*Journal of Pakistan Association of Dermatologists*. 2023;**33(4)**:1701-1707.

**Case Report**

# Clinico-histopathological correlation in 3 patients with Lucio phenomenon: A serial case report

**Anggun Putri Yuniaswan, Diah Prabawati Retnan*, Dhelya Widasmara, Dhany Prafita Ekasari, Adya Sitaresmi**

Departement of Dermatology and Venerology, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia.
* Departement of Pathology Anatomy, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia.

**Abstract** Lucio Phenomenon (LPh) is a reactional state usually observed in untreated or inadequately treated leprosy and is a life-threatening medical emergency. Several cases of LPh have been reported in Indonesia, which is an endemic country with highest burden of new case besides India and Brazil. Generally, histopathological findings in LPh reveal granulomatous and panniculitis reactions with vascular infiltration of acid fast bacilli. However, it is still debatable whether the main pathophysiology of necrosis is due to occlusive vasculopathy or immune complex-mediated process. In this study, we report clinical and histopathological descriptions of 3 patients with LPh. The first case was resulted with severe necrosis, mortality and massive bacilli infiltration with endothelial damage on histopathology examination. The second and third case presented less severe manifestation with multiple ulcers covered with hemorrhagic crust and mild necrosis. The histopathology examination showed minimal inflammation on the endothelial. This serial case report showed that histopathological examination might be useful as a prediction value on LPh since it can characterize the basic pathogenesis process. Lucio Phenomenon (LPh) is a reactionary state usually observed in untreated or inadequately treated leprosy and is a life-threatening medical emergency.

***Key words***
Lucio phenomenon; Histopathology; Leprosy; Manifestation.

## Introduction

Lucio Phenomenon (LPh) first described in a paper (1852) by Rafael Lucio and Ignacio Alvarado as red and painful spots form of Leprosy, which then undergoing necrosis. This paper supported the previously finding by Ladislao de la Pascua.[1] Later, at the 5th International Congress of Leprosy held in Havana in 1948, Latapı´ and Chevez-Zamora mentioned that the underlying condition of this form was generalized diffuse cutaneous infiltration, termed ‘pure and primitive diffuse lepromatosis’ or Diffuse Lepromatous Leprosy (DLL).[1-3]

Diffuse Lepromatous Leprosy (DLL) is considered the most anergic of the all-immunological spectrum of leprosy. This type of leprosy was known exclusively in Mexico and Central America.[3,4] However, several cases are being reported sporadically worldwide nowadays, such as from South Asian and South East Asian countries, including Indonesia.[4]

Leprabonita leprosy is a skin variant of erythema

**Address for correspondence**
Dr. Anggun Putri Yuniaswan
Departement of Dermatology and Venerology, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia.
Jalan Jaksa Agung Suprapto No.2, Klojen, Kec. Klojen, Kota Malang, Jawa Timur, Indonesia.
Ph: +6281236391019
Email: yuniaswanputri83@gmail.com

nodusum leprosum (ENL) that is characterized by generalized infiltration, shininess, myxedematous appearance, and loss of skin creases. LPh almost exclusively found in DLL, manifested as red to purple, purpuric patches with blister which then evolve to ulcer and leaving jagged scar in recovery process.[2,3,5] LPh resembles necrotic variant of erythema nodusum leprosum (ENL) based on the clinical presentation.[1,2] The ulcers or necrotic lesion of LPh are commonly painless although some patients experience burning sensation. ENL, on the other hand, is marked by painful, erythematous tender plaques or nodules that may be superficial or deep-seated with high fever and malaise. It may also present as edema of the face, hands and feet, iritis, episcleritis, arthritis, arthralgia, dactylitis, lymphadenopathy, organomegaly and orchitis, all of which are rare or totally absent in LPh.[2,3,5,6]

LPh is a type of reaction commonly found in neglected or inadequately treated patients. It may not be easily recognized and is sometimes misdiagnosed. Histologic features of this form of leprosy were first reported by Martinez Baez in 1941 and focused on acute vasculitis with nuclear dust and thickening, occluding the larger vessels.[1,2,5] The most common finding is vascular involvement with massive bacterial invasion. The etiopathogenesis is not fully understood, and the relevance of vascular damage to the clinical manifestations is still unclear.

## Case Report

***Case 1*** A 33-year-old man consulted from Internal Medicine Department with a suspicion of Toxic Epidermal Necrolysis. The chief complaint was scattered blisters and ulcers throughout the body. He started to develop purplish blue patches and blisters four days earlier. Previously, both of his legs were swollen, slightly painful, and accompanied by fever. Some of the spots then became blistering and necrotizing, leaving deep, irregular ulcers. His eyebrows and eyelashes were diminished since one year before. He also occasionally felt numbness on both arms and legs, but it was never diagnosed as leprosy. Dermatological examination showed multiple violaceus patches and plaques, varying in shapes and sizes, on almost all of the body.

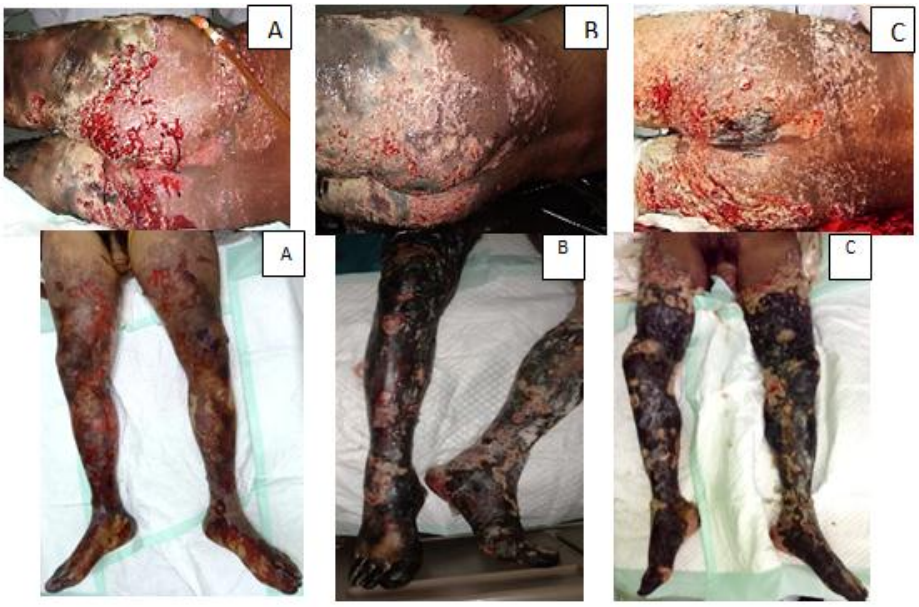


**Figure 1** Clinical presentation of patient no.1, during the hospitalization from first week to the third week(A-C).

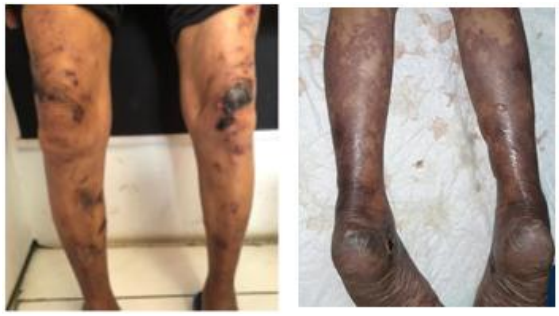

**Figure 2** Clinical presentation of patients 2 and 3. Necrotic area with blackish crust and some atrophic scars on patient no. 2. Purpuric reticulated patches and blisters on patient no. 3

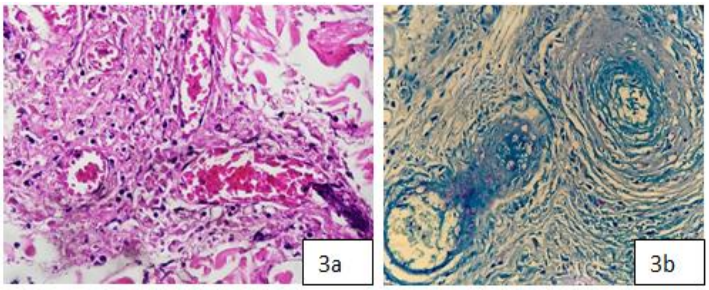


**Figure 3** Leukocytoclastic vasculitis with vascular dilatation, endothel damage, polymorphonuclear infiltrate and thrombosis (3a). Granulomatous reaction with lumen obliteration and AFB infiltration on endothel.

**Table 1** Patients demographics and clinical characteristics

| *No* | *Gender, age* | *Clinical findings* | *Location* | *History of leprosy* |
|---|---|---|---|---|
| 1 | M, 33 yrs. | Violaceous patches and plaques, necrotic ulcers<br>Facies leonine (+) | Arms and legs<br>Hands<br>Buttock | Newly diagnosed |
| 2 | M, 60 yrs. | Multiple erythematous nodul, ulcer with black crust, erosions and atrophic scar | Legs | Newly diagnosed |
| 3 | F, 66 yrs. | Purpuric reticulated patches and blisters | Legs | Previously diagnosed 15 years, incomplete treatment |

On both arms and legs, multiple bullae, ulceration with angulated margins, and necrosis were present, with Body Surface Area (BSA) reaching 40%. CT angiography on both inferior extremities revealed vascular patency; however, saturation was extremely low.

BI was +6 and MI was 1% based on earlobe slit skin smear examinations. Histopathology examination found massive leukocytoclastic vasculitis, paniculitis, and vascular damage. There were also dermal necrotic and granulomatous inflammatory reactions, dominated by foamy macrophages, as suggested by LP. He also got anemia, neutrophilia, hyperkalemia, monocytosis, severe hypoalbuminemia, azotemia, and lymphocytopenia.

He was treated with MB MDT without Dapsone, Cloxacillin 500 mg four times a day, methylprednisolone 48 mg/day, or routine wound care. During the hospitalization, no new ulcers appeared, but fortunately, the necrotizing process continued to develop. He also had a septic condition, with the culture growth of the ulcer revealing *Pseudomonas luteola* and *Klebsiella pneumoniae*. He died on the 20th day of hospitalization.

***Case 2*** A 60-year-old man presented with multiple wounds on both arms and legs since one month before admission. Those wounds had been recurring for the past three years. It began with reddish patches, which transformed into blisters and ulcers. The ulcers healed spontaneously and left atrophic scars. There is no pain or burning sensation from those wounds. He had never been diagnosed with leprosy previously. He also occasionally had tingling sensations on both legs. Physical examination revealed madarosis and infiltrates on both earlobes. There were multiple shallow ulcers covered with black crust, hyperpigmented patches, and atrophic scars on both knees and legs. AFB were found in the earlobe's slit skin

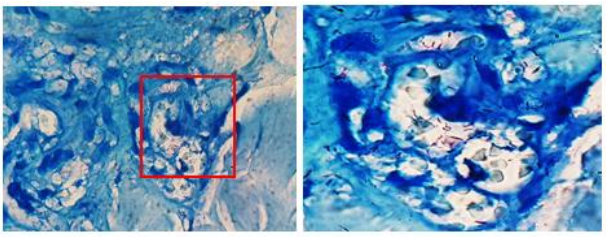

**Figure 4** Colonisation of AFB in endothelium walls (Ziehl Neelsen staining).

and ulcer's base, with BI of +5 and MI of 2%. A granulomatous reaction was seen on the histological examination. There were also AFB invasions on the endothel with a minimal infiltrate along with blood vessel congestion. He was diagnosed with LP and treated with an MDT regimen for MB from the WHO and topical fusidic acid for the ulcers. He showed clinical improvement with the treatment.

***Case 3*** A 66-year-old woman presented with red, purple spots on both of her upper and lower extremities since the previous nine days. Some spots developed into blisters and ulcers with pain and burning sensations. She had no fever or any constitutional symptoms. She had been diagnosed with leprosy 15 years ago, but the treatment was incomplete. For the past years, she did not have any specific symptoms such as reccurring fever, painful nodules, myalgia, or tingling and numbness sensations. Based on her physical examination, she had madarosis, a saddle nose, and infiltration on both earlobes.

Dermatological examination revealed multiple red violaceus patches, sharply delineated, and loose bullae were found scattered on the extremities. Slit-skin smear showed +6 BI and 50% MI. A skin biopsy showed a granulomatous reaction with foamy macrophages, lymphocytes around the periadnexal, and a mild vasculitis reaction. There was also endothelium swelling and obliteration of the lumen. A diagnosis of LP was made, and she was treated with the MDT regimen and showed marked improvement.

## Discussion

Leprosy is a chronic infectious disease that predominantly affects the skin and peripheral nerves. Systemic manifestation is very likely to occur, mostly in lepromatous or multibacillary patients. There is an important pathological observation in LL patients: the invasion of endothelium of blood vessels and lymphatics. [1,7] Unlike other bacterial infections, the bacilli do not secrete any toxins, and the infection remains silent while the bacilli have already spread to almost every part of the body. [7]

*M. leprae* commonly attacks macrophages but sometimes also colonizes endothelial cells, most notably those lining the pineurial and perineurial blood vessels. The study oof the *M. leprae* genome has led to the identification of surface proteins called adhesins that appear to play a prominent role in their dissemination by helping the attachment of bacilli to Schwann cells and endothelial cells. [1,2] Another finding of immune reactivity to endothelial cells suggests that the bacteria reside and multiply within these cells. The infection of endothelial cells has long been documented in lepromatous disease, but the

**Table 2** Histopathological findings.

| *Histopathological findings* | *Case 1* | *Case 2* | *Case 3* |
|---|---|---|---|
| Epidermal necrosis | + | - | - |
| Polymononuclear infiltrate | ++ | + | + |
| Leukocytoclastic vasculitis | ++ | + | + |
| Vascular occlusion and thrombosis | + | + | - |
| Lumen obliteration | - | + | - |
| AFB in endothelial cells | ++ | + | + |
| Panvasculitis | ++ | - | - |

colonization is not exclusively found in necrotizing lesions. However, in LPh, the infiltration of the endothelial cells seemed to be the main focus and was responsible for the pathogenesis of cutaneous infarcts.[8]

Another hypothesis is that different species are the causative agents of DLL. Han *et al*. (2008) reported their findings based on the cases of two Mexican patients with cutaneous infarct and multiple organ vasculitis. Gene research of the species with the PCR technique and the clinicopathologic features led Han *et al.* to propose *Mycobacterium lepromatosis*. They propose that this species, with its longer incubation period compared to *M. leprae*, may account for some of the clinical and geographic variability of DLL. Other research lately has supported the idea of the new species, using the database by Hans *et al*.[8]

Clinical presentations of DLL are barely visible, and the patient often does not notice the diffuse infiltration. Other characteristics are similar to the lepromatous type of leprosy, such as alopecia of the eyebrow and deformity of the nose cartilage, known as "saddle nose". This feature of DLL was present in all patients in this serial case. However, two patients have not been diagnosed with leprosy, while the other had been diagnosed 15 years previously.[8]

DLL patients may develop a specific reaction state, namely LPh. Typical skin lesions of LPh begin with clusters of reddish-blue to purple spots that are slightly indurated. These spots then evolve into purpuric and necrotic lesions, with or without blister formation. Later, the necrotic eschar detached easily, leaving atrophic scars. It takes several weeks for the lesions to develop, while the patient usually remains afebrile. All patients in this case series developed ulcerations and necrotic lesions, mostly in the lower extremities. According to other case reports, lesions typically present in the lower extremities before moving upward to the trunk and upper extremities. However, the severity and extent of the damage were different in each case. The first case had the most severe manifestation, and the necrosis kept progressing within days and showed no improvement with MDT treatment. The patient passed away due to an extensive necrotic lesion which led to a septic condition.[8]

Some authors declare that LPh clinical manifestation is similar to the necrotic variant of Erythema nodusum leprosum. However, based on histopathology, LPh can be differentiated from necrotican ENL by the minimal number of polymorphonuclear infiltrates in the deeper layer of the dermis and subcutis in LPh. There has been no consensus about the histopathological abnormalities of LPh.[9]

Ocampo *et al*. divided histologic changes into five stages: the early stage, bacillary dissemination; the well-developed stage, ischaemic necrosis due to non-inflammatory vascular occlusion; and the last stage, necrosis by vascular occlusion plus leprosy reaction. The main feature of the fourth and fifth stages was focused on the blood vessel's damage.[1]

The histological vascular characteristics of LPh consist of several outstanding features. The presence of *M. leprae* in endothelial cells seemed to disseminate from the deep plexus to all cutaneous blood vessels and be responsible for this vascular pathology. The histopathological changes are observed throughout the thickness of the vessel wall, which includes homogenization of the vessel wall and fibrosis. The typical vascular features are endothelial proliferation, thickening of vessel walls to the point of obliteration, angiogenesis, vascular ectasia, and thrombosis.[1,2] LPh is also associated with

necrosis of arterioles, whose endothelium is massively invaded by *M. leprae*. It is markedly associated with vasculitis and thrombosis of the superficial and deep vessels, resulting in hemorrhage and skin infarction.[1,2] Well-developed lepromatous *granulomata* in the intima of the veins may also distort the lumen. Granulomatous reaction with vascular obliteration can be seen in the third case.[6]

Based on the histopathological examination recorded in these serial cases, all patients presented with vascular changes. There were inflammatory infiltrates of polymorphonuclear cells and macrophages around the vessels, thickened walls, and thrombosis. There were also massive leukocytoclastic vasculitis, endothelial fibrinoid necrosis, and lumen occlusion (Case 1). These findings are in accordance with Marissa *et al*., who reported granulomatous inflammation with epidermis and dermis necrosis.[4] They also found thickened walls, edema, and lumen occlusion. Rea *et al*. published the histopathologic alterations of 30 pure and primitive diffuse lepromatous leprosy cases with Lucio's phenomenon, in which the vascular changes were predominant and defined as lepromatous-granulomatous vasculitis.[3]

Magana *et al*. declared that LPh is a distinct kind of vasculitis that has an excess of antigen, leading to ischemic necrosis of the dependent tissues. They also conducted a retrospective clinical-pathological study to gain supporting evidence for the hypothesis of panvasculitis as the pathogenesis of LPh. The study showed that all kinds and all sizes of blood vessels are also involved in the process in the form of infiltration by macrophages and/or damage to vessel walls. The first case showed occlusive vasculopathy with panniculitis and neutrophilic infiltrate, while the second and third revealed less reactive vasculopathy.[10]

Based on the histological features, there are two types of Lucio's phenomenon. The first type is characterized by leukocytoclastic vasculitis due to immune complex involvement induced by *M. leprae* antigen. The second type is marked by endothelial cell proliferation, thrombosis, and ischemic necrosis as a result of direct invasion by *M. leprae*. This different finding is probably due to biopsy site and timing variation as LP may evolve.[11]

However, in this study, the vascular damage relates to the clinical manifestation. In the first case, the severe necrosis was marked by massive vascular damage and panvasculitis. While the second and third cases revealed less severe manifestations that correlated with minimal inflammatory reactions on histology findings.

## Conclusion

Increased recognition of LPh cases is reported from South Asian and South-East Asian countries. Thus, clinicians should be aware, especially when clinical manifestations are relevant to DLL and LPh. The findings in this case support the hypothesis that infiltration of bacilli into endothelial cells might induce vascular reactivity, which leads to necrosis, and might correlate with the severity of the disease. It suggests that histopathological examination might be useful as a prediction value for LPh since it can characterize the basic pathogenesis process. However, these findings need to be confirmed with a larger number of LPh cases.

## References

1. Vargas-Ocampo F. Diffuse leprosy of Lucio and Latapí: a histologic study. Leprosy review 2007; 78 (3): 248–60. doi: 18035776.
2. Frade MAC, Coltro PS, Filho FB *et al*. Lucio's phenomenon: A systematic literature review of definition, clinical features, histopathogenesis and management. Indian Journal of

Dermatology, Venereology and Leprology 2021; 88 464. doi: 10.25259/IJDVL_909_19.

3. Rea TH, Jerskey RS. Clinical and histologic variations among thirty patients with Lucio's phenomenon and pure and primitive diffuse lepromatosis (Latapi's lepromatosis). International journal of leprosy and other mycobacterial diseases : official organ of the International Leprosy Association 2005; 73 (3): 169–88.
4. Marissa M, Rihatmadja R, Surya D *et al*. Lucio's phenomenon: A report on six patients in a tertiary referral hospital in Indonesia. Journal of General-Procedural Dermatology and Venereology Indonesia 2020; 5 (1): 40–47. doi: 10.19100/jdvi.v5i1.225.
5. Jurado F, Rodriguez O, Novales J *et al*. Lucio's leprosy: A clinical and therapeutic challenge. Clinics in Dermatology 2015; 33 (1): 66–78. doi: 10.1016/j.clindermatol.2014.07.004.
6. Nath I, Chaduvula M (2017) Immunological Aspects. In: IAL Textb. Lepr. Jaypee Brothers Medical Publishers, p 144.
7. Ramesh V, Kataria KJ. Systemic Involvement and Special Situations of Leprosy. In: Kumar B, Kar KH (eds) IAL Textb. Lepr. The Health Sciences Publisher 2017; pp 331–332.
8. Han XY, Sizer KC, Velarde-Félix JS *et al*. The leprosy agents Mycobacterium lepromatosis and Mycobacterium leprae in Mexico. International Journal of Dermatology 2012; 51 (8): 952–959. doi: 10.1111/j.1365-4632.2011.05414.x.
9. Scollard DM. Association of Mycobacterium Leprae with Human Endothelial Cells In Vitro. Laboratory Investigation 2000; 80 (5): 663–669. doi: 10.1038/labinvest.3780069.
10. Magaña M, Fernández-Díez J, Magaña ML. Lucio's Phenomenon Is a Necrotizing Panvasculitis: Mostly a Medium-Sized Granulomatous Arteritis. The American Journal of Dermatopathology 2008; 30 (6): 555–560. doi: 10.1097/DAD.0b013e318181270a.
11. Benard G, Sakai-Valente NY, Bianconcini Trindade MA. Concomitant Lucio Phenomenon and Erythema Nodosum in a Leprosy Patient: Clues for Their Distinct Pathogeneses. The American Journal of Dermatopathology 2009; 31 (3): 288–292. doi: 10.1097/DAD.0b013e318193c74c.