Case Report

Fungal Periprosthetic Joint Infection after Total Knee Arthroplasty

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Total knee replacement is an effective procedure for severely diseased knee joints; however, one of the major problems resulting in failure of arthroplasty is periprosthetic joint infection. Fungal infection is rarely found perprosthetic joints infection, but the incidence may be increased in high risk patients. Progression of the disease and definitive treatment guidelines have not yet been established. In two cases of fungal periprosthetic joint infection the organism was identified from cultures as Candida spp. Those patients had developed symptoms of pain and local knee inflammation six years after total knee replacement. A two-stage operation was carried out. The first operation removed the prosthesis, the polyethylene surface, the cement mantle and the infected tissue. After identification of the organism, the correct antibiotic was administered until the infection was controlled. A second operation was carried out to re-implant the prosthesis after the infection had subsided. A summary of reports in the literature regarding treatment of fungal periprosthetic infections as well as an algorithm for treatment decision making are presented.

Keywords: *Fungus, Periprosthetic joint infection, Total knee arthroplasty*

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Total Knee replacement is a safe and effective procedure when carried out on an appropriate patient. Chiang Rai regional hospital has done an average of approximately 350 knee joint replacement procedures each year over the past 10 years. The infection rate following this procedure has been about 2%; however, during the period 2012-2013 two cases of septic loosening knee prosthesis cultured positive for fungus. Previous reports have indicated that fungal periprosthetic joint infection (PJI) is responsible for only 1% of all cases of septic loosening. Some risk factors have been identified, but the effective management of the condition is still controversial. This study reports on two cases of fungal periprosthetic joint infection which occurred six years after total knee replacement. Risk factors and treatment of fungal periprosthetic infection are reviewed and discussed.

Case Report

Case 1

A healthy 69-year-old Thai male from a rural area and working atan administrative position in an office with a fair community was able to ambulate without gait aid. His BMI was about 26 kg/m^2. In 2006, he came to the hospital with pain in his left knee; the diagnosis was primary osteoarthritis of the left knee. Total knee replacement was carried out including fitting a knee prosthesis, and prophylactic antibiotic treatment was administered. His condition was classified as ASA class 2; operation time was three hours. The results of the procedure were good: he could walk with gait aid four days after the procedure and the wound condition was normal during the short period of follow-up, although a small amount of pain was experienced in the left knee when walking. In 2012, he again developed pain in his left knee, but with no history of trauma or fever. Three months later, he came to the hospital where radiographic investigation showed osteolytic lesions around the prosthesis. Chemical analysis showed ESR = 39 mm/hr and CRP = 13.73 mg/L. Gram strain, modified AFB, and KOH preparation from aspirated joint fluid were all negative for organisms. It was decided to carry out a two-stage operation because septic loosening from PJI could not be ruled out. All of the prosthesis and cement was removed. Antibiotic cement (Palacos R+G) was used as a spacer. A tissue biopsy was taken and cultured,giving a positive result for *Candida* spp. Some transudate discharge occurred sporadically from the surgical wound. Twenty weeks later, redebridement was done, retaining the cement spacer mixed with Amphotericin B 250 mg. Oral Fluconazole was initiated at the same time and continued for

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twenty-three weeks, achieving ESR = 38 mm/hr and CRP = 9.31 mg/L; at that time, there was no sign of inflammation and the transudate had disappeared. He could walk with support for a short distance and the range of motion was 5-100 degrees. Ametaphyseal sleeve with porous stem was implanted for correction of the tibial defect ALRI II as well as a femoral stem with distal and posterior augmentation for correction of the femoral defect ALRI I.

During the operation, all metallosis-affected tissue and debris tissue were removed from his left knee and six tissue samples were sent for testing for various bacteria, TB and fungus. Antibiotic impregnated bone cement (gentamicin) was used. The white blood cell count was 11,900/mm^3 and ESR level was 77 at one month post operation. The patient received oral fluconazole for three months after which the white blood cell count was 11,300/mm^3, ESR level was 39 and the wound was healed. The culture results were negative for bacteria and tuberculosis in two specimens. During the three month period the patient was able to walk with a walker for 100 meters. Fluconazole was stopped for one month, but then the knee joint appeared swollen and some transudate came from the lower end of the wound, although without fever. Oral fluconazole was started again and follow-up checks were performed monthly. Nine months after the operation the patient could walk without gait aid for 500 meters and could go up and down 30 stairs to the next floor. He had an active range of motion of 0-110 degrees and was able to return to work at his previous positon. His knee was of normal appearance and there was no discharge.

Fig. 1 Postoperative reimplantation radiography of case 1. Femoral stem, tibial metaphysical sleeve and tibial stem were used.

Case 2

A 74-year-old Thai female came to hospital with pain in her left knee. Her BMI was approximately 24. Underlying diseases included hypertension, chronic renal failure (no dialysis), primary gonarthrosis with a left total knee replacement in August 2007. The ASA score was class 2 and the operation time was about two hours. After the operation, she felt pain in her left knee during a walk within her home community and she needed to use a gait aid for distances greater than 100 meters. She needed analgesic medication occasionally. The surgical wound healed well. She did not have a history of hospital admission at anytime during the two years following surgery. In 2011, the wound appeared red, was painful and there was a decreased range of motion for two months prior to coming to hospital. Radiographic investigation showed osteolytic lesions around the prosthesis-bone interface

Fig. 2 Postoperative reimplantation. Range of motion, active flexion (above) and active extension (below) with a good extensor mechanism.

both on the femoral and tibial side. Blood chemistry showed ESR = 101 mm/hr, CRP = 81.18 mg/L and a white blood cell count = 8,100/mm^3. A two stage operation was planned. During the operation one cloaca and one sinus tract were found. Good cement-prosthesis fixation with bone defect at the medial compartment was accomplished. Tissue was taken from the bone defect to culture for bacteria, TB and fungus. The culture was positive for *Candida* spp. In two specimens, KOH examination was negative. Cement without antibiotic was used for the spacer. Cefazolin was used as the post-operative antibiotic, which was changed to oral Fluconazole 400 mg OD after removal of the drain and catheter.

At a one month follow-up the wound had healed without complications. The patient could walk around the house with a walker. At six weeks, however, fever and dyspnea developed. The patient was admitted for treatment of bronchitis and given an antibiotic. After that episode, the wound was still good and the active range of motion was 30-45 degrees, but ambulatory function was poor and a decubitus ulcer grade II had developed at the coccyx area. Fluconazole was still being administered and the second stage operation was conducted at the normal time.

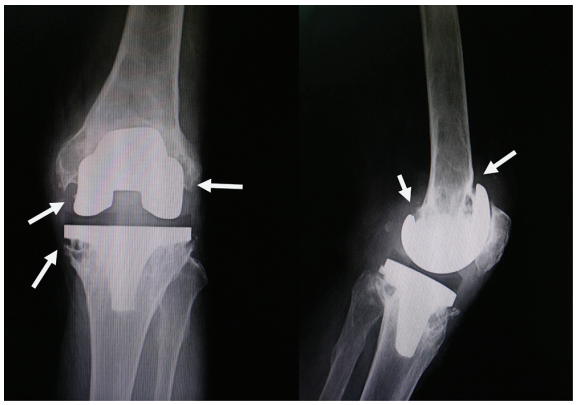

Fig. 3 Preoperative radiography of case 2: Osteolytic lesion around the prosthesis on both the femoral and tibial side.

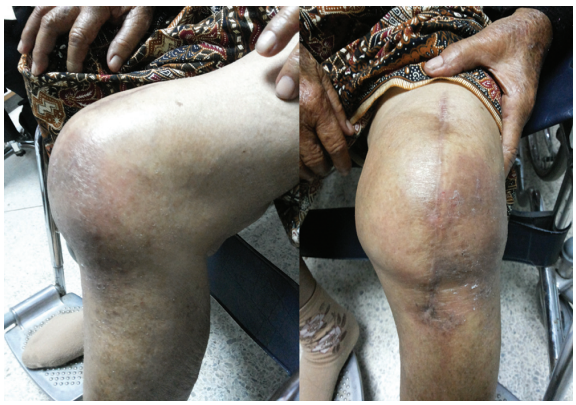

Fig. 4 Condition six months after the first stage operation of case 2. Six months after the operation, there was some knee swelling but without discharge.

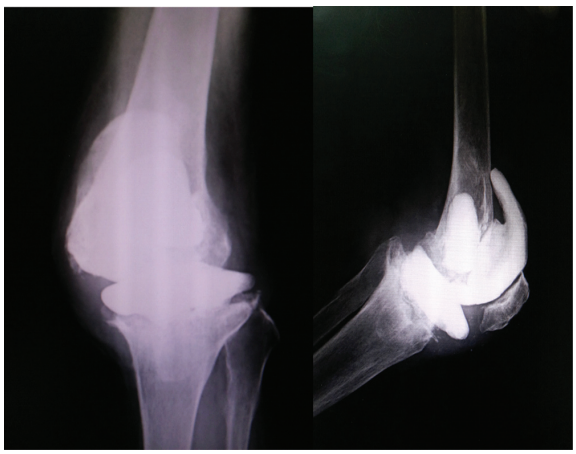

Fig. 5 Post first stage operation radiography of case 2 showing subluxation of the cement spacer six months after the operation.

Discussion

Fungal periprosthetic joint infection was first reported in 1979 by MacGregor et al[1]. Between 1979 and 2000, there were fewer than 100 cases of PJI due to *Candida* spp. describedin the medical literature, although some cases maynot have been reported so the total may be higher. Most fungal infections are due to *Candida albican*. Other fungal species causing infection are those from the genus *Aspergillus*[2]. Factors linked with contracting fungal PJI include immunosuppression, neutropenia, chronic or prolonged use of antibiotics, the presence of indwelling intravenous catheters, parenteral hyperalimentation, malnutrition, diabetes mellitus, rheumatoid arthritis, cirrhosis, a history of multiple abdominal surgeries, a history of renal transplantation, severe burns and injection of drugs[3]. Risk factors for Candidiasis infection include haematological malignancy, neutropenia, age under month or over 65 years, and recent abdominal surgery[4]. Risk factors for Aspergillosis infection include acute myelogenous leukaemia or myelodysplastic syndrome during remission induction chemotherapy for patients undergoing allogeneic haematopoietic stem cell transplantation; recipients of solid organ transplants

and those with other conditions resulting insevere and prolonged immunosuppression[5]. Other risk factors for invasive fungal infection are central venous catheters, the use of broad spectrum antibacterials, prolonged stays in an intensive care unit, total parenteral nutrition, mucosal *Candida* spp. colonization and renal failure[6].

Candida is an important fungal organism causing nosocomial infection. It can produce *Candida* biofilm on many types of medical devices, the hypha-negative mutant being produced only on the basal layer, and the yeast-negative mutant being produced only on the outer layer. Gentle shaking can enhance biofilm formation. *Candida albican* can form biofilm more easily and is also more complex than other species. It can resist 30-2,000 times the concentration of fluconazole, ketoconazole, or amphotericin B compared with planktonic cells. Biofilm can resist amphotericin B concentrations of 11 times the MIC. Most cases are symptomatic within two years after a joint replacement operation[7]. A literature report describes successful non-resection arthroplasty with amphotericin B[8]. Some literature reports compare the results of using fluconazole to using ketoconazole[9,10]. The two-stage operation has been reported as a successful option[1,3,11,12].

A large group of patients with fungal PJI have been reported[1], including 46 cases of candidal PJI that occurred during the period 1969-1999. The median time from prosthesis implantation to the onset of symptoms was 20.3 months. The median time from resection arthroplasty to reimplantation for THAs and TKAs was 8.6 months (range: 2.4-17.7 months) and 2.3 months (range: 0.3-6.0 months), respectively. Definitive treatment included 25 permanent resection arthroplasties[1], 10 delayed reimplantation arthroplasties (22.7%), 5 debridements with prosthesis retention (11.4%), 2 direct exchanges (4.5%), 1 amputation (2.3%), and 1 case treated with medical therapy alone (2.3%). The author concludes MacGregor et al conclude that "delayed reimplantation arthroplasty offers the best opportunity for a good functional outcome". Antifungal therapy appears to be an important component in the successful treatment of candidal PJI; however, the duration of therapy can range from weeks to months. Recurrent infection after delayed reimplantation is a serious complication and often results in permanent removal of the joint prosthesis and usually in poor functional outcome. Some reports describe how the occurrence of fungal PJI began asa local wound problem, with low grade pain and local joint reaction symptoms appearing several years after the arthroplasty procedure had been carried out.

In the two patients in this study, the main risk of fungal infection was related to their age. In addition, the second patient also had renal failure. The operating theatre used was not an arthroplasty-specific facility. For example, similar to most public hospital operating rooms, there is no laminar air flow system. The operating room is closed at midnight. Instruments are auto claved and every tray is checked for organism contamination before the start of each operation. Orthopedic surgeons and surgical team members strictly adhere to the standards for arthroplasty procedures. The arthroplasty procedures described in this study were completed as the first case of the day, directly after the operating room had been cleaned. At noon, the room was still being used for general orthopedic procedures. A check at noon found fungal organisms in the operating room environment.

Several reports state that for successful treatment of fungal PJI an early diagnosis from two positive culture specimens is essential and further recommend that a two-stage procedure should take place (removal of the infected prosthesis with debridement and spacer implantation followed by prosthesis reimplantation). When the organism has been correctly identified, there should be a prolonged use of an antifungal drug[12]. Together with routine debridement at surgery in patient's intact immune system, suppressive doses of ketoconazole have been reported to be successful[8]. Fluconazole may be useful as a follow-up therapy after a course of amphotericin B and combined with resection arthroplasty[14]. Both clinical and experimental data demonstrate high in vivo activity of fluconazole with most *Candida* species, with good synovial fluid penetration activity. Duration of treatment in reported cases ranged from six weeks to nine months, with the median being six weeks for patients who received amphotericin B and slightly more than 17 weeks for patients who received fluconazole[1,13]. The optimal period before reimplantation for patients with candidal PJI has not been determined because candidal PJIs are notoriously indolent and there is no consistent test for successful eradication. The average period before reimplantation for THA was longer than that for TKA (8.6 versus 2.3 months, respectively)[1]. The infection-free interval suggested in one study, which was based on two cases of successful hip reimplantation after candidal PJI, was three months. New antifungal bone cement compositions that contain the fungicidal drug

micafungin have greatly increased the infection-free interval. In vitro studies have demonstrated that micafungin-impregnated bone cement effectively kills *C. albicans*. If re-implantation is appropriate, the surgical incision will need to be carefully considered. Adequate exposure, removal of the cement spacer and all debris tissues, evaluation of the bone defect and postoperative management are all essential. Metal augmentation maybe required to improve the stability of the joint. Postoperative pain control and early rehabilitation will also be necessary. There are no recommendations about the optimal time for switching from intravenous to oral administration of the antifungal drug. The risk of fungal infection recurrence is high; close regular follow-up is necessary for early detection of any further infection after reimplantation.

Conclusion

In the first patient, the major risk factor for candidiasis infection was age. The second patient's risk factors were age and renal failure. Treatment for both patients was a two-stage operation and continued antifungal drug treatment until the clinical and blood parameters reached satisfactory levels. The first patient may require oral antifungal drugs for at least one year; the general condition of the second patient is still under observation. If a second-stage operation would improve their quality of life, reimplantation will be conducted. It cannot be stressed too much that great care must be taken to prevent fungal infection in periprosthetic joints. Careful regular examinations of the patients and culture checks of specimens for fungus are recommended. The local operating theater environment and other controllable factors should be monitored before starting an arthroplasty operation.

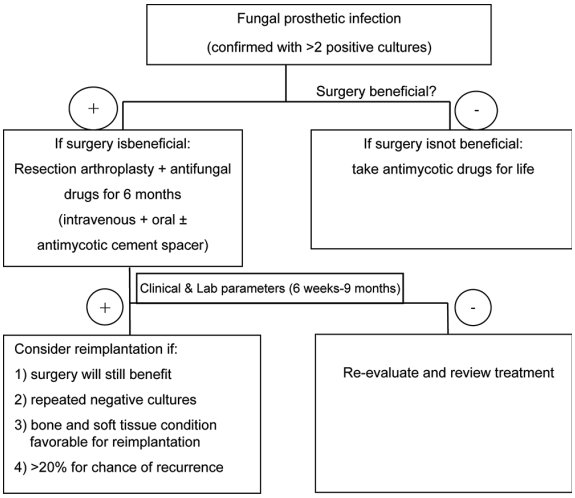

Fig. 6 Algorithm for management of fungal prosthesis joint infection.

What is already known on this topic?

Fungal perprosthetic infection is uncommon complication after total Knee Arthroplasty. History, sing and symptom are not specific, slow progression of condition due to confusion and misdiagnosis of this condition. Sometime it make difficult to treat, high cost and poor result. Previous study show fungal perprosthetic infection in non-Thai patient and context due are different from general hospital in Thailand.

What this study adds?

From review previous study show risk of fungal perprosthetic joint infection, *Candida* infection (most fungal infection) and Aspergillosis for remind surgeon before operate arthroplasty and after operated done is patient had any abnormal symptom. Benefit for non-delay diagnosis and poor result treatment. Including present algorhythm for guidance in Thai. Another factor than patient factor may be concern, especially tropical country like Thailand, example Operating Room that we found fungal culture positive.

Acknowledgement

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Potential conflicts of interest

None.

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การติดเชื้อราภายหลังการผ่าตัดเปลี่ยนข้อเข่าเทียม

นัฐวุฒิ วิวรรธนวรางค์

การผ่าตัดเปลี่ยนข้อเข่าเทียมเป็นการผ่าตัดที่คาดหวังผลดีได้เป็นส่วนใหญ่ ปัญหาสำคัญที่นำไปสู่การล้มเหลวของการผ่าตัดสาเหตุหนึ่งคือ การติดเชื้อรอบข้อเข่าเทียม เชื้อราเป็นเชื้อก่อโรคที่พบได้ไม่บ่อย แต่มีความสำคัญเนื่องจากมีผู้ป่วยกลุ่มเสี่ยงมากขึ้น การดำเนินโรคที่ยาวนานและแนวทางการรักษาที่ยังไม่เป็นที่แน่ชัด ผู้นิพนธ์พบผู้ป่วยที่มีการติดเชื้อรารอบข้อเข่าเทียม 2 ราย ที่ยืนยันจากการเพาะเชื้อพบเป็น Candida spp. โดยมีอาการจนมาพบแพทย์หลังได้รับการผ่าตัดเปลี่ยนข้อเข่าเทียมไปแล้วมากกว่า 6 ปี ผู้ป่วยได้รับการรักษาแบบ 2 stage operation โดยการผ่าตัดครั้งแรก จะนำข้อเทียม ผิวข้อ ซีเมนต์ และเนื้อเยื่อส่วนที่ติดเชื้อออกให้มากที่สุด หาเชื้อโรคที่เป็นสาเหตุและให้ยาฆ่าเชื้อที่เหมาะสมจนการติดเชื้อนั้นหายดี จึงทำการผ่าตัดครั้งที่สองเพื่อใส่ข้อเทียมซ้ำ ผู้นิพนธ์บทความนี้ยังได้ทบทวนการศึกษาที่เกี่ยวข้องกับการรักษาภาวะติดเชื้อรารอบข้อเข่าเทียม เพื่อรวบรวมเป็นข้อเสนอเป็นแนวทางในการดูแลผู้ป่วยต่อไป