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Limb amputation in squamous cell carcinoma patient with history of leprosy

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ABSTRACT

Leprosy is a chronic granulomatous disease affecting the skin and peripheral nerves caused by *Mycobacterium leprae* that results in neuropathy, deformity, and auto-amputation of digits. If auto-amputation does not occur, wound will lead to chronic skin injury which become one of risk factors for squamous cell carcinoma (SCC). Early diagnosis and prompt treatment was essential to treat chronic limb ulcer to prevent further development of SCC. To report a patient with history of leprosy with chronic ulcer in right foot that first started as a marble-sized boil a year ago. The patient underwent below knee amputation for treatment. Methods is Clinical case documentation and the patient medical record was collected and narrated chronologically in a case report. Literature review was conducted non-systematically by article database and manual searching through search engine. A 46-years old male with history of leprosy was admitted with chronic ulcer in right foot, difficulty walking and enlarged lymph nodes in both of inguinal region. The patient underwent below-knee amputation and lymph node excisional biopsy. Histopathology finding was squamous cell carcinoma without metastasis to the lymph nodes. The patient showed good outcomes post-operatively and currently undergoing rehabilitation for artificial limbs. Main treatment for SCC is wide excision, but when abnormalities are found in limbs and interferes with function, wide excision can be performed as below-knee amputation for complete treatment. This procedure can also treat chronic limb ulcer in patient with history of leprosy to prevent further development of SCC

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INTRODUCTION

Leprosy is a chronic granulomatous disease affecting the skin and peripheral nerves caused by *Mycobacterium leprae* that resulting with neuropathy and long term effects such as deformity and disability (Cooreman et al., 2018; Sewon kang et al., 2018). The condition is often being stigmatized

by the community, especially when deformities are apparent. Eighty cases of leprosy discriminations were identified in four countries including Indonesia. The battle against leprosy has seen significant success, as shown by the elimination of leprosy as a public health problem in 2000 internationally and at the national level in most countries by 2005 (Cooreman et al., 2018; WHO, 2021). The number of new leprosy cases reported in 2020 was 127.396 globally, which shows a 37.1% reduction compare to new cases reported in 2019. In this era, leprosy is mostly found in tropical and subtropical areas. Three nations account for more than 80% of all new cases, namely India, Brazil, and Indonesia (Cooreman et al., 2018; Sewon kang et al., 2018; WHO, 2021).

Schwann cells (SCs) are a common site of *M. leprae* infection that results in nerve damage, demyelination, and disability. Because cutaneous nerves are damaged in all kinds of leprosy, anaesthetic or hypoaesthetic lesions may occur. Furthermore, in patients with sensory loss, any skin infection or injury is not being recognized, therefore vascular supply is impaired with continual use. This eventually leads to trophic ulcers and digit auto amputation (Bhat & Prakash, 2012; Sukmawati, 2018). Trophic ulceration in leprosy patients not only results in poor healing but also greatly reduces quality of life. It also acts as a nidus for secondary infection, that required surgical intervention, such as amputation. Amputation of the implicated digits or limb may be required in circumstances such as untreated lesion, secondary infection, and infection of the underlying structures including muscle, tendons, and even deeper to the bone. Therefore, preserving the limb or digits is a critical steps for patients with this condition (Bhat & Prakash, 2012; Pathania et al., 2018; WHO, 2017).

Below-knee amputation is a transtibial amputation that involves removing the foot, ankle joint, distal tibia, fibula, and corresponding soft tissue structures. However, amputation in leprosy is very rare and few. The primary indications for amputation are long-standing consequences of plantar ulcers and severe bone/joint disintegration (Andersen, 1976; Faber et al., 2021; Pathania et al., 2018).

RESEARCH METHOD

This type of research is qualitative with a case study approach (Sugiyono, 2017, 2018, 2019). A 45 years old man who lives in Cibubur, East Jakarta presented with a worsening ulcer & pain in his right foot since 4 months ago. This condition was accompanied by fever a few days before admission to the hospital. The patient describe the pain as a deep pulsating pain in his right foot. The ulcer first occured a year ago. It started as a marble-sized boil which progressed into a tennis ball-sized boil 2 months later. The boil then ruptured and was only self-treated with povidone-iodine. The infection continued until fistulas were formed in the lateral malleolus that penetrate to the medial malleolus. These fistulas release a large amount of pus when pressed. During the last 1 month, the wound and pain have been spreading upwards into his calf. This condition interferes with the patient's daily activities. Within that period of time, the patient hesitates to seek medical help due to fear of COVID-19.

RESULT AND DISCUSSION

The patient has had leprosy since 11 years old and regularly consumes the recommended 3-drug regimen. Since young, the patient's fingers and toes began to contract and deform. This process continues until the patient's fingers become clawed and undergo auto-amputation. Since then, the patient has lost every sensation such as pain, touch, warmth and cold. This patient has no history of diabetes mellitus, hypertension, and past operation procedure. Patient had a history of smoking 1 pack of cigarettes since age 14 until now. Because his feet were always covered by shoes, the patient's daily exposure to UV radiation on both feet was modest. The patient has been a welder for the last two years. And years before as an air conditioner technician.

Physical examination showed lagophthalmos of the left eye. Extremities examination showed amputated 2nd, 3rd, 4th, and 5th fingers in both hands and feet, deformity in right feet &

fingers, open granulomatous lesion with an uneven surface, yellow and black discoloration, multiple fistulas with pus, and pain on palpation. Lymph node examination showed multiple lymphadenopathy in both inguinal regions (Figure 1).



Figure 1. Right Pedis Ulcer a) plantar view, b) anterior view

Laboratory findings showed low hemoglobin (10.7 g/dL) & haematocrit content (33.5 %), low MCV, MCH, MCHC (74.0 fL, 23.6 pg, 31.9% respectively) suggesting a microcytic anemia. Thrombocytosis ($631 \times 10^3/\mu\text{L}$) & leukocytosis ($12.7 \times 10^3/\mu\text{L}$) with high number of segmental neutrophils. Post prandial blood glucose was in normal range (89 mg/dL). Chest Xray showed normal results. Right pedis Xray in oblique & AP projections showed destruction of distal tibia & fibula, complete destruction of right pedis bones and soft tissue swelling in right ankle & pedis (Figure.2).



Figure 2 . Right Pedis Xray a) Lateral projection, b) AP Projection

The intervention to this case consists of below-knee amputation followed with reconstruction of posterior skin flap over the stump (Figure.3), excision biopsy of the inguinal lymph nodes, and IV antibiotic with ceftriaxone preoperatively and ceftriaxone & metronidazole post operatively. Below knee amputation was considered due to advanced deformity, neuropathic status, and risk of further spread of infection. After below knee amputation was done, tissue & bone marrow specimens were taken for histopathology examination. Excision biopsy of the inguinal lymph nodes results in 2 lymph nodes from the right inguinal and 1 lymph nodes from the left inguinal region, which also sent to the lab for histopathology examination.



Figure 3. Intraoperative a) Below knee amputation flap marking, b) Posterior flap after suturing

Histopathological findings of the right pedis tumor showed tissue lined with stratified squamous epithelium which is hyperplastic and turns into an malignant epithelial tumor that infiltrates the connective tissue (Figure.4). Locally visible ulcerations filled with dense acute inflammatory cells. Tumor mass arranged in trabeculae. Tumor cells are medium-large, pleomorphic nucleoli, hyperchromatic, partially prominent nucleoli, eosinophilic cytoplasm. Local epithelials with keratin pearl. Mitosis 6/10. Lymphovascular and perivascular invasion were found. The stroma is densely packed with lymphocytes, plasma cells and polymorphonuclear (PMN) cells. Inflammatory cells are also present in sudoriferous glands. No granulomas, epithelioid cells or datia cells were found. The bone marrow-derived specimen shows fragments of bone trabeculae that are partially necrotic and normocellular bone marrow. No malignant tumor mass was found in this specimen.

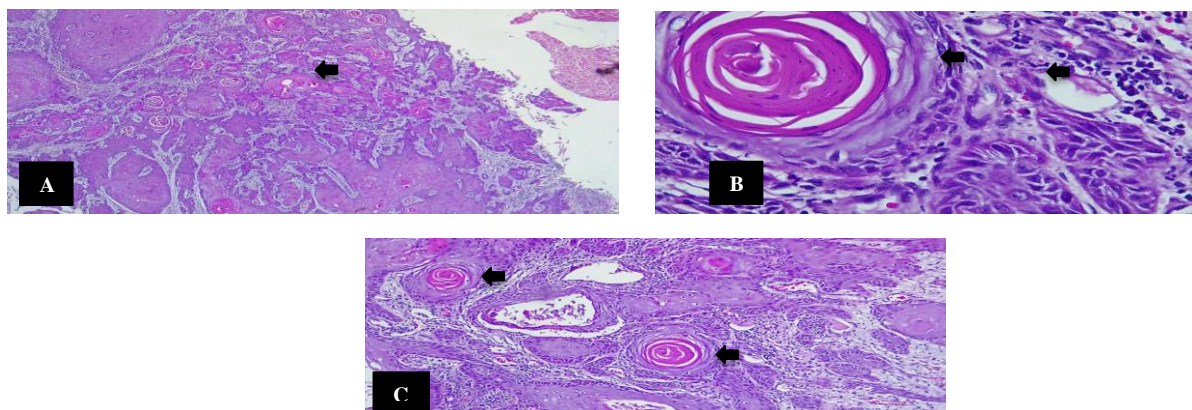


Figure 4. Well differentiated SCC a)10x, b) 40x, c) 100x
black arrow : keratin pearl, white arrow : pleomorphic nucleoli

Histopathological findings from the bilateral inguinal lymph nodes specimen showed chronic non specific lymphadenitis with no sign of malignancy. The patient continues to attend regular follow up visits in the hospital with healthy wound healing and no recurrence of infection (Figure.5).



Figure 5. One month post-operatively

Lagophthalmus, contracted & auto-amputated fingers and toes, in this patient occurred due to primary and secondary deformities of *M. Leprae* infections (Nath et al., 2015). Primary deformity is a direct result of the granuloma formed in reaction to *M. leprae*, which pushes and invades the surrounding tissues, namely the skin, upper respiratory tract mucosa, finger bones, and face. Secondary deformity occurs as a response of primary deformity, especially damage of sensory, motoric, and autonomic nerves, including joint contractures, mutilation of hands and feet. The patient had also lost every sensation such as pain, touch, warmth and cold. This could happen as a result of an increased number of bacteria in the body, and the infection triggers the immune system in the form of lymphocytes and histiocytes (macrophages) to attack infected tissues. At this stage, clinical manifestations may appear as nerve involvement accompanied by decreased sensation (Lee DJ, Rea TH, 2012; Wang & Pancholi, 2014).

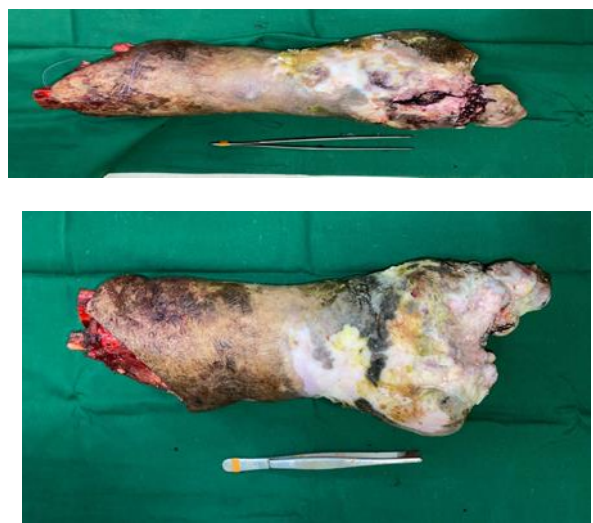


Figure.6 Amputated limb

Open granulomatous lesions with an uneven surface, yellow and black discoloration can occur due to Th1 cell cytokines production that are associated with the protective and destructive

immunity of *M. leprae*. Lymph node enlargement in both inguinal regions happen as a result of the immune system trying to prevent further spread of infection (Yan, 2020). Laboratory findings suggesting a microcytic anemia as a result of chronic disease. Leukocytosis with high number of segmental neutrophils can be caused by an infection or indicate certain diseases, such as blood disorders or cancer. Post prandial blood glucose was in normal range (89 mg/dL). Which indicates that this disease is not a diabetic ulcer.

Amputation is indicated in this patient due to evidence of untreated lesion, advanced deformity, neuropathic status, and risk of further spread of infection. Amputation helps remove the injured segment, but the stump in the functional segment must be appropriate for prosthesis to make sure the patient is able to walk in order to improve the patient's quality of life (Faleiro et al., 2016). There are multiple elements that are important for the management of this patient, such as continued observation for the existence of ulcers or sores on the stump, gait training, and a suitable prosthesis.¹⁰ Recommendation of treatments for leprosy disease are explained in Figure.7.

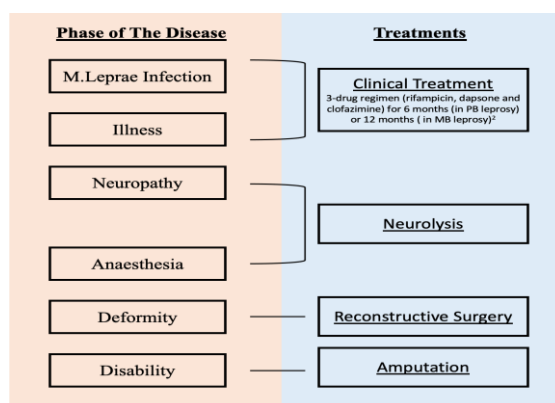


Figure 7. Recommendation of treatments for Leprosy^{2,11}

A case report study in Morocco stated that surgery is the first treatment choice for squamous cell carcinoma on plantar leprosy ulcer. If palpable lymphadenopathy present, ganglion dissection is indicated. Radiotherapy is indicated in cases with advanced inoperable primary lesion, recurrent tumor, involvement of lymph node, cutaneous SCC at risk (if tumor excision incomplete), presence of peri-neural invasion, and if excision margin is positive. Chemotherapy, electrochemotherapy, targeted therapies, and immunotherapies could also be done in cases with metastatic and advanced squamous cell carcinoma (Achehboune K, Elloudi S, Issoual K, Dahhouki S, 2022).

Another study reported a leprosy patient with trophic ulcers & associated complication suggest a four pronged approach to avoid below knee amputation. The four pronged treatment plan was 1) assessment of limb damage followed with exploration & proper debridement of the soft tissues including the dead muscle & tendon. Antiseptic wound dressing & oral antibiotic was also given in this step. 2) daily dressing followed with topical application of fenitoin solution to promote the growth of granulation tissue. 3) syringing the sinus tract to "flush out" debris, pus, and any material deposited in the sinus tract with a mixture of povidone iodine solution and hydrogen peroxide, and after that with normal saline solution. Antibiotic (namely, gentamycin & metronidazole) were also instilled to the sinus tract. 4) the fourth step was done in order to obliterate the sinus tract with injecting diluted phenol solution into the sinus tract. This study stated that this approach has shown promising results & advised to be implemented as a treatment choice to prevent amputation (Chowdhry S, Priya, Meena A, Sahu R, Dhali T, 2020).

The histopathology examination of the tissue & bone marrow specimens shows no indication of Leprosy. Other than that, the examination revealed a well differentiated keratinizing squamous cell carcinoma with no metastasis to the bone marrow. The mechanism of malignant

progression of chronic ulcers in leprosy is unknown, however several causes have been described, including long-lasting ulcers, continuous irritation, hygiene, trauma, environmental factors, and genetic predisposition (Bauk et al., 2006). Chronic ulcers and tumors are typically found on the foot, which is also the most prevalent site of neuropathic ulcers in leprosy patients. Upper limb malignant neoplasm is less common (Barella et al., 2013; Gomes FG, Frade MAC, 2007).

A cross sectional study conducted in India, showed cauliflower-like growth on ulcers in 3% of the individuals investigated (2 out of 66 patients observed) that indicates squamous cell carcinoma (SCC). The study stated that repeated damage caused by sensory loss and chronic inflammation contributes to the malignant development of long-standing ulcers (Upputuri et al., 2020). The annual incidence rate of SCC formation in leprosy patients is reported to be 0.79:1000 (WHO, 2017).

Squamous cell carcinoma (SCC) is the second most prevalent skin cancer behind basal cell carcinoma (Sewon kang et al., 2018; Koh et al., 2003). SCC primarily affects those 60 years of age and men has incidence of this disease (Diffey & Langtry, 2005; Mora, 1989).^{19,20} SCCs are more common in long term diseased or chronic skin injury & inflammation, such as skin with chronic ulcers, burn scars, or dermatitis due to radiation exposure (Alam M; Ratner, 2001; Sewon kang et al., 2018).

In this case, wide excision in the form of below-knee amputation is indicated to treat SCC and chronic limb ulcer with history of leprosy to prevent further development of SCC. When there is abnormality in the limb and interferes with function, below-knee amputation can be one of the choices for complete treatment. Currently, the post-operative condition of the patient is good and he is undergoing rehabilitation for artificial limbs.

CONCLUSION

Wide excision is the main treatment for SCC, but wide excision can be performed as complete treatment in the form of below-knee amputation especially when abnormalities interfere with function. In chronic limb ulcer patient as presented in this case report, below-knee amputation can be a chosen treatment and a strategy to prevent further development of SCC.

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