

Oral Amoxicillin Clavulanic Acid as Systemic Therapy in a Patient Suspected with Actinomycetoma

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Abstract: Actinomycetoma is a local chronic granulomatous infectious disease that affects both cutaneous and subcutaneous tissues, and is caused by anaerobic facultative Gram-positive filamentous bacteria of the *Actinomycetaceae* and *Propionibacteriaceae* family. *Propionibacterium propionicum* (family *Propionibacteriaceae*) and *Actinomyces* species are very sensitive to beta lactam antibiotics, especially penicillin G or amoxicillin. A rare case of actinomycetoma in a 38-year-old woman was reported. The working diagnosis was based on clinical features and anaerobic bacterial culture from the erythematous papules and nodules of the left arm, left elbow, right hip, and buttocks, as well as shallow ulcers on the left buttocks, and the growth of *Propionibacterium propionicum*. Based on antibiotic susceptibility test results, the patient was treated with amoxicillin clavulanic acid for 7 days. The size of ulcerative lesion with granulation tissues became smaller. Various antibiotics combination therapy may be given to actinomycetoma, but the combination of amoxicillin and clavulanic acid has significant effect.

1 INTRODUCTION

Mycetoma known as Maduramycosis or Madura foot is a chronic localized granulomatous infection that affects cutaneous and subcutaneous tissues. Infections caused by fungi are called eumycetoma, and actinomycetoma are caused by filamentous bacteria (Branscomb, 2003; Sobera & Elewski, 2008; Hay & Asbee, 2010; Hay, 2012). The filamentous bacteria that cause mycetoma are *Actinomyces sp.*, *Streptomyces sp.*, and *Nocardia sp.* (Welsh et al., 2007; Bravo et al., 2012). Actinomycetoma is a bacterial infection of the skin, subcutaneous tissues, muscles, and bones with a chronic and suppurative joint gaps, due to endemic facultative anaerobic bacteria (Sardana et al., 2001; Bravo et al., 2012). The Gram-positive bacilli family were *Actinomycetaceae* and *Propionibacteriaceae* (Bravo et al., 2012). Actinomycetoma can be diagnosed when there is one of three clinical features, which are the existence of an inflammatory infiltration of the skin or subcutaneous tissue, a sinus formation with drainage, and responsiveness to short-term antibiotics (Reichenbach, 2009; Bravo et al., 2012). The most common predilections of actinomycetoma are the legs, lower limbs, hands, head and back (Hay, 2012).

In the case reported, the lesions on the buttocks atypical mycetoma (Chaves et al., 2002). *Actinomyces sp.* a bacteria which sensitive to beta lactam antibiotics especially penicillin G or amoxicillin. Therefore, the appropriate treatment options were penicillin G or amoxicillin (Valour et al., 2014). There were two cases of actinomycetoma treated with amoxicillin clavulanic acid. The first case was treated for 5 months and the second case for 6 months. There were a clinical improvements and bone improvements as shown by the radiological examination. Also the absence of grain was shown by direct mycological microscopy examination (Gomez et al., 1993). To our knowledge, this is a rare case of actinomycetoma which could be treated by oral amoxicillin clavulanic acid.

2 CASE

A 38-year-old woman, came with the chief complaint of multiple painful ulcers on the left buttock, and nodules on the left arm, left elbow, right waist, and buttock that sometimes feels itchy. Since two months before the consultation, there were nodules on the left arm, left elbow, right hip, and buttock that sometimes

felt itchy. Since a month before consultation, the nodules on the left buttock were getting bigger and became ulcers which were accompanied by edema and induration around the nodules. There were no lymphadenitis. A history of black, red, or pale grain in the fluid from an ulcer on the left buttock was denied.

Three weeks before the consultation, the nodules were getting bigger. The patient went to the dermatologist and was given systemic and topical therapy but there was no improvement, after which the patient was referred to the RSHS Bandung. There was no a history of insects bite, trauma, or skin disorders, before the ulcers appeared. The patient did not have diabetes mellitus, tuberculosis, hepatitis, in her family history. She was a textile worker who did not do any gardening, farming, or working in swamps or fish ponds. She did not have pets at home. The hygiene of the patient was quite good. The general status shown by the physical examination was within normal limits. Direct microscopic examination with

10% potassium hydroxide (KOH) solution showed that there were no hyphae nor spores. There were no Gram positive, Gram negative, or acid-fast from the ulcer on the left buttock. *Propionibacterium propionicum* was identified by anaerobic bacterial culture from the tissue, and the antibiotic susceptibility test showed those to be sensitive to amikacin, amoxicillin clavulanic acid, clindamycin, ceftriaxone, ceftazidime, ciprofloxacin, orbenin, gentamicin, aztreonam, and vancomycin. There was hyalinization of fibrocollagenous tissue with inflammation cells (lymphocytes, histiocytes, eosinofil, and polymorphonuclear cells). The histopathology examination showed lymphocytes on the perivascular tissue, no spores, no hyphae, no epitelioid datia Langhans cells or caseous necrosis.

3 DISCUSSION



Figure 1: Clinical manifestation.

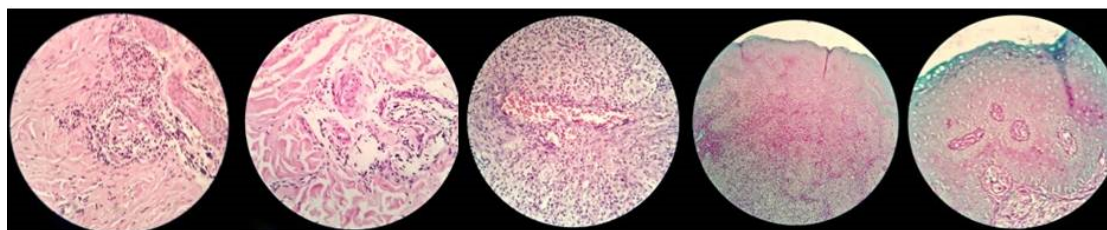


Figure 2: Histopathological results revealed lymphocytes on the perivascular tissue, no spores, no hyphae, no epithelioid datia Langhans cells or caseous necrosis (hematoxylin and eosin, x400).

Mycetoma is a common disease in tropical and subtropical developing countries (Linchon & Khachemoune, 2006; Hay, 2012). Actinomycetoma is more common in Central and South America. The incidence rate of mycetoma in Indonesia has not been clearly documented (Prasetyo & Suyoso, 2011). Males are generally more affected than females, The male to females rate in mycetoma patients is 3: 12 (Branscomb, 2003). Mycetoma affected mostly adults (20 to 50 years) (Hay, 2012). Mycetoma is more common among people with livelihoods as farmers, laborers, or shepherds (Bravo et al., 2012; WHO, 2015). In this case, the patient was a 38 years old woman that worked as a textile worker. The commonest predilection of mycetoma are the feet (68.7%), as in many cases their feet not protected by footwear. In addition, mycetoma can occur on the lower limbs (11.3%), the body (6.1%), the hands (4%), arm (2.9%), head (2.1%), and buttocks (1.3 %). There is one case report of mycetoma on the buttocks which is a atypical mycetoma case in Senegal. The lesions from that case were similar to this case report were the affected area was the left buttock which is an unusual predilection area.

The most common causes of actinomycetoma are *Nocardia brasiliensis*, *Actinomadura madurae*, *Actinomadura pelletieri*, and *Streptomyces somaliensis*^{5,12} which can be found in plants and soils.¹ Whereas *Actinomyces sp.* and *Nocardia sp.* are filamentous bacteria which have the same Class as *Actinobacteria* and same Order as *Actinomycetales* which can cause disease in the human skin. Aerobic bacteria like *Actinomyces sp.* normally live at the respiratory, digestive, and genitourinary systems and can cause local suppurative disease by forming fistulae. The aerobic environment of *Nocardia sp.* and *Actinomyces sp.* can cause actinomycetoma (Bravo et al., 2012). *Propionibacterium propionicum* known as *Actinomyces meyeri* is a form of *Actinomyces* species bacteria (Bravo et al., 2012). Actinomycetoma in this case report was caused by *Propionibacterium propionicum* that could be found by anaerobic bacteria tissue culture.

The trias of mycetoma symptoms are tumefaction, grains in the abscess, and the sinuses thorough which that grains can emerge and reach the skin surface (Sobera et al., 2008). At the early stages of mycetoma the symptoms were, a small chronic solitary lesion of painless subcutaneous nodules which have a hard or soft consistency, and no erythema lesion around the nodules (Hay, 2012). The clinical forms of actinomycetoma and eumycetoma are very similar, but there are some differences between them. At the early stage, the lesions of actinomycetoma are firm nodules which tend to coalesce with the surrounding tissues and progress rapidly (Branscomb, 2003). Grains are the product of organisms that grow and survive after inoculation. Grains are the components of filamentous bacteria or fungi (Sobera & Elewski, 2008). Grain can be found in the abscess and contain polymorphonuclear (PMN) cells, which will come out onto the skin surface through the sinus tract (Hay, 2012). The size of the grains vary from 0.2 to 5 mm and can be seen as sand grains attached to the sinuses (Hay, 2012). Direct microscopic examination is important to examine the grain because it can determine the cause of mycetoma. Fungal grain is black or brown, *Actinomycetaceae* grain is red or pink, when the grain is white, this could be cause by fungi and bacteria (Sobera & Elewski, 2008; Hay & Ashbee, 2010; Hay, 2012). A single case of mycetoma was reported in a man who had no history of grain. Histopathologic examination with hematoxylin-eosin-safran (HES) and Periodic Acid-Schiff (PAS) staining diagnosed the patient with mycetoma. Mycetoma can be diagnosed from the culture of fungal and bacteria from the grains, exudate or from tissue or aspiration (Branscomb, 2003). However, the culture often does not produce satisfactory results due to various conditions such as, bacterial contamination, or cultured tissue obtained from late stage lesion containing fibrosis tissue rather than purulent exudates. The negative cultured results occur because the fungi did not grow as it has received antibiotic therapy before. Direct microscopic examination using Ziehl-Neelsen

staining was done to detect the presence of acid fast bacilli that could cause cutaneous tuberculosis or infections of atypical Mycobacteria.

Polymerase chain reaction (PCR) examination can detect the tuberculosis and nontuberculous bacteria DNA from skin tissue. In this case report, the patient first complained of painless nodules in the left arm, left elbow, right hip, and buttocks since two months before consultation. The nodules were getting bigger and multiplied in the month before consultation and the nodules on the left buttock became ulcers. There was edema and indurations around the nodules. There was no history of lymphadenitis or grain in the fluid from the ulcer, no fungal growth in the fungal cultures, no acid fast bacteria from the Ziehl-Neelsen staining, and the results from the PCR was negative. The results from the bacterial culture was anaerobic bacteria (*Propionibacterium propionicum*). Histopathology examination showed hyalinisation of the fibrocollagenous tissue with inflammation cells (lymphocytes, histiocytes, eosinophil, and polymorphonuclear cells), there were lymphocytes on the perivascular tissue, no spores, no hyphae, and no epithelioid giant cells or caseous necrosis.

The treatment of actinomycetoma could be done with antimicrobial agents and surgery. Amputation as a single therapy rarely gives good results. Surgery can remove small lesions or reduce the size of the lesion. The recommendations of drug regimens are based on expert experience. There are no randomized controlled trials for effective therapy regimens for mycetoma. The treatment is given in combination regimens to prevent drug resistance. The duration of therapy is 3-24 months depending on the response of the patient. The healing of the lesions can be assessed based on subcutaneous nodules and sinus, or indurations of the skin. Various antibiotic therapies for actinomycetoma are aminoglycosides (amikacin or netilmicin), rifampicin, amoxicillin-clavulanic acid, fusidic acid, clindamycin, imipenem-silastin, (Hay, 2012) moxifloxacin, or the tetracycline group (oxytetracycline, minocycline, or doxycycline) (Bravo et al., 2012).

There is a case reporting actinomycetoma in a 32-year-old woman treated with benzylpenicillin 8,000,000 IU injections four times daily and cotrimoxazole tablet twice daily for twenty days, followed by twice daily cotrimoxazole and 500 mg amoxicillin four times daily. Two months after the therapy there was significant improvement of sinus fibrosis, no induration, no secretions, no new lesions, and no systemic symptoms. The mechanism of action of beta lactam antibiotics is bactericidal by binding to specific proteins of penicillin-binding, inhibit

peptidoglycan synthesis and inhibit the autolytic enzymes of bacterial cell walls. Clavulanic acid obtained from isolated metabolite *Streptomyces clavuligerus*,¹¹ can inhibit beta lactamase.¹¹ Amoxicillin-clavulanic acid has a major influence for Gram positive and Gram negative bacteria.¹¹ In this case the patient was given amoxicillin clavulanic acid based on the results of antibiotic susceptibility test against *Propionibacterium propionicum* and the recommended therapy for actinomycetoma.

4 CONCLUSION

Our case demonstrates actinomycetoma with oral amoxicillin clavulanic acid for therapy. *Actinomyces sp.* can cause actinomycetoma. *Propionibacterium propionicum* or known as *Actinomyces meyeri* is a form of bacteria incorporated in the species *Actinomyces* microorganisms cause actinomycetoma (Bravo et al., 2012). Various regimens of antibiotics can be given for actinomycetoma, such as aminoglycoside group, rifampicin, amoxicillin-clavulanic acid, fusidic acid, clindamycin, imipenem-silastin, moxifloxacin, or tetracycline group (oxytetracycline, minocycline, or doxycycline). Amoxicillin is often combined with clavulanic acid which has a major effect on disease therapy infections caused by Gram positive and Gram negative bacteria. In this case patients are given amoxicillin clavulanic acid therapy in accordance with the results of antibiotic susceptibility test against *Propionibacterium propionicum* and recommended therapy for actinomycetoma.

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