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CASE REPORT

Bilateral periprosthetic joint infection with *Ureaplasma urealyticum* in an immunocompromised patient

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Abstract This case study discusses how we diagnosed and treated a patient with a late haematogenous bilateral periprosthetic joint infection (PJI) after total knee arthroplasties caused by *Ureaplasma urealyticum*. This has never been reported before. We will discuss how we used a PET-CT, synovial fluid cell count, and synovial fluid analysis by 16S rRNA gene sequencing to diagnose this PJI. We will also discuss how we treated this patient to obtain full recovery.

Keywords PJI · Prosthetic · Infection · Ureaplasma · Immunocompromised · 16S rRNA

Case report

In November 2015, a 69-year-old woman presented herself to the Emergency Room (ER) Department to see her oncologist because of fever after chemotherapy with a temperature of 39.5 °C. Her past medical history revealed a non-insulin-dependent diabetes, pulmonary embolism and a cerebral vascular accident. In May 2015, she was diagnosed with non-Hodgkin lymphoma stage 4A. At presentation the lymphoma was in remission, and 1-month earlier, she had received the last of 8 chemotherapy treatments with rituximab-cyclofosfamide-doxorubicin-vincristin-prednisone (R-CHOP). She underwent a TKA on the right side 11 years ago and on the left side TKA 1.5 years ago. Both arthroplasties were uncomplicated.

The patient reported a productive cough with clear mucus. There was no dyspnoea or chest pain. Furthermore, she had nausea and vomiting and pain in both knees. Her vital signs showed a heart frequency of 120 bpm, blood pressure of 125/60 mmHg, respiratory rate of 16/min, saturation of 97 % without additional oxygen, and a capillary refill <2 s. On auscultation of the lungs, crackles were heard over the right lower lobe. In addition to bilateral knee pain, no further abnormalities were found on physical examination. Chest X-ray was normal. Complete blood count revealed serum leucocytes 6.3 $\times$ 10^9, c-reactive protein (CRP) 101. An urine sample was negative for leucocytes, erythrocytes, and nitrite. Urine antigen tests voor *L. pneumophila* and *S. pneumonia* were negative and no antibodies against *M. pneumoniae* were found. The patient was admitted under the suspicion of community acquired pneumonia after chemotherapy with a viral infection as differential diagnosis. For 3 days, the patient was treated with cefuroxime 4500 mg; however, this did not result in clinical improvement. Instead, the patient became increasingly ill. Urine and blood cultures both remained negative. Then attention turned to the knees.

The patient experienced an acute pain in both knees, which she never had before. The evening before her presentation at the ER, she had danced without any complaints. The next day, she was not able to walk and she could barely stand on her legs. Examination of the knees showed moderate effusion with tenderness to palpation. Movement was severely impaired: flexion/extension on the left side 30-10-0, on the right side 10-10-0. The patient was not able to stand on her feet and axial compression was positive for

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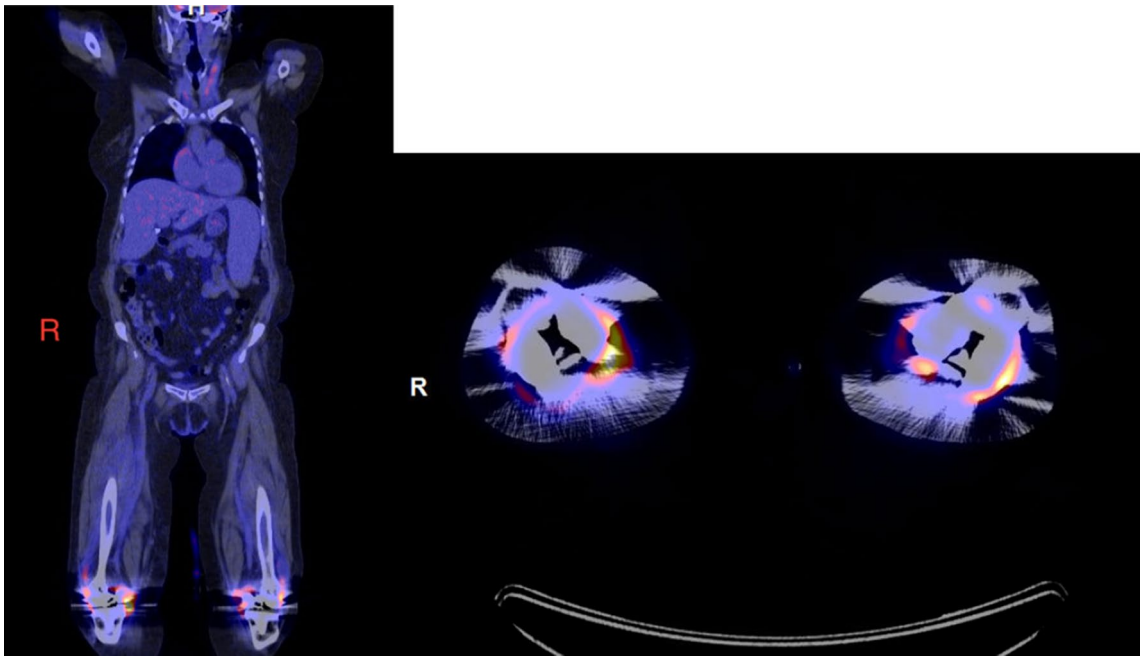

Fig. 1 FDG PET-CT. *Left* coronal view, *right* axial view

Table 1 Outcome synovial fluid analysis

	Right knee	Left knee
WBC ($\times 10^9$/L)	12.3	8.6
PMN (%)	97	75

knee pain. The pain was progressive, did not respond to pain medication, and was present day and night, irrespective of activity. Radiographically, both TKAs appeared well fixed. No signs of loosening and no osseous abnormalities were found. On day 4, a PET-CT was made to determine an infection focus other than the TKA and to rule out skeletal distribution of non-Hodgkin lymphoma. In addition to signs of a PJI (Fig. 1) present at both sides, the PET-CT revealed no other focuses of infection. Arthrocentesis of the right knee was performed on day 6. These results were known on day 8 and revealed a white blood cell count (WBC) of 12.3×10^9 (referral is $>10 \times 10^9$ for acute knee infection), polymorphonuclear neutrophil percentage (PMN%) of 97 % (referral is >90 % for acute knee infection) (Table 1). For the left knee, the WBC was 8.6×10^9 and a PMN of 75 %. A bilateral arthrotomy was planned. Antibiotic therapy was switched to vancomycin and rifampicin, to which ciprofloxacin was added after an insufficient response. Then, the patient presented acute clinical symptoms as fever, tachycardia, tachypnoea, diminished consciousness, progressive neutropenia of 0.3×10^9 (on admission this was 5.4×10^9), and elevating serum creatinine, what made this a life threatening situation. We performed an arthroscopic debridement and lavage with saline to both knees, because a bilateral arthrotomy was considered too great risk. During the procedure on day 11, peri-operative material was obtained for cultures.

No organisms were seen on Gram stain and no aerobic, anaerobic or fungal micro-organisms were found. Direct 16S rRNA gene sequence analysis of synovial fluid obtained during arthrocentesis was positive for *Ureaplasma urealyticum* in both knees. We switched antibiotics to moxifloxacin 400 mg once a day and doxycyclin 100 mg twice a day. The patient was recovering slowly. Knee function improved, as did clinical and laboratory results. One day after arthroscopic treatment, she was able to walk again. Two days later, however, both knees became progressively painful again. We decided to perform a Debridement-Antibiotics-Implant-Retention (DAIR) by bilateral arthrotomy and polyethylene inserts were exchanged. The patient regained full recovery within 1 month after surgery. Moxifloxacin and doxycycline were continued for 3 months after DAIR, and CRP and serum leucocytes were monitored. At the moment of discontinuation of antibiotics, CRP and X-ray findings were normal, knee function remained stable (flexion/extension 100-0-0) and the patient did not experience any pain in the knee. Electrocardiograms were made during moxifloxacin treatment to monitor for potential elongation of QT-time, which did not occur. At 6 months follow-up, CRP

was <3, both knees functioned without pain, were fully stable and the range of motion remained the same.

Discussion

In this case, the patient obtained a late acute haematogenous bilateral PJI in both knees. Recent literature describes an incidence between 0.3 and 0.9 % for late PJI's >1 year after arthroplasty [1]. It is known that PJIs are an increasing problem, because the number of joint replacements performed annually is increasing, as well as the expected lifespan of patients with joint replacements [1]. In addition, the threshold for operating vulnerable patients with chronic diseases has decreased [1]. Furthermore, the real incidence of PJI's might even be higher as a result of underscoring in the registration of PJIs [2].

Diagnosing PJIs can be challenging. The Workgroup of the Musculoskeletal Infection Society (WMIS) released a definition for PJIs. A sinus tract communicating with the prosthetic joint or two positive cultures with identical organisms are major criteria that can be considered pathognomic for PJI. Besides this, five minor criteria have been defined: an elevated serum ESR and CRP, an elevated WBC in synovial fluid, elevated PMN in synovial fluid, a single positive culture, and a histologic analysis of 5 or more PMN in each of 5, or more high-power fields of periprosthetic tissue. Three minor criteria are needed to diagnose a PJI. It is, however, widely accepted that a PJI can be present without meeting these criteria [3].

In this case, physical examination, blood tests, and X-rays were the initial diagnostic tools. No osteolysis, loosening lines, or sinus tract were seen on X-rays. It is strongly recommended by the WMIS to perform X-rays, although radiological findings are not mentioned in the minor criteria for diagnosing PJIs [3].

Even though some authors report positive results with the use of a PET-CT as a diagnostic tool for PJIs, the WMIS does not recommend any radiological or nuclear imaging besides X-rays [3–5]. In this case, however, the PET-CT did support the diagnosis, but we chose to perform a PET-CT to determine infectious foci other than the knees and to rule out skeletal distribution of non-Hodgkin lymphoma, which were not present [3].

Retrospectively, we should have performed the arthrocentesis to obtain synovial fluid for cultures and for PMN% and WBC count earlier in our diagnostic process. Possibly, we could have diagnosed an infection with *U. urealyticum* before our patient became septic. Synovial fluid WBC and PMN% are well established markers of a PJI [6]. In this case, there was an elevated WBC and an elevated PMN% for the right knee, but not for the left knee. This illustrates that the diagnostic value is not 100 % in patients with an *U. urealyticum* PJI. 16S rRNA gene sequence analysis, however, showed the presence of *U. urealyticum* DNA in both knees.

Ureaplasma urealyticum is a bacterium belonging to the Mycoplasmata and is part of the normal genital flora of both men and women [7]. *U. urealyticum* PJIs are not common. There is only one case study about a patient with a unilateral total hip arthroplasty (THA). This patient was immunocompetent and specific intra-operative cultures were positive for *U. urealyticum* one week after surgery [7].

In our case, specific media for the growth of Mycoplasmata were not used and, therefore, cultures remained negative. It is known infectious agents are not always found in septic arthritis [8].

Our patient was immunocompromised. She received her final (total of 8) R-CHOP course 3 weeks before admission. On admission, she had no febrile neutropenia. During hospitalization the patient became neutropenic. It is known that late onset neutropenia can occur after R-CHOP therapy [9]. This has especially been associated with the use of rituximab [10]. An other possible cause for neutropenia can be an infection with micro-organisms. There are several explanations for this: consumption of neutrophils by infection or attack of neutrophils in peripheral blood or bone marrow by bacterial or viral infections [4].

Neutropenia leads to a vulnerable state of bacterial and fungal infections, especially severe neutropenia with absolute neutrophil counts below 500 per mm^3 (0.5×10^9/l) and with longer periods of neutropenia. Gram-positive and negative bacteria and fungi are frequently found in febrile neutropenia. Diagnosis of the exact site of infection is often difficult in severe neutropenic patients, because signs of infection may be lacking due to the impaired inflammatory response [10]. Opportunistic bacterial and fungal pathogens can also adhere to prosthetic material, such as heart valves or prosthetic joints [11, 12]. Next to neutropenia, our patient might have had circulating B-cell depletion and hypogammaglobulinemia which are known side effects of rituximab, particularly in combination with cyclofosfamide [13, 14]. According to a review about primary antibody deficiencies and infections, more cases of hypogammaglobinemia and *U. urealyticum* poly-arthritis in native joints are reported [15].

The serum gammaglobulin levels were not evaluated in our patient. Hypothetically, hypogammaglobinemia could have been the primary cause of immunodeficiency.

Like diagnosing PJIs, treating them is also in its developmental phase. We initially chose to do an arthroscopic debridement and lavage because of the minimally invasive character in a septic patient. The short-term effect was clinical improvement within 1 day. This lasted several days and

gave the patient time to recuperate; therefore, a bilateral DAIR could be performed on both knees. DAIR is the first choice treatment in acute PJIs [3, 16]. During the debridement, several periprosthetic tissue and fluid samples are collected for cultures and analysis of PMN. In addition, all mobile parts of the prosthesis are exchanged. After collecting these samples, antibiotics can be administered during debridement. In cases where causative micro-organisms are known before surgery, targeted therapy can be administered. Otherwise, broad spectrum antibiotics are recommended [3]. In the previously described case of an acute unilateral *U. urealyticum* PJI after THA, clinicians also performed a DAIR with good results [7]. Therefore, this procedure might be an adequate therapy for *U. urealyticum* PJIs.

The ideal duration of antibiotic therapy in treating PJIs is not known. Currently, it is recommended to prolong antibiotic treatment for at least 3 months. This advice is based on available literature that unfortunately has a low level of evidence [3]. In our patient, we were not able to cultivate the actual causative micro-organism and perform susceptibility tests. When 16S rRNA gene sequence analysis revealed *U. Urealyticum* as cause, a combination of moxifloxacin and doxycyclin was chosen. These antibiotics have been described to be effective against *U. urealyticum* with the lowest minimal inhibitory concentration (MIC) [17].

Conclusions and recommendations

This case illustrates that one should be aware of PJIs when patients with a history of joint arthroplasties experience an infection with an unclear pathomechanism, especially when they are immunocompromised. We also recommend to consider *U. urealyticum* as a causative micro-organism within this group of patients. If physical exam, blood tests or X-rays suggest a PJI, we recommend to perform an arthrocentesis to obtain synovial fluid to determinate the PMN% and WBC count next to obtain material for microbiological diagnostics. If aerobic, anaerobic, and fungal cultures are negative, we advise to perform 16S rRNA gene sequence analysis. 16S rRNA gene sequence analysis seems to be a useful method to determine *U. urealyticum* in synovial fluid. Although the literature is not conclusive about a golden standard for treating PJIs, a DAIR-procedure in an acute *U. urealyticum* PJI seems to have a good clinical outcome.

Compliance with ethical standards

Informed consent The patient has given her informed consent prior to this report.

Conflict of interest The authors declare that they have no conflict of interest.

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