CASE REPORT

Acta Orthop Traumatol Turc 2013;47(3):212-217
doi:10.3944/AOTT.2013.2536

The *Nocardia farcinica* infection developing after total knee arthroplasty surgery

Fırat OZAN[1], Şemmi KOYUNCU[1], Cansın KIZILAY[1], Onur ÖZGENÇ[2]

[1]*Department of Orthopedics and Traumatology, İzmir Bozyaka Training and Research Hospital, İzmir, Turkey;*
[2]*Clinical Microbiology and Infectious Diseases, İzmir Bozyaka Training and Research Hospital, İzmir, Turkey*

Infection is an important complication in total knee prosthesis implementations and possesses a serious morbidity. We present a case of *Nocardia farcinica* infection which appeared after application of cemented total knee prosthesis. A 78-year-old male patient had referred to the outpatient clinic with the complaints of restricted movement, pain and swelling of the knee which started after a month following total knee arthroplasty surgery due to left gonarthrosis. As no improvement could be achieved after arthroscopic debridement, synovectomy and antibiotherapy, the components of the total knee prosthesis were removed from him. Although improvement could not be achieved in the knee of the patient at the end of 20-month therapy, the case has still being followed-up.

Key words: Arthroplasty; infection; knee; *Nocardia*.

Today, arthroplasty is a method that is increasingly used in various conditions. Although prosthetic joint infections are not commonly encountered, they are recognized as the most devastating group of complications due to recurring surgeries, high morbidity, prolonged medical treatment, and raised costs.[1]

In patients with primary hip replacement, the infection rate within the first two years is generally lower than 1%, while it is below 2% in patients with knee replacement.[2] Most of the infections of total joint arthroplasty are associated with Gram-positive bacteria and the most common etiologic agents are *Staphylococcus aureus* and *Staphylococcus epidermidis*.[3]

Nocardia infection, caused by an aerobic pathogen of *Actinomycetes* family first isolated from cattle by French veterinarian Edmond Nocard in 1888 and reported in humans by Eppinger in 1890, causes a quite rare and serious complication in total joint arthroplasty.[4,5]

We report a patient who developed *Nocardia farcinica* infection after total knee arthroplasty due to its rarity in the literature.

Case report

A 78-year-old male patient with no complaint except left knee pain visited our outpatient clinic one month after undergoing cemented total knee arthroplasty due to left gonarthrosis (Fig. 1). He had pain that was increasing by activity and present even at rest, redness, and swelling in the operated knee. Medical history revealed nothing remarkable except a total prosthetic surgery of the right knee due to gonarthrosis dating back 15 years and controlled hypertension. Laboratory parameters at the time of discharge were as follows: C-reactive protein (CRP)

Correspondence: Fırat Ozan, MD. 1320 sk. No:4 D: 1 Pk: 35400, Buca, İzmir, Turkey.
Tel: +90 506 - 504 02 31 e-mail: firatozan9@gmail.com

Submitted: August 30, 2010 **Accepted:** June 29, 2011

Available online at
www.aott.org.tr
doi:10.3944/AOTT.2013.2536
QR (Quick Response) Code:

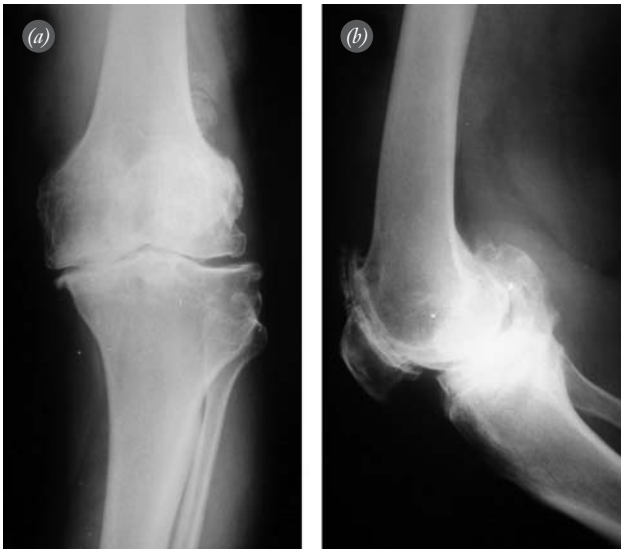

Fig. 1. **(a, b)** Preoperative knee X-rays of the patient.

1.5 mg/l, erythrocyte sedimentation rate (ESR) 28 mm/h, and leukocyte (WBC) count 7800/mm^3. Physical examination revealed tenderness, redness, fever, and a small amount of effusion in the left knee. The range of motion was limited and painful in the left knee with 80° flexion and 0° extension. Body temperature was 37.5°C. Laboratory tests revealed that CRP was 14.2 mg/l, ESR was 75 mm/h, WBC count was 12,100/mm^3, fasting blood sugar was 191 mg/dl, whereas the other blood parameters were normal. Radiologic examination of the knee showed no pathologic finding (Fig. 2).

The patient was suspected of having a prosthetic infection and subjected to diagnostic and therapeutic

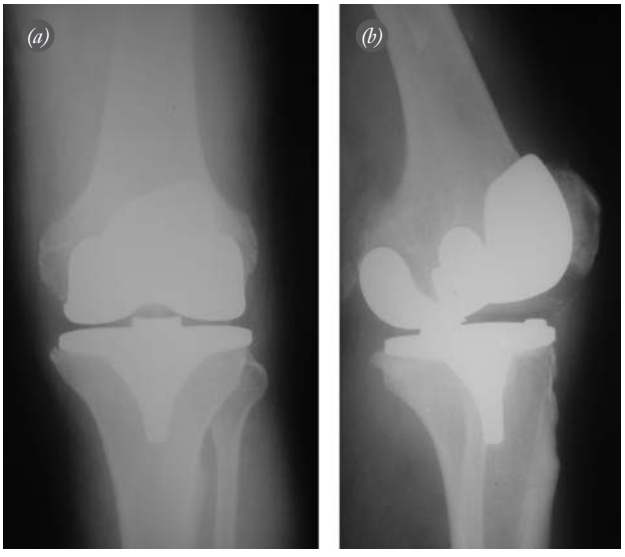

Fig. 2. **(a, b)** Postoperative knee X-rays of the patient.

arthroscopy using standard anteromedial and anterolateral ports. The joint fluid was mildly blurred and of yellow color. There were hypertrophic tissues in the joint. Tissue specimens were collected and irrigated with 15 L isotonic sodium chloride (NaCl) solution. The specimens were evaluated for bacteriologic, mycologic, and microbacteriologic infections. No growth was found after 24 hours in bacteriologic cultures, whereas blood agar cultures demonstrated dry and grey-colored colonies with irregular surface on 5th day. Gram-stained specimen showed filamentous and branching Gram-positive bacilli, while Ehrlich-Ziehl-Neelsen (EZN) staining revealed bacteria resistant against weak acids. The active agent was found to be a member of the aerobic *Actinomycetes* family (*Nocardia*). The bacterial growth was dispatched to a reference laboratory (Mycology Laboratory at the Claude Bernard University, Lyon, France) for diagnostic verification where it was identified specifically as *Nocardia* farcinica.

The result of the antibiotic sensitivity test done by disc diffusion method revealed that the isolate was resistant against vancomycin, teicoplanin, amoxicillin-clavulanic acid, trimethoprim-sulfamethoxazole, erythromycin, ampicillin-sulbactam, clarithromycin, and third generation cephalosporins, whereas it was sensitive to amikacin, linezolid, tigecyclin, imipenem, and ciprofloxacin.

According to the antibiotic sensitivity test, the medical therapy was started with amikacin 500 mg IV BID and linezolid 60 mg PO BID. The patient received cranial magnetic resonance (MR) and thoracic computed tomography (CT) imaging as well as abdominal ultrasonography for detection of any possible nocardiosis-related disseminated infection and evaluation of the underlying malignancy. The imaging studies demonstrated no pathologic finding. In view of the detected microorganism growth, immunosuppression parameters (immunoglobulins, CD4 and CD8, anti-HIV) and hematologic malignancy (peripheral smear and radiologic examinations) were tested, and all of them were found to be either within normal range and/or negative. Advanced history taking and physical examination of the patient revealed no contact with soil, trauma, or cutaneous site of entry that could lead to *Nocardia* inoculation.

Since the patient exhibited no significant recovery with the applied antibiotherapy in terms of discharge, redness, and biochemical profile (CRP 8.38 mg/l, ESR 90 mm/h, WBC 7800/mm^3), following a consultation with the Department of Infectious Diseases during the 3rd week of the antibiotherapy, we decided to remove

the prosthetic components of the knee. By performing an operation, the components were removed, debridement was applied, and a spacer made up of cement was filled into the joint space (Fig. 3). The current antibiotherapy of the patient was continued for 3 months following his hospitalization. After determining improvement in the clinical follow-up data (CRP 2.44 mg/l, ESH 40 mm/h, WBC 6460/mm^3), the patient was discharged with the combined therapy of ciprofloxacin 750 mg TB BID and amikacin 500 mg IV BID. One month later, he was readmitted due to pain, elevated temperature, and discharge in the knee. The knee joint was opened by surgery, debridement was applied, and the former spacer was replaced. Since the culture prepared from the intraoperatively obtained specimen revealed the same bacterial growth and same antibiotic sensitivity pattern, the antibiotic therapy was modified to the combination of imipenem 500 mg IV TID and amikacin 500 mg IV BID. Currently, the clinical follow-up of the patient who fulfilled 20 months of the ongoing treatment shows that although he has a good overall health, there is still pain and mild discharge over the wound site (Fig. 4). The case was decided to be monitored monthly in order to apply a new antimicrobial therapy or to perform amputation.

Discussion

Nocardia, a member of the aerobic *Actinomycetes* family, forms long and branching filaments similar to hyphae of fungi.[6] Although having a Gram-positive character, they are known as acid-resistant aerobic bacteria. *Nocardia* are saprophytic bacteria that live in soil and water that are rich in organic matters.[7] In addition, *Nocardia* are facultative intracellular pathogens that have the ability to proliferate in macrophages and polymorphonuclear (PMN) leukocytes. The main factors underlying its virulence are formation of resistance against phagocytosis by filamentous lag-phase cells, inhibition of phagosome-lysosome fusion, and complex glycolipid cell wall. The superoxide dismutase and catalase enzymes of *Nocardia* maintain resistance to human neutrophils.[4,8] *Nocardia* infection is seen in the respiratory system and primary cutaneous regions.[6] In humans, nocardiosis develops after the inhalation of microorganisms and their primary proliferation in the upper respiratory system or via cutaneous inoculation of the microorganism.[7] While *N. asteroides* is the most common pathogen in humans, the members of the *Nocardia* asteroides complex (*N. brasiliensis*, *N. farcinica*, *N. nova*, *N. transvalensis* and *N. otitidiscaviarum*) are mentioned among other frequently observed *Nocardia* species causing infection in humans.[9]

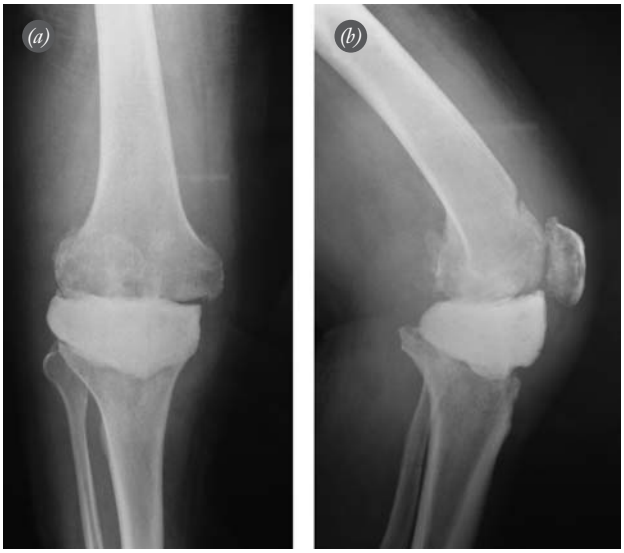

Fig. 3. **(a, b)** X-ray taken after the removal of prosthetic components and placement of cement spacer in the joint space.

Immunosuppression is the most important risk factor for *Nocardia* which are known as opportunistic pathogens. In less than 10% of *Nocardia* patients, there is no predisposing factor for *Nocardia* infection. The factors that the most commonly causes of nocardiosis are chronic obstructive pulmonary disease, long-term steroid use, diabetes, transplant surgery, human immunodeficiency virus (HIV), alcoholism, and malignancies.[7,8]

Nocardiosis is seen as a pulmonary or extensive infection in immunosuppressed patients and the extrapulmonary form of the disease takes place via hematogenous spread associated with primary lung

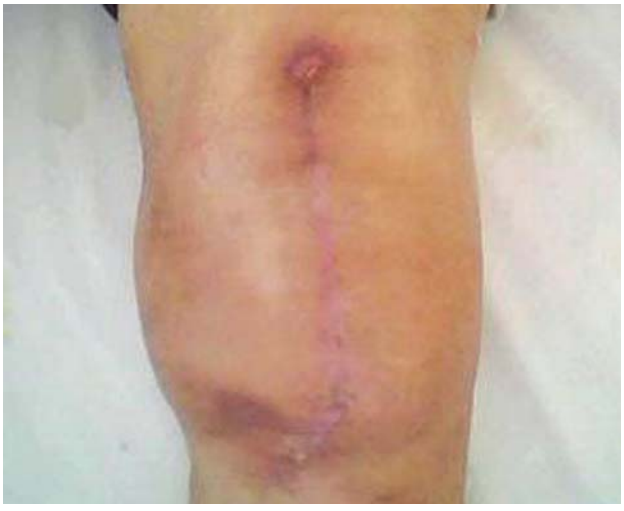

Fig. 4. Frontal view of the knee. [Color figure can be viewed in the online issue, which is available at www.aott.org.tr]

disease. Therefore, approximately half of the patients develop extrapulmonary symptoms, as well.[5] The most commonly affected organs in systemic nocardiosis are central nervous system followed by skin and subcutaneous tissue, eye, heart, lymph nodules, kidneys, intestinal system, and bones and joints.[5,8] While mortality rate exceeds 50% in patients with affected central nervous system, it is observed to be around 20% in patients with no central nervous system involvement.[8,10]

Nocardia infections are primarily of suppurative nature and may develop with necrosis and abscess formation. Clinical diagnosis of *Nocardia* is quite difficult, because while the symptoms, findings, and radiologic images can support the diagnosis, they are not pathognomonic.[8] Although pneumatic course of the disease is more commonly observed, lymphogranulomatous infections similar to sporotrichosis may develop, as well. Cutaneous infection presents with abscess, nodular lymphangitis, cellulitis, and drained sinus tracts.[4,8,11]

Bacteriologic culture is the gold standard diagnostic test for nocardiosis. *Nocardia* colonies require 48-72 hours in order to be apparent in the culture and therefore it may be overlooked in the presence of faster growing bacteria in routine laboratory tests. Since *Nocardia* have a slow growth rate, they should be incubated for at least 4 weeks.[4,8] *Nocardia* can grow in 2-7 days in growth mediums and systems such as 5% blood agar, chocolate agar, and Bactec blood culture.[7] The temperature range for growth is wide and 5-10% CO_2 accelerates the growth process. They can also grow in the growth medium used for *Mycobacterium tuberculosis*.[4]

During the nocardiosis treatment; infection site and severity, immunologic status of the host, potential drug interactions and toxicities, and the responsible *Nocardia* species should be taken into account.[5,12,13] *Nocardia* species generally exhibit a varying sensitivity to various antimicrobial classes. Although the reason behind this varying sensitivity is not known, since many of the infections are of community-acquired nature, the drug resistance in *Nocardia* may be reflecting the structural resistance.[14] To date, no optimal antimicrobial regime has been defined by controlled clinical studies, therefore, a successful treatment should include appropriate surgical drainage and debridement with combined antimicrobial therapies.[5,12,13]

Reportedly, there is a synergy between cefotaxime-imipenem, amikacin-imipenem, and amikacin-cefotaxime. *Nocardia* species such as *Nocardia farcinica* and *N. otitidiscaviarum* show high resistance to antibiotic regimens including sulfonamides. In the treatment of patients who do not respond to sulfonamides and fail to show toleration, as well as of those who are infected with species resistant to antibiotics such as *N. farcinica*, alternative therapeutic regimens should be attempted.[12,13] Today, there is a need for sensitivity test results of reference laboratories, since there is not much clinical data concerning the selection of alternative agents and the *in vitro* studies show varying results. However, there is no internationally recognized reference method for the assessment of antibiotic sensitivity and there are only a few trials reporting consistent laboratory and clinical results. However, linezolid, a new oxazolidinone, appears to be a promising agent in primary nocardiosis treatment, because it has been shown to be effective in all the *Nocardia* species with a 100% bioavailability. Currently, the use of linezolid is limited because it is expensive, has a licence only for short-term use, and has been reported to have important toxic effects such as bone marrow suppression.[12,13] Nonetheless, in view of the antimicrobial sensitivity test results, ciprofloxacin, the only option for extrahospital use via oral route, is ineffective against many species and its efficiency against *N. farcinica* is reported to be 68-88%.[12]

In patients who give a delayed treatment response, durations of parenteral and subsequent oral therapies are prolonged.[12] However, there is no general consensus over the optimal duration of therapy and application of a long-term therapy is recommended due to the recurrent nature of the infection.[15] Recommendations for treatment process are primarily based on case reports. A treatment period of 1-3 months is noted to be generally sufficient for primary cutaneous infection, whereas it is suggested to prolong this period up to 6-12 months in pulmonary and systemic nocardiosis in immunosuppressed hosts, and sometimes over 12 months in cases of CNS involvement.[12,13,16,17] The Infectious Disease Society of America (IDSA) recommends a treatment period of 6-24 months for the cutaneous form of nocardiosis including surgical debridement and drainage for large subcutaneous abscesses depending on the extent of the disease, ie. disseminated or local nature, and underlying immunosuppression.[18] Moylett et al.[19] prolonged the treatment period up to 24.5 months in one of their cases.[12,13] Some centers continue to apply prophylaxis after the treatment, as well.[20] Unresponsiveness is associated with primary drug resistance, inadequate delivery of the drug over the infection site, or formation of an abscess requiring surgical drainage.[12] Furthermore, improvement and recurrences of the infection are reported throughout the course of the disease.[5,21,22]

There are also different factors that are reported to cause problems during treatment. Members of the *Nocardia* asteroides complex have the ability to inhibit

phagocytic functions and thus force the organism to live continuously on the host.[19] *Nocardia* species are phagocytosed by active macrophages, however, they may avoid the macrophages and live on intracellularly which may lead to recurrent infections.[23] Furthermore, it is a point of discussion that the *in vitro* efficacy of antimicrobial agents should be shown in animal models. In one trial, amikacin was found to have no inhibition effect on *Nocardia* growth because it was observed to metabolize very fast resulting in failure to attain the expected plasma levels and reach the infected region.[24]

In this case of *Nocardia*l prosthetic infection, the only risk factor of infection was diabetes. In the literature, two cases of spontaneous septic arthritis affecting the knee joint have been reported.[25,26] One of those was a renal transplant patient in Turkey. Nizam et al.[27] reported a septic arthritis case associated with *N. Nova* that developed 5 months after the placement of knee prosthesis. They achieved full recovery by first performing irrigation and synovectomy followed by a triple combination of antibiotic therapy consisted of clarithromycin, amoxicillin-clavulonic acid, and trimethroprim-sulfamethoxazole for 2.5 years.

The pathophysiology of prosthetic infections has characteristic features. Some serum components, particularly albumin, are stored on the foreign body and inhibit neutrophil activation. Therefore, bacterial adhesion over the prosthetic surface becomes easier. As planctonic bacteria, it leads a silent life in a biofilm. Bacteria in biofilm are not affected by antibiotics during the stationary phase. Bacteria with intercellular persistance show low sensitivity to aminoglycosides. Some microorganisms, especially staphylococci, secrete a glycocaliceal substance of polysaccharid structure that is called as 'slime'. Slime prevents the penetration of antibiotics into bacteria and reduces the chemotaxis of neutrophils.[2]

It appears to be obvious that there are various factors involved in the negative response to nocardiosis therapy. Today, other than advanced age and controlled diabetes, there is no event of immunosuppressive influence. In our case, failure of the antimicrobial therapy can be explained with the collective presence of several important components including; *Nocardia* being a species (eg. *N. farcinica*) resistant to antibiotics, limited oral antimicrobial options for the maintenance of treatment, focus of prosthetic infection located in the most difficult location that antibiotics can be effective, and failure to achieve bacterial eradication. Therefore, a multidisciplinary and long-term approach is required for the treatment and follow-up of prosthetic infections caused by bacteria such as *Nocardia*.

Acknowledgement

The authors would like to extend their thanks to Prof. Dr. Patrick Boiron, the Head of the Mycology Laboratory at the Claude Bernard University, Lyon, France; and Prof. Dr. Ramazan Inci, the Head of the Mycology Laboratory at the Ege University, Izmir, Turkey for their contributions to identification of *Nocardia* farcinica.

Conflicts of Interest: No conflicts declared.

References

1. Steckelberg JM, Osmon DR. Prosthetic joint infection. In: Bisno AL, Waldvogel FA, editors. Infections associated with indwelling medical devices. 3rd ed. Washington, DC: American Society for Microbiology; 2000. p. 173-209.
2. Widmer AF. New developments in diagnosis and treatment of infection in orthopedic implants. Clin Infect Dis 2001;33: 94-106.
3. Garvin KL, Hanssen AD. Infection after total hip arthroplasty: past, present and future. J Bone Joint Surg Am 1995; 77:1576-88.
4. Brown-Elliott BA, Brown JM, Conville PS, Wallace RJ. Clinical and laboratory features of the Nocardia spp. based on current molecular taxonomy. Clin Microbiol Rev 2006; 19:259-82.
5. Corti ME, Villafane-Fioti MF. Nocardiosis: a review. Int J Infect Dis 2003;7:243-50.
6. McNeil MM, Brown JM. The medically important aerobic actinomycetes, epidemiology and microbiology. Clin Microbiol Rev 1994;7:358-417.
7. Saubolle MA, Sussland D. Nocardiosis: review of clinical and laboratory experience. J Clin Microbiol 2003;41:4497-501.
8. Beaman BL, Beaman L. *Nocardia* species: host-parasite relationship. Clin Microbiol Rev 1994;7:213-64.
9. Lerner PI. Nocardiosis. Clin Infect Dis 1996;22:891-903.
10. Mamelak AN, Obana WG, Flaherty JF, Rosenblum ML. Nocardial brain abscess: treatment strategies and factors influencing outcome. Neurosurgery 1994;35:622-31.
11. Kalb RE, Kaplan MH, Grossman ME. Cutaneous nocardiosis. Case reports and review. J Am Acad Dermatol 1985;13: 125-33.
12. Sorrell TC, Mitchell DH, Iredell JR. *Nocardia* species. Mandell GL, Bennett JE, Dolin R, editors. In: Mandell, Douglas, and Bennett's principles and practice of infectious diseases. 6th ed. Philadelphia: Elsevier Churchill Livingston; 2005. p. 2916-24.
13. Munksgaard B. *Nocardia* infections. Am J Transplant 2004;4: 47-50.
14. Wallace RJ, Steele LC, Sumter GY, Smith JM. Antimicrobial susceptibility patterns of *Nocardia asteroides*. Antimicrob Agents Chemother 1988;32:1776-9.
15. Matulionyte R, Rohner P, Uckay I, Lew D, Garbino J. Secular trends of *Nocardia* infection over 15 years in a tertiary care hospital. J Clin Pathol 2004;57:807-12.
16. Menéndez R, Cordero PJ, Santos M, Gobernado M, Marco V. Pulmonary infection with *Nocardia* species: a report of 10 cases and review. Eur Respir J 1997;10:1542-6.
17. Yildiz O, Alp E, Tokgoz B, Tucer B, Aygen B, Sumerkan B, et al. Nocardiosis in a teaching hospital in the Central

Anatolia region of Turkey: treatment and outcome. Clin Microbiol Infect Dis 2005;11:493-512.

18. Stevens DL, Bisno AL, Chambers HF, Everett ED, Dellinger P, Goldstein EJ, et al.; Infectious Diseases Society of America. Practice guideliness for the diagnosis and management of skin and soft-tissue infections. Clin Infect Dis 2005;41:1373-406.
19. Moylett EH, Pacheco SE, Brown-Elliott BA, Perry TR, Buescher ES, Birmingham MC, et al. Clinical experience with linezolid for the treatment of *Nocardia* infection. Clin Infect Dis 2003;36:313-8.
20. Geiseler PJ, Andersen BR. Results of therapy in systemic nocardiosis. Am J Med Sci 1979;278:188-94.
21. Ambrosioni J, Lew D, Garbino J. Nocardiosis: updated clinical review and experience at a tertiary center. Infection 2010;38:89-97.
22. Provost F, Laurent F, Camacho Uzcategui R, Boiron P. Molecular study of persistance of *Nocardia asteroides* and *Nocardia otitidiscaviarum* strains in patients with long-term nocardiosis. J Clin Microbiol 1997;35:1157-60.
23. Kanemitsu K, Kunishima H, Saga T, Harigae H, Ishikawa S, Takemura H, et al. Efficacy of amikacin combinations for nocardiosis. Tohoku J Exp Med 2003;201:157-63.
24. Gomez-Flores A, Welsh O, Said-Fernandez S, Lozano-Garza G, Tavarez-Alejandro RE, Vera-Cabrera L. *In vitro* and *in vivo* activities of antimicrobials against *Nocardia brasiliensis*. Antimicrob Agents Chemother 2004;48:832-37.
25. Audenaert E, Almafragi A, Vuylsteke M, Verdonckt C, Verdonk R. *Nocardia farcinica* arthritis of the knee. A case report. Acta Orthop Belg 2004;70:386-8.
26. Kahraman S, Genctoy G, Arici M, Cetinkaya Y, Altun B, Caglar S. Septic arthritis caused by Nocardia asteroides in a renal transplant recipient. Transplant Proc 2004;36:1415-8.
27. Nizam I, Kohan L, Kerr D. *Nocardia nova* septic arthritis following total knee replacement: a case report. J Orthop Surg 2007;15:390-2.