCLUSION

Long-term aggressive antibiotic therapy in combination with staged surgical treatment yields success. This requires the coordinated work of bacteriologists, orthopedists, clinical pharmacologists and infectious disease specialists. Practitioners need to be aware of possible non-tuberculosis mycobacterial orthopedic infection and correctly perform differential diagnosis with other infectious diseases.

Conflict of interest *Not declared.*

Financing *The work was prepared without sponsorship.*

Ethical review *Not required.*

Informed Consent *All patients sign an informed voluntary consent for the use of the results of their treatment for educational and scientific purposes.*

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