

6-30-2023

Lucio phenomenon in pregnancy: A histopathology review

Siti Efrida Fiqnasyani

Departement of Dermatology and Venereology, Faculty of Medicine, University of Sebelas Maret, Dr. Moewardi General Hospital, Surakarta, Indonesia

Triasari Oktavriana,

Departement of Dermatology and Venereology, Faculty of Medicine, University of Sebelas Maret, Dr. Moewardi General Hospital, Surakarta, Indonesia

Ervina Rosmarwati

Departement of Dermatology and Venereology, Faculty of Medicine, University of Sebelas Maret, Dr. Moewardi General Hospital, Surakarta, Indonesia

See next page for additional authors

Follow this and additional works at: <https://scholarhub.ui.ac.id/jdvi>



Part of the [Dermatology Commons](#), [Integumentary System Commons](#), and the [Skin and Connective Tissue Diseases Commons](#)

Recommended Citation

Fiqnasyani, Siti Efrida; Oktavriana,, Triasari; Rosmarwati, Ervina; Novriana, Dita Eka; and Mudigdo, Ambar (2023) "Lucio phenomenon in pregnancy: A histopathology review," *Journal of General - Procedural Dermatology & Venereology Indonesia*: Vol. 7: Iss. 1, Article 8.

DOI: 10.7454/jdvi.v7i1.1142

Available at: <https://scholarhub.ui.ac.id/jdvi/vol7/iss1/8>

This Article is brought to you for free and open access by the Faculty of Medicine at UI Scholars Hub. It has been accepted for inclusion in Journal of General - Procedural Dermatology & Venereology Indonesia by an authorized editor of UI Scholars Hub.

Lucio phenomenon in pregnancy: A histopathology review

Authors

- Siti Efrida Fiqnasyani
Departement of Dermatology and Venereology, Faculty of Medicine, University of Sebelas Maret, Dr. Moewardi General Hospital, Surakarta, Indonesia
- Triasari Oktavriana,
Departement of Dermatology and Venereology, Faculty of Medicine, University of Sebelas Maret, Dr. Moewardi General Hospital, Surakarta, Indonesia
- Ervina Rosmarwati
Departement of Dermatology and Venereology, Faculty of Medicine, University of Sebelas Maret, Dr. Moewardi General Hospital, Surakarta, Indonesia
- Dita Eka Novriana
Departement of Dermatology and Venereology, Faculty of Medicine, University of Sebelas Maret, Dr. Moewardi General Hospital, Surakarta, Indonesia
- Ambar Mudigdo
Departement of Pathology Anatomy, Faculty of Medicine, University of Sebelas Maret Dr. Moewardi General Hospital, Surakarta, Indonesia

Case Report

Lucio phenomenon in pregnancy : a histopathology review

Siti Efrida Fiqnasyani¹, Triasari Oktavriana¹, Ervina Rosmarwati¹, Dita Eka Novriana¹
Ambar Mudigdo²

¹Departement of Dermatology and Venereology, Faculty of Medicine, University of Sebelas Maret
Dr. Moewardi General Hospital, Surakarta, Indonesia

²Departement of Pathology Anatomy, Faculty of Medicine, University of Sebelas Maret
Dr. Moewardi General Hospital, Surakarta, Indonesia

Email: fiqnasyani@gmail.com

Abstract

Background: Lucio's phenomenon (LP) is a reaction occurring in lepromatous, non-nodular, diffuse leprosy patients who have not received multidrug therapy (MDT). The diagnosis of LP are based on clinical features and supported by histopathological examination. This report was conducted to establish a diagnosis of LP by histopathological examination, considering that cases of LP in pregnancy are quite rare so that clinicians can be more precise.

Case: A 35-year-old pregnant woman complained of extensive ulcers on her hand and legs. Madarosis, saddle nose, and earlobes were found. A slit skin smear examination showed a bacterial index of +4 and a morphological index of 20%. A skin biopsy from a leg ulcer with HE staining revealed thinning of the epidermis, foamy macrophages, inflammatory cell infiltrate in the dermis and subcutaneous layers, necrotizing vasculitis with thickening of blood vessel walls, and perivascular lymphohistiocytic infiltrate. Histopathological examination of auricular infiltrate showed basket weave type hyperkeratosis, grenz zone, lymphohistiocytic inflammatory cell infiltrates, foamy and touton cells. Histopathological examination by FF staining showed a heavy *M. leprae* invasion.

Discussion: Histopathological characteristics of LP in this patient found flattened epidermis, subepidermal grenz zone, aggregates and sheets of foamy macrophages admixed with predominantly huge numbers of acid-fast bacilli, foamy macrophages and touton cells. The main microscopic features also found subcutis necrotizing vasculitis. Histopathological examinations are essential to diagnose LP.

Conclusion: Histopathology of Lucio Phenomenon found grenz zone, inflammatory cell infiltrate and foamy cells. This histopathology will support the diagnosis and best treatment for LP patient.

Keywords: *Lucio's Leprosy, Lucio's phenomenon, pregnancy*

Background

Leprosy or Morbus Hansen (MH) disease is a chronic granulomatous disease caused by *Mycobacterium leprae* (*M. leprae*). Leprosy mainly affects skin and nerves.¹ Tuberculoid leprosy with low bacterial counts (paucibacillary-PB) tends to be suffered by patients with adequate immune, whereas patients with impaired immune system tend to lead from lepromatous leprosy (LL) with many bacteria (multibacillary-MB).^{2,3}

World Health Organization (WHO) reported that

the incidence of leprosy at the end of 2017 was 210,671 cases from 38 countries. Southeast Asia has most leprosy cases, with an incidence rate of 153,487. Indonesia consistently ranked as the third largest leprosy with incidence reaching 15,910 cases.^{4,5} Widodo and Menaldi (2012) reported that out of 1,021 leprosy patients, 24.2% of patients had leprosy reactions.^{5,6}

The first case of Lucio's phenomenon (LP) during pregnancy in Indonesia was reported by Dr. Soetomo Surabaya.⁷ Clinical manifestations of LL MH are nodular LL and diffuse LL or Lucio's leprosy. The characteristics of nodular LL is the

presence of scattered nodules as diffuse infiltrate, whereas, in Lucio leprosy, it is a generalized infiltrate without nodules. Lucio's leprosy is known as Lucio's phenomenon (LP) or necrotizing erythema by Latapi.²

Histopathological findings of LL are infiltrative, massive, and diffuse inflammatory cells that reach the epidermis and an area free of inflammatory cells called the Grenz zone. Foamy macrophages are found in the dermis layer and inflammatory cell infiltration is in peri adnexal or perivascular.^{10,12} There are blood vessel dilatation, endothelial proliferation, luminal occlusion, superficial and middle dermis vascular thrombosis dermis.⁹ Histopathological differential diagnosis of LP in leprosy is necrotizing Erythema Nodosum Leprosum (ENL) and Tuberculosis (TB) cutaneous.^{12,13,14}

The patient's management were given MultiDrug Therapy (MDT) of MB leprosy and administration of steroids.¹⁵ This paper aimed to report a rare case of LP in an MH MB type LL pregnant patient and to perform a histopathological examination for diagnosis as appropriate therapy can be given.

Case

A 36-year-old Javanese woman G2P1A0 36 weeks gestation, working as a housewife, came to the Emergency Room (ER) at General Regional Hospital Dr. Moewardi complained of wounds and scabs on both legs. The patient also complained of feeling weak, abdominal contraction, leg pain, and wound on the leg getting wider. Three months before, the patient complained of developing painful blisters on both lower limbs. The blisters expand and burst to form sores that are partly scabbed. Then, the patient went to the doctor and was given amoxicillin, mefenamic acid, cetirizine, and injection yet the patient did not know drug's name afterward her symptoms improved. Two weeks before, the patient returned to the same doctor and received the same treatment. The patient complained the wounds on the feet were widened and the number increased extending to hands and body, some of which were wet and smelly. Obstetrics and gynecology colleagues consulted and referred the patient to a dermatologist regarding the patient's complaints.

In previous medical history, the patient admitted there was no complaint of fever, numb spots, and red bumps. The patient had experienced similar symptoms, presence of red spots and wounds on both legs during the first patient's pregnancy four years ago. The patient was diagnosed with

vasculitis and was hospitalized. Symptoms improved a few months after the patient gave birth. The patient had never been diagnosed with MH before. Symptoms of similar illness, numb spotting, and consumption of packaged drugs in the patient's family were also denied. There were no leprosy contacts in the family and no tests were performed to undermine the diagnosis of infection.

Physical examination showed that the patient's general condition appeared to be moderately ill, with compos mentis, vital signs within normal limits, and a pain score of 2. Sensory examination results showed hyposensitivity to touch, pain, and temperature in the upper and lower extremities. The nerve thickening examination showed nerve enlargement in the greater auricular, ulnar, common peroneus, and posterior tibial nerve. Nerve examination showed no abnormalities in the facial nerve, trigeminal nerve, ulnar nerve, median nerve, radial nerve, lateral popliteal nerve, and posterior tibial nerve.

In the facial region appeared like madarosis, saddle nose, and right and left auricular regions showed infiltrates. In the abdominal region, purpuric, discrete multiple erythematous plaques are partly confluent. In bilateral inferior et superior limb region, purpuric, discrete multiple ulcerations partially confluent, well-defined, and irregular borders with necrotic tissue at several sites (Figure 1). Obstetric examination showed no abnormalities in pregnancy and fetus.

A simple laboratory examination of a slit-skin smear (SSS) with Ziehl-Nielsen staining showed the results of acid-resistant bacilli (ARB) with BI +4 and MI of 20% (Figure 2). Gram staining of ulcer specimens, polymorphonuclear (PMN) 50-70/high power field (HPF) were obtained, gram-positive cocci >100/HPF and gram-negative rods >100/HPF. A culture examination of ulcer specimen did not show any bacterial or fungal growth. Laboratory tests revealed anemia with Hb 6.6 g/dl, decreased hematocrit (HCT) 20%, slight leukocytosis 11.2 thousand/ul, decreased eritrocyte 2.51 thousand/ul and hypoalbuminemia 2.1 g/dl.

The skin biopsy were taken from two different places, namely the auricular and the femoral regions. The shape of the lesion were irregular and taken perpendicular to the depth of subcutis.



Figure 1. A-C: Facial region showed madarosis and saddle nose; D-E: Right auricular atrophy and infiltrates; F-G: Anterior et posterior trunk with purpuric, ulcer, multiple, mostly discrete, and erythematous plaques; H-K: Bilateral regions of superior and inferior limbs showed purpuric and multiple necrotic tissue partly confluent, irregularly defined purpura and ulcers, mostly covered by blackish necrotic tissue

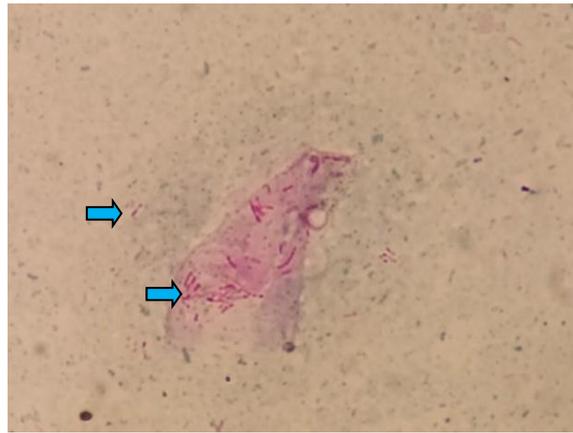


Figure 2. Slit skin smear examination taken from the ear shows acid-resistant bacilli (blue arrow) with bacterial index (BI) +4 and morphological index (MI) of 20%

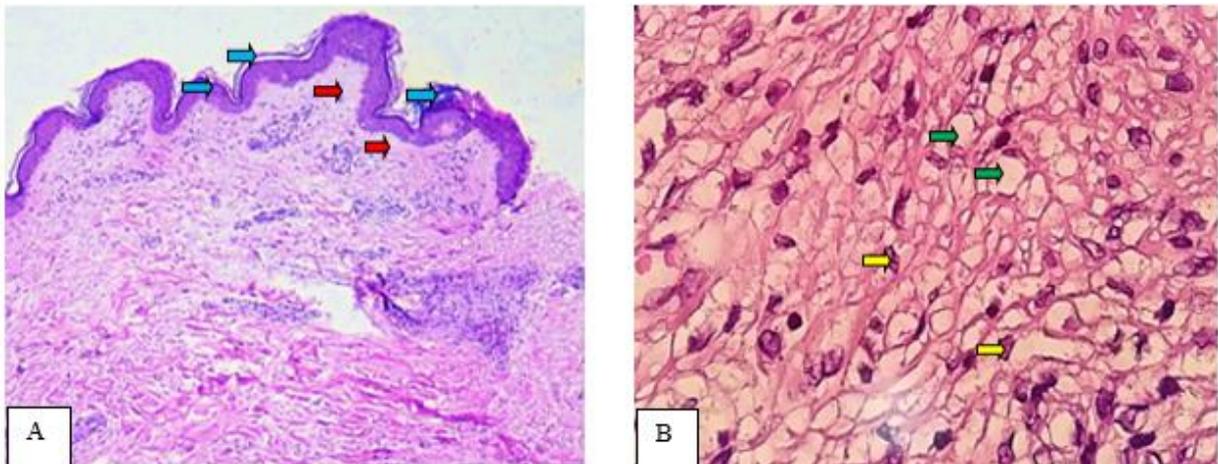


Figure 3. Hematoxylin and Eosin (HE) staining, skin biopsy taken from auricular region with clinical manifestation auricular atrophy; A (20x): a basket weave type hyperkeratosis is visible (blue arrow), Grenz zone appeared as a clear zone (red arrow); B (40x) Foamy macrophages (green arrow) and inflammatory cell infiltrates consisting of histiocytes and lymphocytes (yellow arrows)

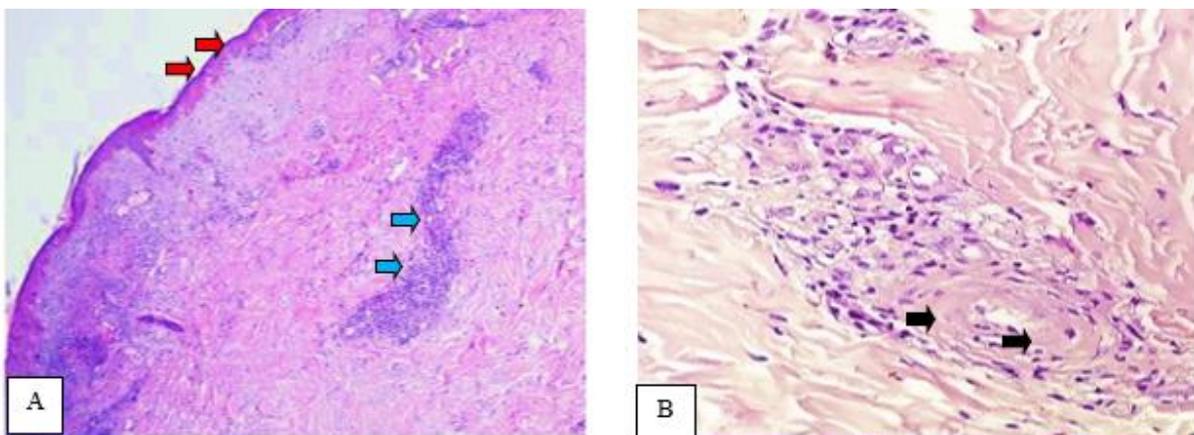


Figure 4. HE examination of the femoral region; A (10x): thinning epidermis (red arrow) and inflammatory cell infiltrates in the dermis layer (blue arrow); B (40x): Necrotizing vasculitis with thickening of the vessel wall (black arrow) and surrounding inflammatory cell infiltrates

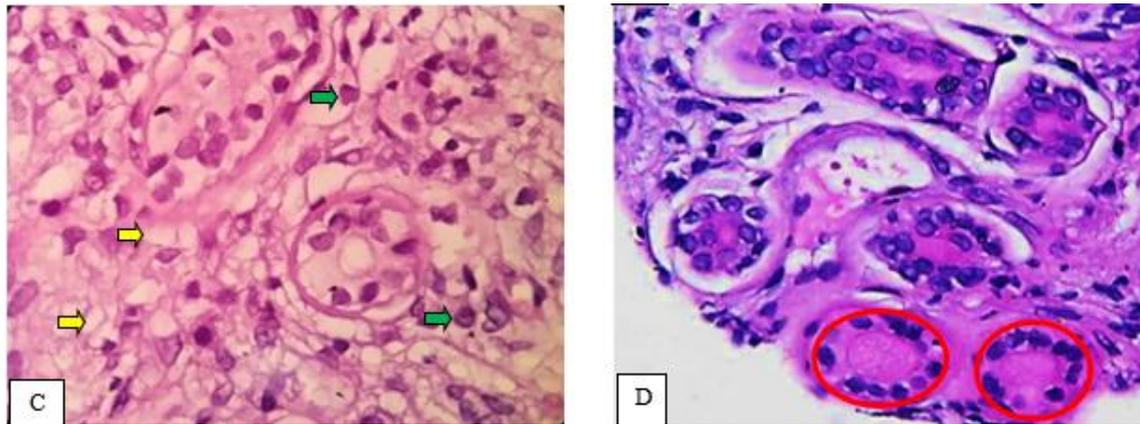


Figure 4. HE examination of the femoral region; C (100x): Infiltrates lymphohistiocytic inflammatory cells (green arrows) and foamy macrophages (yellow arrows) in dermis to subcutis layer; D (100x): Touton cells in the dermis layer (red circle)

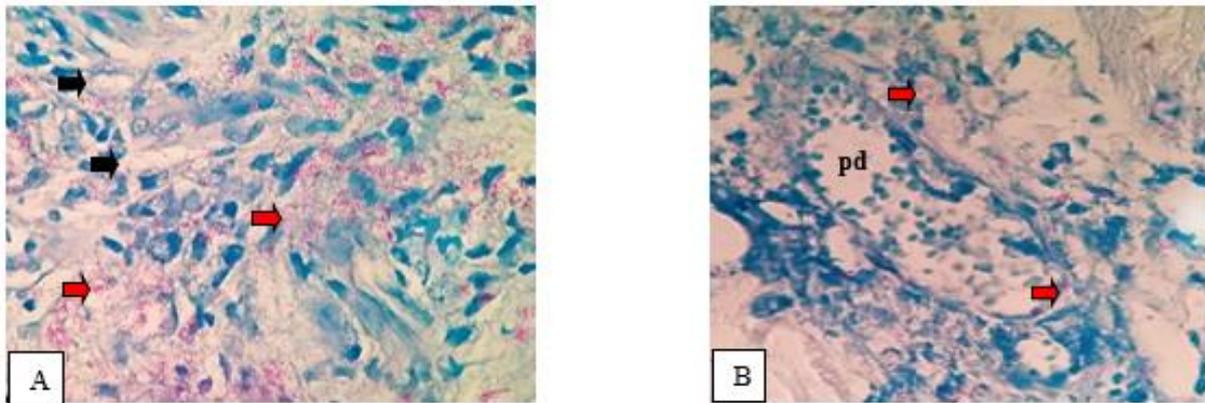


Figure 5. FF staining (100x); A: ARB (red arrow) in the dermis between the foamy macrophages (black arrow), partly forming globus; B: ARB (red arrow) in the endothelial lining of blood vessels (pd), partly visible in the lumen of blood vessel

Histopathological examination taken from auricular region with HE staining in epidermis showed basketweave-type hyperkeratosis accompanied by inflammatory cell infiltrates. In dermis, grenz zone appears free of inflammatory cells. Many foamy macrophages were found starting from the upper dermis to the subcutis layer (Figure 3). Histopathological examination taken from femoral region with the same staining showed thinning of the epidermis. Dermis shows foamy macrophages, and inflammatory cell infiltrates in the dermis, subcutis, and perivascular layers, as well as necrotizing vasculitis with thickening of the walls of blood vessels. Touton cells are found in the dermis layer (Figure 4). Skin biopsy taken from auricular and femoral region were then stained with Fite-Faraco (FF), showing positive results ARB was found in the dermis between the foamy macrophages with partially forming globus, ARB was also found in the endothelial lining of blood

vessels, partly visible in the lumen of blood vessels (Figure 5).

The working diagnosis in this patient was Lucio's phenomenon in pregnancy with MH MB type LL. Patient was hospitalized for a total of 14 days, on the 11th day of hospitalization the patient underwent sectio caesarea right at 37 weeks of gestation, 3 days after that the patient was discharged. During hospitalization, patients were given adult MB MDT therapy without dapsone, namely rifampin 600 mg/month, clofazimine 300 mg/month, and clofazimine 50 mg/day for 12 months, and injection of methylprednisolone (MP) 62.5 mg/day for one week yet LP lesion had not improved therefore MP continued with a dose of 37.5 for 5 days before delivery. The patient had an anaemia and because of that the patient were not given dapsone. Wound care is done with a compress of NaCl 0.9 %, and then mupirocin ointment twice daily. Pregnancy that triggers an

immunosuppressive condition inducing Lucio's phenomenon as in the case, can also lead to the emergence of resistance to dapsone, beside the USA FDA also still categorizes the use of dapsone in pregnancy in category C (risk cannot be ruled out) because there are no satisfactory studies in pregnant women, but animal studies demonstrated a risk to the fetus. Evaluation of the lesion after parturition showed improvement in the LP lesion thus consumption of MP was discontinued.

Treatment from the obstetric colleague was transfusion of packed red cells (PRC) to treat the anemia and conservative therapy with the maintenance of pregnancy until the age of full-term pregnancy, then planned c-section delivery. Maintenance therapy from obstetric colleague were given ferrum and folic acid supplementation.

Discussion

Rafael Lucio and Alvarado first described the Lucio phenomenon in 1852 as a necrotic skin reaction in non-nodular lepromatous Leprosy patients in Mexico.² Latapi and Zamora (1948) determined that the cause of this variant leprosy reaction was vasculitis. They stated that this incident is particularly case for non-nodular, diffuse, and untreated Leprosy, which is known as pure and primitive diffuse lepromatous or "Lucio's leprosy".¹⁹ Latapi and Zamora called this necrotic reaction the eponym "Lucio phenomenon" and "necrotizing erythema".²⁰ Lucio phenomenon is a type 2 leprosy reaction or ENL with more severe symptoms. Lucio phenomenon usually occurs in chronic leprosy patients who have not received MDT treatment or did not complete therapy.^{16,17}

The pathophysiology of LP is not fully understood. Medium-sized blood vessels are the primary site of LP infection where the immune complexes in the blood vessels, especially in dermis blood vessels, are found in many bacterial manifestations so antibody-antigen complex migrates to the blood vessels to destroy bacteria.^{18,19} cytokine secreted by macrophages, Tumor Necrosis Factor-Alpha (TNF- α), is thought to cause changes in vascular endothelial cells. TNF- α produced by macrophages and activated by T lymphocytes, antigens, natural killer (NK) cells, and mast cells, is usually undetectable in healthy individuals yet is often found in conditions of inflammation and infection.^{20,21} These cytokines cause thrombus formation and coagulopathy. TNF- α cytokines also increase the aggregation and adhesion of PMN leukocytes, causing an inflammatory response directly or through endothelial stimulation by interleukin-1 (IL-1). This mechanism plays a role in

the pathogenesis of systemic vasculitis accompanied by necrosis in LP.^{22,23} Rea and Levan (1978) found that serum immunoglobulins in LP patients experienced a significant increase.²⁴ Latapi and Zamora (1948) mentioned Lucio's reaction as a hypersensitivity response due to antigen-antibody reactions and synergism between *M. leprae* and body immunity.^{19,24} Destruction of granulomas by immune reactions causes the releases of excess lipids, resulting in massive foamy macrophages on LP.^{21,25}

The clinical symptoms of Lucio's phenomenon usually begin as a painful purpuric lesion that transforms into a serrated stellate ulcer of geometric shape involving the legs, thighs, hands, forearms, and sometimes the trunk and face. The ulcer heals in about 2-8 weeks later, leaving an atrophic hypochromic scab lesion with surrounding hyperpigmentation. Fever was not found to be associated with constitutional symptoms, systemic involvement and neuritis.²⁶

The characteristics of LP are skin ulceration, vascular thrombosis, and invasion of blood vessel walls by ARB. The clinical criteria for LP are diffuse non-nodular infiltration of the skin. The infiltrates in the ears are highly visible, making them appear thick and edematous on the face. This clinical appearance tends to cause the loss of wrinkles and gives the face a younger appearance, especially in older patients, so Lucio's Leprosy is also known as "pretty leprosy" or Bonita's Leprosy. Nodule formation will not be found in this type of Leprosy kind.^{27,28} In this case, the patient complained about scabs and wounds in both legs. Complained of scabs and sores that felt more painful, and blisters appeared. The blisters multiply and then burst to form a partly scabbed wound. Purpuric lesions began to appear in several parts of the body one day before being admitted to ER (Figure 1), were painful, and after receiving treatment, the purpuric lesions reduced and evolved into ulceration, and no nodules were found. Clinically the patient, in this case, was by the clinical picture of the LP patient.

Pregnant women tend to experience a decrease in the cellular immune system which at risk of *M. leprae* infection, especially in the third trimester. Suppression of cellular immunity occurs primarily through decreased T helper 1 response and interleukin 2 production. The incidence of relapse after completion of treatment generally begins with symptoms of leprosy, neuritis, and erythema nodosum leprosum. Pregnancy contributes to the progression of leprosy, especially in untreated cases. A study 20-30% of pregnant women experience early symptoms of leprosy or

immediately experience LP.⁷ Difference related to LP in pregnant women and non-pregnant women is the trigger itself, pregnancy as trigger tends to suppress cellular immunity which triggers an exacerbation of leprosy, after the trigger is gone and the patient is completely treated, the patient's leprosy complaints will improve, yet if the patient is triggered again, such as becomes pregnant again, then there is a chance to experience a relapse. Furthermore, in relation to immune system, leprosy in pregnancy is more likely the LL MB type.⁷

Histopathological examination is beneficial to assist in the diagnosis of LP. The histopathology of LP has features of leukocytoclastic vasculitis as the main pathological change, dilatation of blood vessels, endothelial proliferation, lumen occlusion, mild mononuclear cell infiltration, blood vessel thrombosis of the superficial and middle dermis, which is clinically seen as ischemic or necrotic.

Aggregation of AFB in the vascular endothelium is often seen on histopathological examination.^{7,30,36} (Figure 6) Epidermal necrosis, subpapillary vascular involvement, minimal neutrophils, and multiple ARB is a histopathological diagnostic guide, and this feature can differentiate between LP and necrotic ENL.^{14,33} Acid-resistant bacilli were seen on histopathological examination with FF staining.³¹ In this patient, vasculitis was also found, and ARB appeared in endothelial lining of blood vessels, some of which appeared in the patient's blood vessel lumen.

Histopathological examination results from the ulcer biopsy in the femoral region with HE staining showed thinning of the epidermis, foamy macrophages, inflammatory cell infiltrates in the dermis layer to the subcutis, necrotizing vasculitis with thickened blood vessel walls and lymphohistiocytic infiltrates. Histopathological examination results from samples of the auricular region with HE staining showed hyperkeratosis of the basket weave type, Grenz zone, lymphohistiocytic inflammatory cell infiltrates, and many foamy cells were found starting from the upper dermis layer to the subcutaneous layer (Figure 7). Both samples were stained with FF staining as well, they showed many smears in the upper dermis layer to the subcutis, and in the endothelial layer of blood vessels, some of the bacilli formed globes. The histopathologic features found in this patient led to a diagnosis of MH MB type LL with LP (Figure 8).

The differential diagnosis in these patients are tuberculosis cutis and necrotizing ENL.^{1,32}

Necrotizing ENL histopathologic features looked like dominant inflammatory cell infiltration of neutrophils and have the type of leukocytoclastic vasculitis. In addition, the appearance of foamy macrophages accompanied by PMN infiltrates (Figure 9).³⁰ The histopathological features of necrotizing ENL can resemble LP, but the typical symptoms of purpuric lesions and pain are only found in LP.^{1,9,32} The clinical features in this patient are more directed towards LP and unsuitable for necrotizing ENL.

Cutaneous tuberculosis has histopathological features of a caseous granuloma form, which is confluent and indefinitely surrounded by lymphocytes and plasma cells and shows Langhans giant cells (Figure 10).^{30,33} In this patient, there were no features of caseous granuloma or Langhans giant cells, so it was unsuitable for cutaneous tuberculosis. It is known that both lepromatous leprosy and LP should have more Langhans giant cells than foreign body giant cells (FBGC). However, this case's contradiction could be explained by the fact that FBGCs can also be found in tissues with large foreign particle sizes allowing macrophage phagocytosis because of their large size and surface characteristics, these substances contribute to a chronic series of reactions, Foreign Body Response (FBR).^{30,33}

WHO recommended MDT MB as a therapy for the Lucio phenomenon. Additional therapy in the form of corticosteroid 1 mg/kg body weight each day and clofazimine starting with 300 mg/day will give a good response.³⁴ Therapeutic response is assessed for 4-6 weeks. Antibiotics can be given to treat secondary infections.³⁵ MDT MB therapy in this patient was rifampin 600 mg/month, clofazimine 300 mg/month, and 50 mg/day, without dapsone because of anemia. Proper treatment can improve the clinical condition of Lucio's Leprosy.

The strength of this study showed a concordance between history, physical examination, histopathological examination, and ARB, however the limitation of this study is that investigations such as polymerase chain reaction (PCR) have not been carried out to detect *M. leprae* DNA using primary pF-LpR. Other supporting examinations that can be carried out are serological examinations through the patient's peripheral blood or umbilical cord using the Enzyme-Linked Immunosorbent Assay (ELISA) in which samples should be obtained during the patient's cesarean section.

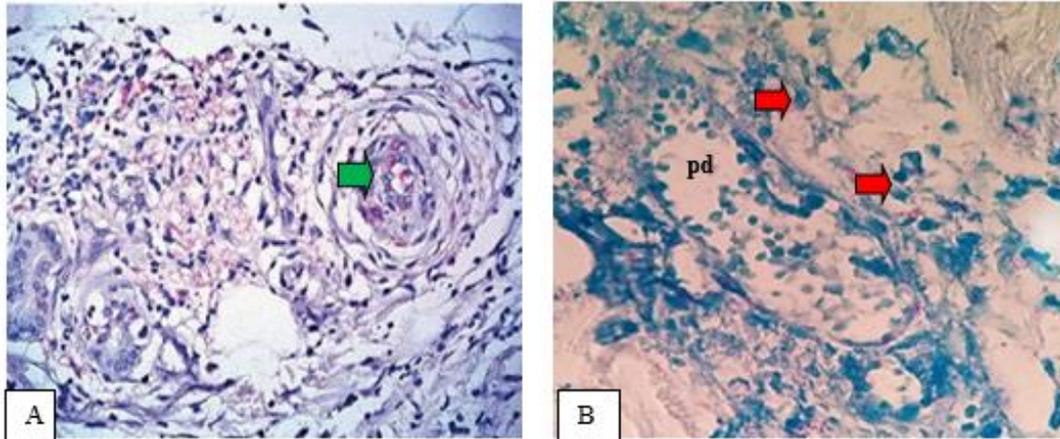


Figure 6. Features of vasculitis in LP with FF staining; A (40x): Blood vessels in the dermis showing vasculitis (green arrow) with bacteria on the endothelial wal; B (100x): ARB (red arrow) in the endothelial lining of blood vessels (pd), partially visible in the patient's vascular lumen

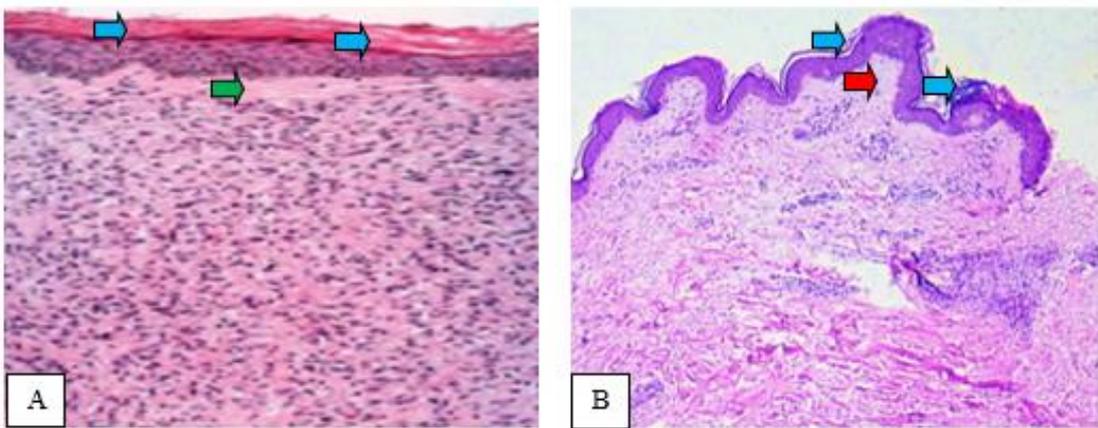


Figure 7. Grenz zone appearance in HE staining; A (40x): hyperkeratosis (blue arrow) with a visible area of the Grenz zone (green arrow); B (20x): Hyperkeratosis of the basket weave type (blue arrow), the Grenz zone appears as a clear zone (red arrow)

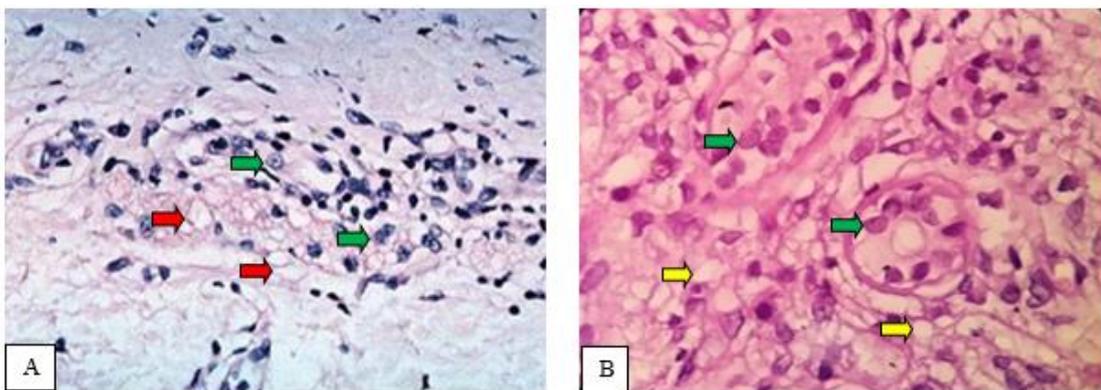


Figure 8. Foamy macrophages appearance in HE staining; A (100x): Lymphohistiocytic inflammatory cell infiltrates (green arrows) and foamy macrophages (red arrows); B (100x): Infiltrates lymphohistiocytic inflammatory cells (green arrows) and foamy macrophages (yellow arrows) in the dermis to the subcutis layer

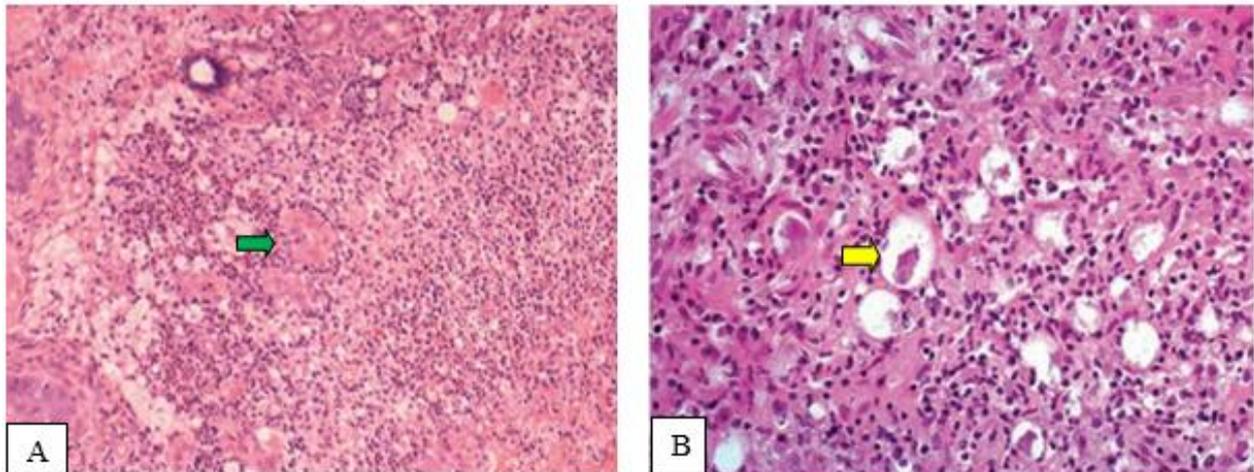


Figure 9. Features of vasculitis in necrotizing ENL HE staining; A (10x): Necrotizing ENL shows inflammatory cell infiltrates with multiple vasculitis (green arrow) called neutrophils and leukocytoclastic vasculitis; B (40x): Macrophage (yellow arrow) is seen with vacuoles and PMN infiltrates

Conclusion

A 36-year-old G2P1A0 woman complained of wounds and scabs on her extremities. Dermatology examination revealed facial appearance of madarosis, saddle nose, and infiltrative auricular. In abdominal, purpuric, discrete multiple erythematous plaques are partly confluent. Extremities appear purpuric, with multiple discrete ulcers, well-defined and irregular margins, partly confluent with necrotic tissue at several sites. The physical examination revealed hyposensitivity and nerve enlargement. SSS found BI+4 and MI 20%. The auricula sample showed hyperkeratosis with a Grenz zone, inflammatory cell infiltrates, and foamy cells, whereas the femoral sample exhibited thinning epidermis, inflammatory cell infiltrates, and necrotizing vasculitis. This present case, supports the diagnosis of Lucio's phenomenon in pregnancy with LL type MH MB.

References

1. Salgado CG, de Brito AC, Salgado UI, Spencer JS. Bacterial infection : Leprosy. In: Kang S, Amagai M, Brucjner AL, et al. editors. Fitzpatrick's dermatology. 9th ed. New York : McGraw Hill Education; 2019;p. 2892-924.
2. Jurado F, Rodriguez O, Novales J, Navarette G, Rodriguez M. Lucio's Leprosy: A clinical and therapeutic challenge. Clin Dermatol. 2015;33(1):66-78.
3. Suzuki K, Akama T, Kawashima A, Yoshihara A, Yotsu RR, Ishii N. Current status of Leprosy: Epidemiology, basic science and clinical perspectives. J Dermatol. 2012;39(2): 121-9.
4. World Health Organization. Weekly epidemiological record. WHO. 2018;89(36): 389-400.
5. Firdaus F. Risiko keterlambatan berobat dan reaksi kusta dengan cacat tingkat 2 [in Indonesian]. J Ber Epid Airlangga. 2019;7(1):25-32.
6. Widodo AA, Menaldi SL. Characteristics of leprosy patients in Jakarta. J Indon Med Assoc. 2012;62(11):423-7.
7. Prakoeswa CRS, Herwanto N, Agusni RI, et al. Lucio phenomenon of leprosy LL type on pregnancy: A rare case. Lepr Rev. 2016; 87(4):526-31.
8. Fogagnolo L, Souza EMD, Cintra ML, Velho PENF. Vasculonecrotic reactions in Leprosy. Braz J Infect Dis. 2007;11(3):378-82.
9. Rocha RH, Emerich PS, Diniz LM, Oliveira MBBd, Cabral ANF, Amaral ACVd. Lucio's Phenomenon: Exuberant case report and review of brazilian cases. A Bras Dermatol. 2016;91(5 Supl 1):60-3.
10. Han, XY, Quintanilla M. Diffuse Lepromatous Leprosy Due to Mycobacterium lepromatosis in Quintana Roo, Mexico. J Clin Microbiol. 2015;53(11):3695-98
11. Elder DE, Elenitas R, Rosenbach M, et al. Bacterial. 10th ed. In Elenitsas R, Junior BLJ., George F. Murphy GF, Xu X. editors. Lever's Histopathology of the Skin. 10th ed, Philadelphia: Lippincotts William & Walkins; 2015;p.1310-53.

12. Scolard DM. Pathogenesis and pathology of Leprosy in the international textbook of Leprosy. India : Jaype Brothers Medical Publisers;2015;p. 11-13.
13. Sharma P, Kumar A, Tuknayat A, Thami GP, Kundu, R. Lucio phenomenon: A rare presentation of hansen's disease. *J. Clin Aesthet Dermatol.* 2019;12(12):35-8.
14. Laga, Alvaro Laga and Danny A Milner Jr. Bacterial infection in Lever's Histopathology of the Skin. Rosalie Elenitsas, Bernett L. Johnson Jr., George F. Murphy, Xiaowei Xu penyunting. Philadelphia: Wolter Kluwer Publisng; 2015: 1310-33.
15. Kamath S, Vaccaro SA, Rea TH, Ochoa MT. Recognizing and managing the immunologic reactions in Leprosy. *JAAD case rep.* 2014; 71(4):2-4.
16. Rea TH, Moldlin RL. Leprosy. In: Wolff K, Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, Fitzpatrick TB, Editors. *Fitzpatrick's Dermatology in General Medicine.* 7th ed. Kang S, Amagai M, Brucjner AL, Enk AH, Margolis DJ, McMichael AJ, dkk, penyunting. New York: McGraw-Hill; 2008: 1786–96.
17. Lockwood DNJ. Leprosy In: Burns T, Breathnach SB, Cox N, Griffiths C, Rook's TB, editors. *Rook's Textbook of Dermatology.* Christopher Griffith, Jonathan Barker, Tanya Bleiker, Robert Chalmer dan Daniel Creamer, Editors. 8th ed. Oxford: Wiley-Blackwell. 2010; 32: 1–20.
18. Suchonwanit P, Triamchaisri S, Wittayakornrerk S, Rattanakaemakorn P. Leprosy reaction in thai population: A 20-Year Retrospective Study. *Dermatol Res Pract.* 2015;S15(5):253-54.
19. Prem Anand P, Oommen N, Sunil S, Deepa S, Potturu M. Pretty leprosy: Another face of hansen's disease: A review. *Egypt J Chest Dis Tuberc.* 2014;63(4):1087-90.
20. Agusni I. Imunologi Penyakit Kusta. Dalam: *Buku makalah legkap kursus Immunodermatologi I Dokter Spesialis Kulit dan Kelamin* [in Indonesian]. Sudigdoadi, Sutedja E, Agusni YH, Sugiri U, Editors. Bandung: RSUP Hasan Sadikin ;2000:p231–44.
21. Baratawidjaja KG, Rengganis I. *Immunologi dasar* [in Indonesian]. Arjatmo Tjokronegoro, Hendra Utama, editors. 12th ed. Jakarta: Fakultas Kedokteran Univesitas Indonesia Press;2018: p34-52.
22. Sarno EN, Grau GE, Vieira LMM, Nery JA. Serum level of tumor necrosis factor – alpha and interleukin – 1 β during Leprosy reactional states. *Clin. Exp Immunol.* 1991;84:103–8.
23. Listiawan MY. *Perbandingan ekspresi TLR1/2, NF κ B p150/50, NF- κ B p65 dan TNF- α pada makrofag penderita eritema nodosum leprosum dengan kusta multibasiler sebagai tanda aktivitas kekebalan alamiah* [in Indonesian]. *BIK* 3. 2011;23(3):207–15.
24. Herath S, Navinan M, Liyanage I, et al. Lucio's phenomenon, an uncommon occurrence among leprosy patients in Sri Lanka. *BMC Res. Notes.* 2015;10(11):4-15.
25. Serrano-Coll HA, Beltrán-Alzate JC, Buitrago SM, Cardona-Castro N. Lepromatous leprosy and human immunodeficiency virus co-infection associated with phenomenon of Lucio versus immune reconstitution inflammatory syndrome. *J. Infect.* October, 2016;20(4):272-5.
26. Lezcano L, Di Martino B, Galeano G, et al. Vasculonecrotic reactions in leprosy. Two cases of Lucio's phenomenon. *Med Cutan Ibero Lat Am.* 2010;38(4):1-7.
27. Geluk A, Bobosha K, Schip JJvd, et al. New biomarkers with relevance to leprosy diagnosis applicable in areas hyperendemic for Leprosy. *J Immunol.* 2012;188(10):4782-91.
28. Misra DP, Parida JR, Chowdhury AC, Pani KC, Kumari N, Krishnani N, et al. Lepra reaction with lucio phenomenon mimicking cutaneous vasculitis. *Case Reports Immunol.* 2014; 2014: 641989.
29. Rojas-Espinosa O, Gonzales-mendoza A., Estrada-Parra, S. Et al. Presence of soluble Mycobacterium leprae-derived antigen in the inflammatory exudate of reactional lepromatous Leprosy. *Lepr. Rev.* 2010;56(3): 229-38.
30. Magana M. Lucio-latapi leprosy. Dalam: *Leprosy: A practical guide.* Nunzi E, Massone C, penyunting. Springer: 2012; 111-4.
31. Pradana P, Rosandi R, Daili ESS, Sirait SP, Rihatmadja R, Marissa M, et al. *Gambaran Klinis dan Histopatologi Fenomena Lucio* [in Indonesian]. *MDVI.* 2016;43(4):147-52.
32. Sehgal VN. Lucio's Phenomenon/Erythema Necroticans. *Int J Dermatol.* 2005;44(7):602-5.
33. Johnston RB. The vasculopathic reaction pattern. In: *Weedon Skin Pathology Essential.* Hosler GA, Editor. 2nd ed Vol 6. Florida: Elsevier; 2017;p.137-8.
34. Peixoto AB, Portela PS, Leal FRP de C, Brotas AM, Rodrigues NC dos S. Lucio's Phenomenon. Case Study of an Exceptional Response to Treatment Exclusively with Multibacillary Multidrug Therapy. *An Bras Dermatol.* 2013;88(6 Suppl 1):93–6.

35. Kar HK, Sharma P. Leprosy reactions: pathological and clinical features. In: IAL Textbook of Leprosy. Kar HK, Kumar B, penyunting. 1st ed. New Delhi: Jaypee Brothers Medical Publishers Ltd; 2010:269-89.
36. Ranugha PSS, Chandrashekar L, Kumari R, Thappa DM, Badhe B. Is it Lucio Phenomenon or Necrotic Erythema Nodosum Leprosum?. Indian J Dermatol. 2013;58(2): 160-9.