Lucio phenomenon with concomitant necrotizing fasciitis and acute kidney injury

Thomas Norman[1] BA, Joseph Zikry[2] MD, Scott Worswick[2] MD, Gene Kim[2] MD, Maria T Ochoa[2] MD

Affiliations: [1]Keck School of Medicine, University of Southern California, Los Angeles, California, USA, [2]Department of Dermatology, Keck School of Medicine, University of Southern California, Los Angeles, California, USA

Corresponding Author: Maria T Ochoa MD, 1450 San Pablo Street Suite 2000, Los Angeles, CA 90033, Tel: 323-442-6200 Email: maria.ochoa@med.usc.edu

Abstract

Lucio phenomenon is a rare vasculopathy that can occur in patients with Hansen disease, particularly diffuse lepromatous leprosy. It is characterized by retiform purpura and necrotic ulcerations, most commonly affecting the extremities. Diagnosing Lucio phenomenon can be challenging, especially when secondary bacterial infections occur. We report a patient with Lucio phenomenon who presented with acute necrotizing fasciitis of his left upper extremity and a 10-year history of chronic ulcerations. Shortly following admission, he also developed acute kidney injury. The necrotizing fasciitis was treated with prompt surgical debridement and intravenous antibiotics. Biopsy and PCR of a right upper extremity ulcer confirmed the presence of *Mycobacterium lepromatosis*. Multidrug therapy and prednisone were used to treat the Lucio phenomenon. After initiating treatment, no new lesions developed, kidney function improved, and the patient underwent successful skin graft of his left upper extremity. Although corticosteroid use is controversial, our patient's marked response to multidrug therapy with prednisone highlights the importance of this regimen in severe presentations of Lucio phenomenon. To the best of our knowledge, only two other cases of Lucio phenomenon confirmed to be caused by *M. lepromatosis* have been reported in living patients (rather than retrospectively identified post-mortem), underscoring the importance of the presented clinical course and treatment regimen.

Keywords: acute, clofazimine, glomerulonephritis, group A strep, Hansen disease, leprosy, Lucio phenomenon, minocycline, Mycobacterium lepromatosis, necrotizing fasciitis, prednisone, renal insufficiency, retiform, rifampin, ulcers, vasculopathy

Introduction

Lucio phenomenon is a rare vasculopathy seen in patients with Hansen's disease. It is characterized by retiform purpura that develops central ulcerations and necrosis. Systemic manifestations including fever, anemia, hepatosplenomegaly, and glomerulonephritis have been observed [1-3]. Death can occur, often related to sepsis from a secondary bacterial infection [3]. Herein, we report a case of Lucio phenomenon with necrotizing fasciitis and renal dysfunction.

Case Synopsis

A 51-year-old man presented to the emergency department with a two-week history of worsening, painful ulcerations of his left upper extremity (LUE) and a greater than 10-year history of upper and lower extremity ulcerations of unknown etiology. On physical examination, he had large, purulent ulcerations of the LUE with violaceous borders and surrounding retiform purpura. Hemorrhagic bullae were distributed throughout the LUE **(Figure 1A**). The trunk and extremities had scattered non-inflammatory crusted ulcerations on a background of dyspigmentation and scarring **(Figure 1B**). He also had eyebrow alopecia, a collapsed nasal bridge, hepatosplenomegaly, and right median nerve tenderness. He was febrile and hypotensive with a leukocytosis, lactic acidosis, and elevated C-reactive protein. Laboratory data were positive for rapid

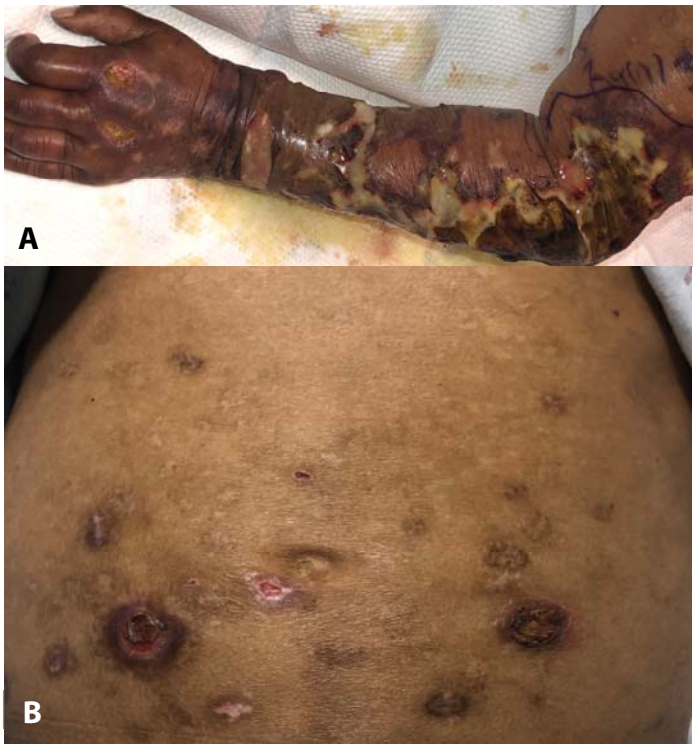

Figure 1. ***A)*** *Ulcerations and hemorrhagic bullae on the left upper extremity upon admission.* ***B)*** *Chronic non-inflammatory lesions on abdomen upon admission.*

plasma reagent (RPR; titer 1:1), antiphospholipid antibodies (anti-cardiolipin, anti-B2 glycoprotein, and lupus anticoagulant), and QuantiFERON gold. D-Dimer was elevated and C3, proteins C and S, antithrombin III, and factor V were decreased. He was anemic, with hypoalbuminemia and proteinuria. HIV, hepatitis B and C, antinuclear antibody, antineutrophil cytoplasmic antibody, and urine toxicology results were negative.

Biopsy of a LUE ulceration revealed gram-positive cocci extending into the dermis. Tissue culture grew group A streptococci. Left upper extremity X-rays showed soft tissue swelling, gas, and ulceration. Given high clinical suspicion for necrotizing fasciitis, a LUE dermatofasciectomy was performed. Over the following six weeks, the patient underwent three additional LUE debridements, with placement of meshed bilayer wound matrix during the last surgery.

A few days following the original dermatofasciectomy, the patient's renal function worsened, with serum creatinine increasing above normal. He concurrently developed painless retiform ulcerations with overlying eschars on his right upper extremity (RUE). These new findings suggested a chronic underlying etiology, which had predisposed him to LUE necrotizing fasciitis. The differential diagnosis included antiphospholipid syndrome, Hansen disease with Lucio phenomenon, an anti-neutrophil cytoplasmic antibody vasculitis, or another vasculitis such as polyarteritis nodosa.

Biopsy of a newly formed RUE ulcer revealed perivascular and periadnexal dermatitis with occasional clusters of foamy histocytes containing

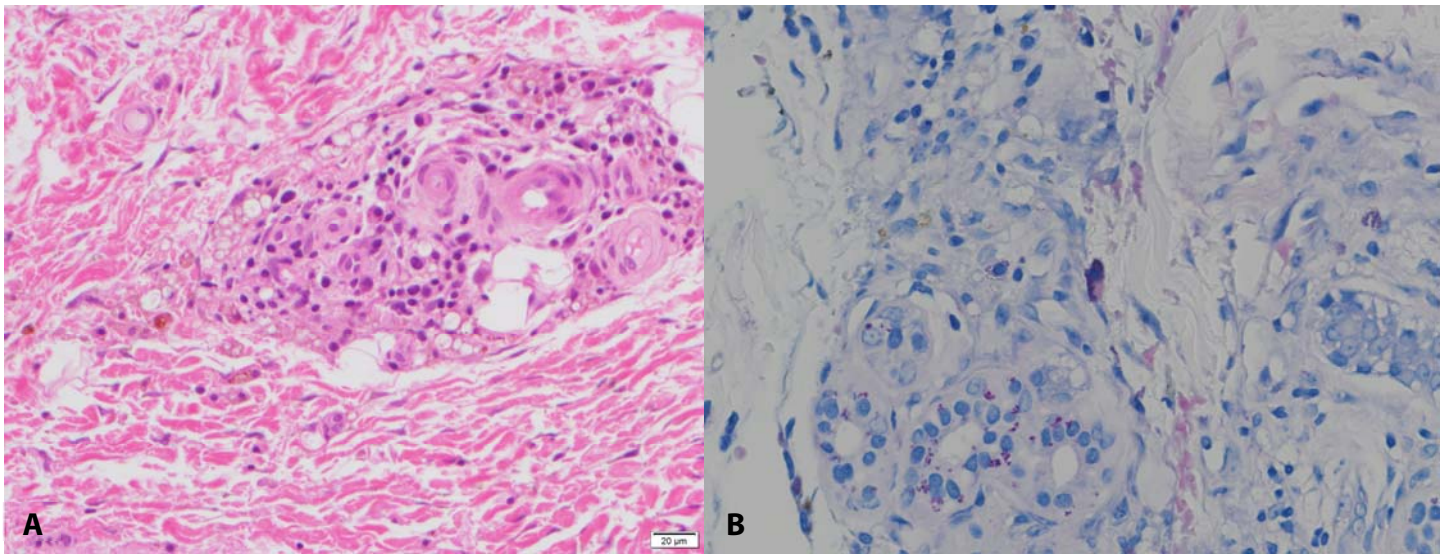

Figure 2. ***A)*** *Hematoxylin and eosin from the right upper extremity ulcer revealing foamy macrophages around the vasculature with scattered lymphocytes in the dermis, 400×.* ***B)*** *Acid-fast bacilli stain from the right upper extremity ulcer showing bacilli infecting endothelial cells, 40×.*

Figure 3*: Left upper extremity after skin grafting.*

acid-fast bacilli, consistent with Hansen disease (**Figure 2**). Subsequent PCR revealed *Mycobacterium lepromatosis* as the causative agent. Treatment was initiated with oral rifampin 600mg monthly, oral minocycline 100mg daily, oral clofazimine 50mg twice daily, and oral prednisone 60mg daily. After one week, rifampin was increased to 600mg orally daily and a gradual prednisone taper was initiated.

The patient's ulcerations began to improve one week after initiating treatment. His serum creatinine peaked at 3.98mg/dL (upper limit of normal: 1.30mg/dL) 4 days after initiating anti-mycobacterial therapy, then decreased over the next five weeks to 1.67mg/dL, stabilizing near this value thereafter. The patient underwent two split thickness skin grafts, nine and twelve weeks after beginning treatment. The prednisone had been discontinued by the time of his first skin graft. He was discharged one week after the second skin graft (**Figure 3**).

Case Discussion

Lucio phenomenon or erythema necroticum is most frequently observed in diffuse lepromatous leprosy (DLL), often in untreated or inadequately treated patients [1-4]. Clinically, DLL is characterized by diffusely infiltrated skin and lack of dermal nodules. Affected patients can also exhibit eyebrow and eyelash alopecia, rhinitis, nasal septal defects, and impaired sensation in the extremities [2,4]. Lucio phenomenon is characterized clinically by dark red-to-violaceous plaques with sharp, irregular borders that develop central ulcerations and necrosis, as seen in this case. The lesions can be painful or non-painful. They most commonly affect the extremities, particularly the legs, and heal with atrophic scars [2].

Diffuse lepromatous leprosy is usually associated with *Mycobacterium lepromatosis* but may also be caused by *Mycobacterium leprae* or co-infections of both bacteria [5]. The relatively high frequency of *M. lepromatosis* in Mexico could explain why DLL and Lucio phenomenon have been most frequently reported in this region [6]. Nevertheless, since *M. leprae* can also cause Lucio phenomenon, it has been suggested that host factors, specifically a poor immune response, may be more important than type of bacteria when it comes to the likelihood of developing this vasculopathy [5].

Although the exact cause of Lucio phenomenon is unclear, Vargas-Ocampo demonstrated that the pathogenesis likely begins with massive bacillary replication in vessel walls [7]. Endothelial disruption induces proliferation or thrombosis, resulting in vascular occlusion and ultimately ischemia of the overlying epidermis. The resulting necrosis stimulates local accumulation of inflammatory cells and deposition of immune complexes. This pathogenesis explains why both a non-inflammatory occlusive vasculopathy and a leukocytoclastic vasculitis have been reported as histopathologic findings in Lucio phenomenon [7,8].

Erythema nodosum leprosum is another necrotizing reaction that can occur in patients with DLL. Clinically, it appears as round necrotic ulcers and plaques overlying nodules and usually develops after starting treatment. Erythema nodosum is believed to result from antigen-antibody complex deposition, whereas Lucio phenomenon is largely triggered by a heavy bacterial load [8]. However, these conditions can be difficult to distinguish histologically, as leukocytoclastic vasculitis can be observed in both [7,8].

Our patient had diffusely infiltrated skin, madarosis, and a collapsed nasal septum suggestive of DLL. His RUE ulcerations and chronic ulcer history were consistent with Lucio phenomenon, as were our patient's anemia, hepatosplenomegaly, and hypoalbuminemia. False-positive RPR, rheumatoid factor, and antiphospholipid antibodies have been observed in lepromatous leprosy and Lucio phenomenon [1-3].

Previous reports of Lucio phenomenon histopathology have shown several common features, including acid-fast bacteria in macrophages and endothelial cells, endothelial proliferation, luminal occlusion, thrombosis, ischemic epidermal necrosis, necrotizing vasculitis of small vessels of superficial dermis, and passive venous congestion [9]. However, not all these features are universally observed, perhaps because of varying disease stages or biopsy sites [9,10]. Our RUE biopsy only demonstrated acid-fast bacteria invasion of endothelial cells and macrophages. Although not demonstrating the characteristic histopathology of Lucio phenomenon (non-inflammatory occlusive vasculopathy or leukocytoclastic vasculitis), our patient's clinical picture, supported by histology consistent with Hansen disease, was sufficient to confirm the diagnosis of Lucio phenomenon.

Interestingly, the etiologic organism in our patient was *M. lepromatosis*, the species identified as distinct from *M. leprae* in 2008 by Han et al. [6]. Since then, several cases of Lucio phenomenon attributed to *M. lepromatosis* have been reported, most of which were retrospectively identified post-mortem using archived tissue samples [6,11-13]. To the best of our knowledge, there have only been two other cases of Lucio phenomenon confirmed to be caused by *M. lepromatosis* while patients were still alive [14,15].

When reconciling clinical information in Lucio phenomenon, it is necessary to recognize that superimposed secondary infections can impact the findings. For instance, our patient's low C3, proteins C and S, antithrombin III, and factor V and elevated D-dimer results could be attributed to his necrotizing fasciitis. Optimal treatment for necrotizing fasciitis involves immediate debridement of infected tissue and antibiotic therapy. Delaying this treatment increases amputation risk [16]. To optimize the likelihood of a successful skin graft, we delayed reconstructive surgery until completing six weeks of anti-mycobacterial medications.

Our patient's renal function deteriorated one week after admission. The nephrology service considered his proteinuria and hypoalbuminemia at admission to be consistent with chronic kidney disease related to amyloidosis, which can occur in the setting of Hansen disease, especially the lepromatous type [17]. His rising creatinine was attributed to acute kidney injury of unclear etiology. Glomerulonephritis has been documented in both lepromatous leprosy and Lucio phenomenon, but post-streptococcal glomerulonephritis was another possibility in this case [2,17].

Although there is no consensus regarding treatment for Lucio phenomenon, the World Health Organization's multidrug therapy consisting of rifampin, dapsone, and clofazimine is commonly used to combat the underlying mycobacterial infection. Corticosteroid use is controversial. Some believe it increases secondary infection risk, whereas others underscore the importance of corticosteroids in severe cases [1,18]. Systemic corticosteroids have been used in patients who have survived, as well as in those who died [18]. After diagnosing Lucio phenomenon, our patient was treated with oral rifampin 600mg monthly (increased to 600mg daily after one week), oral minocycline 100mg daily, oral clofazimine 50mg twice daily, and oral prednisone 60mg daily (with a gradual taper initiated after one week).

Conclusion

Lucio phenomenon is a vasculopathy that can be observed in Hansen disease, particularly DLL. Although rare, it is important to include Lucio phenomenon in the differential diagnosis for retiform purpura and chronic ulcerations. Additionally, the possibility of systemic manifestations such as glomerulonephritis and their subsequent management should be considered. The marked clinical improvement observed in our patient supports the use of multidrug therapy and prednisone when managing severe presentations of Lucio phenomenon. This case furthers our understanding of the clinical course and treatment regimen of Lucio phenomenon caused by *M. lepromatosis*.

Potential conflicts of interest

The authors declare no conflicts of interest

References

1. Moschella SL. The lepra reaction with necrotizing skin lesions: a report of six cases. *Arch Dermatol*. 1967;95:565-75. [PMID: 6026941].
2. Rea TH, Levan NE. Lucio's phenomenon and diffuse nonnodular lepromatous leprosy. *Arch Dermatol*. 1978;114:1023-28. [PMID: 686719].
3. Curi PF, Villaroel JS, Migliore N, et al. Lucio's phenomenon: report of five cases. *Clin Rheumatol*. 2016;35:1397-01. [PMID: 24863848].
4. Rea TH, Jerskey RS. Clinical and histologic variations among thirty patients with Lucio's phenomenon and pure and primitive diffuse lepromatosis (Latapi's lepromatosis). *Int J Lepr Other Mycobact Dis*. 2005;73:169-88. [PMID: 16830639].
5. Sharma R, Singh P, McCoy R, et al. Isolation of *Mycobacterium lepromatosis* and development of molecular diagnostic assays to distinguish *Mycobacterium leprae* and *M. lepromatosis*. *Clin Infect Dis*. 2020;71:262-69. [PMID: 31732729].
6. Han XY, Seo YH, Sizer KC, et al. A new Mycobacterium species causing diffuse lepromatous leprosy. *Am J Clin Pathol*. 2008;130:856-64. [PMID: 19019760].
7. Vargas-Ocampo F. Diffuse leprosy of Lucio and Latapi: a histologic study. *Lepr Rev*. 2007;73:169-88. [PMID: 18035776].
8. Bernard G, Sakai-Valente NY, Trindade MAB. Concomitant Lucio phenomenon and erythema nodosum in a leprosy patient: clues for their distinct pathogenesis. *Am J Dermatopathol*. 2009;31:288-92. [PMID: 19384072].
9. Ranugha P, Chandrashekar L, Kumari R, Thappa DM, Badhe B. Is it Lucio phenomenon or necrotic erythema nodosum leprosum? *Indian J Dermatol*. 2013;58:160. [PMID: 23716834].
10. Costa IMC, Kawano LB, Pereira CP, Nogueira LSC. Lucio's phenomenon: a case report and review of the literature. *Int J Dermatol*. 2005;44:566-71. [PMID: 15985025].
11. Vera-Cabrera L, Escalante-Fuentes WG, Gomez-Flores M, et al. Case of diffuse lepromatous leprosy associated with "*Mycobacterium lepromatosis*." *J Clin Microbiol*. 2011;49:4366-68. [PMID: 22012006].
12. Han XY, Jessurun J. Severe leprosy reactions due to *Mycobacterium lepromatosis*. *Am J Med Sci*. 2013;345:65-69. [PMID: 23111393].
13. Han XY, Aung FM, Choon SE, et al. Analysis of the leprosy agents *Mycobacterium leprae* and *Mycobacterium lepromatosis* in four countries. *Am J Clin Pathol*. 2014;142:524-32. [PMID: 25239420].
14. Velarde-Félix JS, Alvarado-Villa G, Vera-Cabrera L. "Lucio's phenomenon" associated with *Mycobacterium lepromatosis*. *Am J Trop Med Hyg*. 2016;94:483-84. [PMID: 26936990].
15. Trave I, Barbarino G, Cavalchini A, Parodi A. Long-term ulcerations caused by *Mycobacterium lepromatosis*. *Int J Mycobacteriol*. 2020;9:223-25. [PMID: 32474550].
16. Anaya DA, Dellinger EP. Necrotizing soft-tissue infection: diagnosis and management. *Clin Infec Dis*. 2007;5:705-10. [PMID: 17278065].
17. Ahsan N, Wheeler DE, Palmer BF. Leprosy-associated renal disease: case report and review of the literature. *J Am Soc Nephrol*. 1995;5:1546-52. [PMID: 7756586].
18. Rocha RH, Emerich PS, Diniz LM, et al. Lucio's phenomenon: exuberant case report and review of Brazilian cases. *An Bras Dermatol*. 2016;91:60-63. [PMID: 28300896].