Diffuse lepromatous leprosy caused by dual infection of *mycobacterium leprae* and *mycobacterium lepromatosis*: A case report

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Abstract

M. lepromatosis is the dominant cause of leprosy in Mexico and it co-exists with *M. leprae* in endemic areas as the once elusive second cause of leprosy. A 41-year-old Madurese woman came with multiple ulcer on her legs, hands and buttock. The ulcers were described as wide and deep, covered with blackish crusts and some exudative area with irregular edges. On face, there were difusse infiltration, madarosis and saddle nose. Histopathology showed thinning of epidermis with a lot of foam cells containing BTA, including endotel and perivascular tissues. Nested PCR examination with LERF2-MLER4 primers for detecting *M. leprae* showed a positive result. Advanced PCR examination using LPMF2-MLER4 primers for detecting *M. lepromatosis* also showed a positive result. Based on the clinical, hystopathological results and PCR examination, it was consistent with diffuse lepromatous leprosy. *M. lepromatosis* mainly causes lepromatous leprosy and also specifically diffuse lepromatous leprosy.

Introduction

Leprosy is one of the oldest recorded human afflictions. Depending upon the immune response mounted against the bacilli, the disease presents with a broad clinical spectrum. At one pole are the tuberculoid (TT) patients, with effective T cell-mediated immunity resulting in very low bacterial numbers, while at the other, the lepromatous (LL) patients mount an ineffective humoral response and exhibit a high bacillary load. Other unstable forms, with characteristics between these poles, can also be observed. A particular variation of lepromatous leprosy involving diffuse nonnodular lesions is more frequent in Mexico than in any other part of the world. This variation has been referred to as diffuse lepromatous leprosy (DLL) or Lucio's phenomenon that cause by new species namely Mycobacterium lepromatosis.[1-8]

DLL cases require management (diagnosis, care, and therapy) that is more specific due to the higher morbidity and even mortality associated with them. Herefore it is necessary to diagnose *M. lepromatosis* and it is even further important to diagnose it early[6].

Two recent papers independently corroborated this new cause of leprosy. Vera-Cabrera et al reported a case of DLL in an 86-year-old woman caused by *M. lepromatosis* from Mexico.[8] From skin biopsy tissue, these authors confirmed the new species by polymerase chain reactions (PCR) and sequencing analyses of 4 genes and also excluded the presence of *M. leprae*. Jessamine and colleagues reported a case of lepromatous leprosy caused by *M. lepromatosis* in a 72-year-old native Canadian man from Ontario, Canada. This patient had suffered from progressive polyneuropathy of all extremities for 2 years before the onset of a maculopapular skin rash that led to the diagnosis through skin biopsy and detection of acid fast bacilli (AFB).[3] *M. lepromatosis* caused not only all DLL cases specifically but also more cases of lepromatous leprosy and other clinical forms of leprosy. This study suggests that *M. lepromatosis* is the dominant cause of leprosy in Mexico and it co-exists with *M. leprae* in endemic areas as the once elusive second cause of leprosy. Both organisms may cause dual infections in a patient[1].

Case Report

A 41-year-old Madurese woman came to our emergency ward with chief complain multiple wound and ulceration on both of her leg, hands, and buttock. Firstly the lesion involving the legs and then spread to the hand and buttock .The lesion reccurent for 1 years. There was rapid progression and the development of new ulcers on his legs and hands since 3 week before hospitalization. The ulceration described as a pain scarlet spots that later darkens and ulcerate. At first, the ulceration was just a redness patches that appeared on both of his leg. The redness patches then gradually progressed to his both leg then to both of his hands. She also complaint malaise and suffered leg stiffness for 3 week before hospitalization. On admission, there were slight fever and and there were eyebrow loss. There were no history of epistaxis and rhinitis. Since 1 years ago she had history suffer malaise and painful wound on her leg. The patient examined herself to public health centre and got prednisone tablet. The lesion didn't get better, then the patient stopped consume the medicine by herself. She went to traditional physician and got some topical medication 3 weeks ago for her wound. The patient was diagnose before with leprosy since 28 years ago, she got multi drug therapy for 12 months from public health centre. She has released from treatment. On the last 3 weeks in 2017, the wound was reappeared and she also treated by herself with sulfanilamid powder and compress with normal saline, but the complaint didn't improve and became worse.

There were no symptoms of numbness patches and history of painful nodule was denied. History of living in leprosy's endemic area was positive. She lives in Madura. The history of family who suffer similar symptoms was denied. History of close contact with leprosy patients was positive which is her friend.

From general examination, the patient is compos mentis, the blood pressure and pulse rate were within normal limit, and the temperature was 37.5°C on the first come. Physical examination revealed polymorphous necrotic-haemorrhagic ulcer with irregular shapes, angulated or 'stellar' on the lower and upper extremities,also buttocks (Figure 1). There were collapse of

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the nasal pyramid, madarosis, thickening of both auricular lobes, diffuse infiltration of the skin of the trunk, atrophy of both thenar and hypothenar eminences of both hands. From cutaneous examination revealed on the regio facialis there were diffuse infiltration without nodule. There were extensive multiple deep and irregular ulcer covered with a blackish crust and in some areas yellow slough eroding the subcutaneous tissue with ragged margins. These ulcers were distributed symmetrically over both legs and both hands. There was gloves and stockings anesthesia. The skin of extremity and trunk were dry. Eyebrows loss and earlobes thickening were positive. The was no claw hand nor drop foot.

A thorough evaluation was performed. Blood examination shows that the patient was anemic (hemoglobin 5.8 g/dL), hypoalbuminemia (serum albumin 1.64 g/dL) and hypokalemia (2.99). Slit skin smear revealed the presence of globi form of acid fast bacilli (AFB) with bacteriological index (BI) was 4+ from earlobes and skin lesion, morphological index (MI) of 2%. The histopathologic evidence from leg's ulcer margin revealed atrophic epidermis with Green Zone, group of foam cells with some of lymphocyte cells were seen on the dermis. Lymphosit cell inflitration in the dermis and subcutaneous fat without vasculitis (Figure 2). By wade-fite staining, AFB were seen prominently within perivascularly and endothelial cells. The conclusion is that the description suitable to Morbus Hansen LL type.

The polymerase chain reactions (PCRs) examination from the skin lesion already performed and was analyzed by Insitute Tropical Disease of Airlangga University. The first PCR examination using the 16S ribosomal RNA (rRNA) gene, known for all described bacteria (~10,000 species), to eliminate the possibility of bacteria contaminats. The result was strong positive for *M. leprae* but the result of *M. lepromatosis* was still unclear. Two rounds of heminested PCRs were used to maximize detection sensitivity (Figure 2) using the LERF2-MLER4 primer was positive for *M. leprae*. While the PCR result for M. lepramatosis using LPMF2-MLER4 primer was positive also.

The patient was treated with multidrug therapy for mutibacillary regimen from World Health Organization (WHO) consisting of rifampicin 600 mg and clofazimine 300 mg once a month, and clofazimine 50 mg/day without dapsone. The dapsone still have not given because the patient with anemic, 5.8 gram/dL. This therapy combine with transfusion of packed red cells (PRC) for correcting the anaemia until the haemoglobine more than 10 gram/dL, albumin transfusion to repair the hypoabuminemia,premix KCl 25 meq infusion to overcome the hypokalemia condition. And also wound care and debridement for the ulcer on her extremity. The patient improved after 1 week of treatment, and she was discharged after 4 weeks in stable condition. The ulcers healed slowly after the wound care. Following treatment resulted in healing with cicatrization. There were hyperchromic border in the lesion about 5 weeks after hospitalization.

Discussion

Leprosy, or Hansen disease (HD), is a chronic infectious disease caused by Mycobacterium leprae which is associated with inflammation that may damage the skin and the peripheral nerves. Nonetheless, an average of 250.000-300.000 new cases have been reported annually during the last 5 years throughout the world. In Indonesia, East Java is the highest state for new cases of Leprosy.[5,7,9] Lepromatous Leprosy may present as a diffuse variant which is characterized by diffuse and massive infiltration of the skin, known as diffuse lepromatous leprosy (DLL). DLL is a unique, severe form of leprosy initially recognized by Lucio and Alvarado in 1852 and further described by Latapi and Chevez-Zamora in 1948, both in Mexico. It is also called Lucio's leprosy. Lucio leprosy is a diffuse type of DLL that corresponds to the polar form of lepromatous leprosy according to Ridley and Jopling This form shows a diffuse cutaneous infiltration, with no nodule or plaque formation, and frequent skin ulceration in the late stage, known as Lucio's phenomenon. DLL has been endemic in western and central Mexico and Costa Rica but rarely reported elsewhere including Asia (India, Srilanka, Malaysia, and Singapore).[4]

In this case, for the first time the lesion involving the lower extremity and reccurent for 1 years. There was rapid progression and the development of new ulcers on his legs and hands since 3 week before hospitalization. The ulcer on both of her leg spreads into both of her hands. Most striking were the presence of extensive multiple deep and irregular ulcer covered with a blackish crust and in some areas yellow slough eroding the subcutaneous tissue with ragged and angular margins. These ulcers were distributed symmetrically. On admission, there were slight fever, she also complaint malaise and leg stiffness for 3 week before hospitalization. Histopathology examination performed on the edge of his leg's ulcer shows that there was no vasculitis with thinning of epidermis with a lot of foam cells. The enormous amount of acid-fast bacilli inside the blood vessels (endothelium) is also seen in wade-fite staining. These clinical manifestations and the results of histopathology examination was Morbus Hansen LL type.

Dual infections by *M. lepromatosis* and *M. leprae* accounted for 14 (16.1%) of all

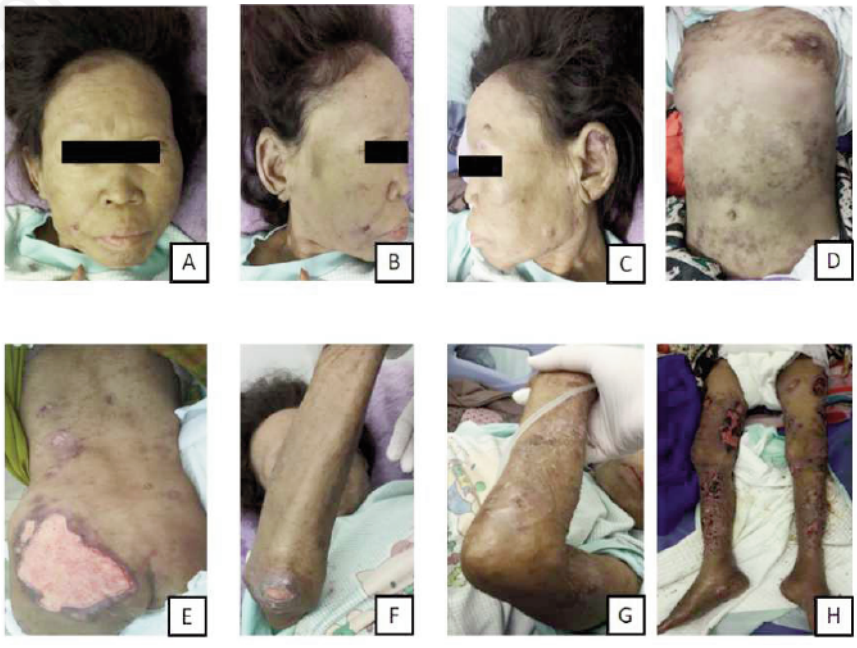

Figure 1. (A) Facial diffuse infiltration and madarosis, (B,C) Earlobes thickening, (D) Hyperpigmented macules on the abdomen, (E,F,G,H) Multiple ulcer and necrotic tissue with slough eroding area.

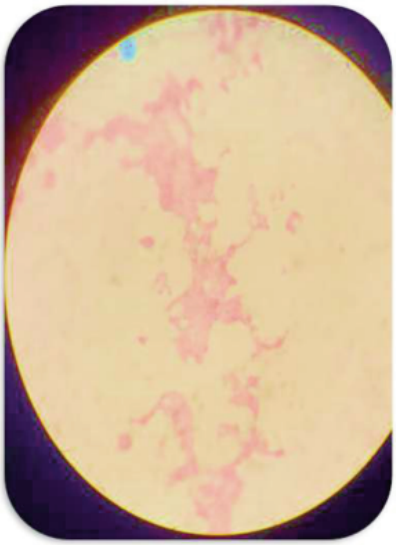

Figure 2. Slit skin smear: globi form of acid fast bacilli (AFB).

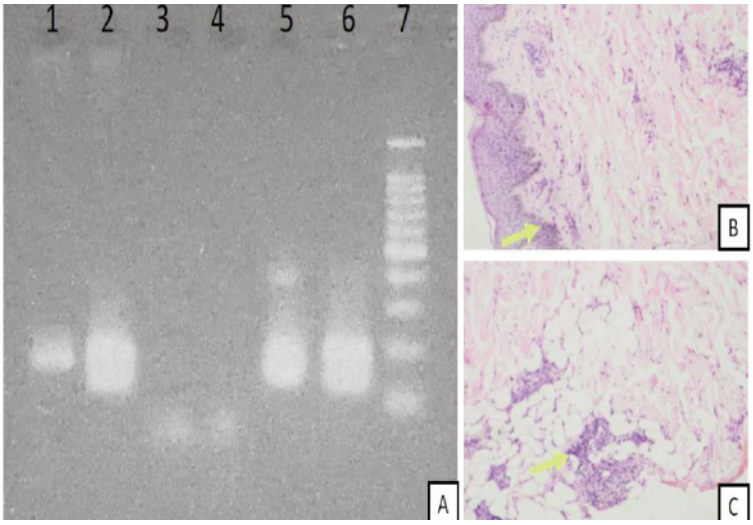

Figure 3. (A) PCR, Primers specific M. lepromatosis (LPMF2-MLER4): line 1 (patient: positive M. lepromatosis), line 2 (patient: positive M. leprae), line 3 (negative control M. lepromatosis), line 4 (negative control M. leprae), line 5 (positive control M. lepromatosis), line 6 (positive control M. leprae), line 7 (100bp DNA ladder). (B) HE staining, 100x magnification, atrophic epidermis with Grenz zone. (C) HE staining, 400x magnification, lymphocyte cells infiltrations on the dermis and group of foamy macrophages.

species confirmed cases[2].The manifestations of these case were more variable than those of a single infection by either species: some cases exhibited mostly features of *M. lepromatosis* infection, such as DLL, younger age, and the extremities as the biopsy site, whereas others exhibited mostly features of *M. leprae* infection, such as the chest and face/ear as biopsy sites. A number of factors may affect the manifestations, including such factors as which species infects the patient first and its duration, whether infection by the second species represents general vulnerability of the patient to these organisms or a mere chance of exposure due to common living environment, the preferred site of infection of each species, and dominance of one species over the other.

The diagnosis of DLL may be delayed, especially in non-endemic areas, resulting in death. Slit skin smear and microscopic observation is relatively easy, but the reliability and sensitivity is limited. Therefore new techniques using PCR are developed. The discovery of *M. lepromatosis* by X. Y. Han in DLL and other forms of leprosy have important implications for the disease spectrum and its clinical picture.[1] Further epidemiological and clinical evidence should be gathered with replication of these findings in different areas of the world. Propagation of *M. leprae* restricted to animal models of armadillo and gene knockout mice is the basic resource for genetic studies. Inoculation of *M. leprae* and *M. lepromatosis* to these animals seems to be useful in comparison of the results for both species. The whole genome sequencing and the further differentiation between *M. leprae* and *M. lepromatosis* is a priority.

Conclusions

M. lepromatosis is another cause of leprosy. It mainly causes lepromatous leprosy and also specifically diffuse lepromatous leprosy. The possibility of mixed infections involving both species still needs further investigation.

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