Lucio's phenomenon: A systematic literature review of definition, clinical features, histopathogenesis and management

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Abstract

Leprosy is a chronic disease with clinical presentations according to the immunologic spectrum. Lepromatous form is the most advanced, with the highest transmissibility and risk of causing disabilities. Lucio's phenomenon is a rare manifestation among lepromatous patients with a rapid and severe evolution and high mortality. It is difficult to differentiate from ulcerative/necrotic erythema nodosum leprosum and has no consensus on how it should be treated. This article is a qualitative review of the literature after the introduction of multidrug therapy, aiming to bring consensus related to the clinical, laboratory and histopathological diagnostic criteria of the disease and its management.

Key words: Erythema nodosum leprosum, leprosy, Lucio phenomenon, *Mycobacterium leprae*

Introduction

Leprosy is a chronic infectious disease caused by *Mycobacterium leprae*, or less commonly by *Mycobacterium lepromatosis*, an acid-fast bacillus (AFB), which multiplies slowly and has an incubation period of about five years.[1,2] The disease primarily affects the peripheral cutaneous nerves, skin, mucosa of the upper respiratory tract and the eyes.[3] Leprosy is curable, and treatment provided in the early stages averts physical disability.[1,3,4]

The number of patients treated for leprosy (the registered prevalence) has declined steadily over the last three decades.[5] However, the number of new cases detected each year has shown a much smaller, although variable decline in different countries.[5,6] Worldwide, the three countries with the highest burden – India, Brazil and Indonesia – accounted for 80.2% of the new case load globally in 2017. Brazil contributed 92.3% of new leprosy cases in the Americas region.[7]

Leprosy reactions are immunological episodes of acute or subacute inflammation, characterized by cutaneous and systemic involvement, disrupting the usual chronic course and clinical stability of the patients.[3,8] Physical disabilities, deformities and morbidity are caused mainly by these episodes.[3] Leprosy reactions can occur before, during or after the end of treatment and can be classified clinically and histopathologically into different variants: reversal reaction (Type I), erythema nodosum leprosum (Type II)[3,8] and Lucio's phenomenon.[9]

Lucio's phenomenon is a type of reaction usually observed in untreated or inadequately treated diffuse forms of lepromatous leprosy and is a life-threatening medical emergency. It is

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always related to advanced forms of leprosy and consequently has a high bacillary load. However, according to Bernardes Filho *et al*., its diagnosis is difficult, especially in non-endemic areas which leads to delay in identifying the disease and loss of treatment time.[10] In addition, the resulting severe deformities and disabilities lead to high morbidity and/or mortality.

The objective of this study was to do a qualitative systematic review of literature to arrive at a consensus on its definition, clinical features, diagnosis, treatment and outcomes.

Methods

Search strategy

A search of PubMed, ScienceDirect, EMBASE and SciELO databases was performed in April 2018, to identify eligible articles for the review. We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart to facilitate a qualitative review of the literature and formed the basis for inclusion or exclusion of the articles.

Eligibility criteria

Studies describing clinical cases (case reports, letters and case series) published from 1981, after the start of multidrug therapy (MDT) by the World Health Organization (WHO), and those considering the clinical, diagnostic, therapeutic and evolutionary aspects of LP were included in this analysis. We included articles in English, Portuguese, Spanish, French and German, using the keywords "Lucio phenomenon" and "Lucio's phenomenon." Articles in which the clinical and diagnostic definitions of LP were not clearly characterized, were excluded from the review.

Study selection

Potentially relevant studies were selected from each database, and duplicates were excluded from the study. We selected, retrieved and reviewed 63 full-text articles. Disagreements on the final inclusion of a study were resolved through consensus between two reviewers (MACF and FBF). Finally, only 39 studies were selected as 24 publications did not meet the inclusion criteria for this review [Figure 1].[11-49]

Data extraction

A table was created to summarize the findings from the selected articles which included: authors, year of publication, number of cases described, sex, age, country of the patients, clinical features and disability grading (considering 0, 1 or 2 for hands, feet and eyes evaluations by the WHO guideline), bacilloscopy of slit skin smear, start of Lucio's phenomenon (pre-, during or post-treatment), clinical diagnosis and histopathology patterns, laboratory tests, antileprosy drugs, treatment of leprosy reactions, antiplatelet and anticoagulant agents, systemic antibiotics, surgical treatments and outcomes [Tables 1 and 2].[7]

Results

The 39 articles included in this review report 49 patients, of whom 29 were men and 20 were women. The patients' ages ranged from 13 to 86 years, with an average of 48.27 years. The cases of LP described were from 17 countries, including: Brazil (12), India (9), Argentina (5), Mexico (4), China (3), Malaysia (3), United States (3), and one each from Colombia, Ecuador, Greece, Iran, Spain, Peru, Polynesia, South Korea, Sri Lanka and Tunisia. As shown in Figure 2, of the 12 Brazilian LP cases, four were from São Paulo state, two from Rio de Janeiro state, and one each from Amazonas, Espírito Santo, Mato Grosso, Paraná, Rio Grande do Sul states and the Federal district. The three patients reported in the United States (US) were originally from Mexico and had been residing in the US for 3, 7 and 10 years, respectively. Among the three patients described in Malaysia, 2 came from Indonesia and had lived in Malaysia for 2 and 3 years, respectively. The LP case reported in Spain was of a patient from Paraguay who had been living in Spain for two years.

Among the included cases, while one and two patients were described as having Grade 1 and Grade 2 physical disabilities, respectively, there were no descriptions for the other 46 cases. While there was no reference to the bacilloscopy in 16 patients, it was available in 33 patients. The slit skin smear was described as negative in one patient, positive in eight cases (with no report of the bacterial index) and a bacterial index of 1+, 2+, 3+ 4+, 5+ and 6+ in 1, 2, 4, 3, 6 and 8 patients, respectively.

Forty two (85.7%) patients were diagnosed with Lucio's phenomenon without a previous leprosy diagnosis. Five patients (10.2%) presented with it during the treatment for leprosy, of which three had a history of irregular treatment. Two (4.1%) patients had it after the end of the leprosy treatment, of which one had a negative bacterial index, while it was not described for the other patient.

Clinically, all the patients reviewed had skin necrosis, irregular skin ulcers, erythematopurpuric macules and diffuse skin infiltration. While livedo was seen in three patients, eyelashes and eyebrows were absent in 37 (75.5%), lepromas were seen in 7 (14.3%) and 27 (55.1%) of them had a fever. Thickened peripheral nerves were described in 18 (36.7%) patients and 11 (22.4%) had a glove and stocking pattern of sensory impairment.

The histopathology of the cases revealed necrosis of the epidermis in 21 (42.8%), superficial and deep lymphohistiocytic inflammatory infiltrate in 42 (85.7%), solid AFB singly and in globi in the macrophages in 16 (32.6%), vessels occluded by a thrombus in 31 (63.3%) and macrophagic infiltrate in the wall and/or AFB in the wall of the skin vessels in 32 cases (65.3%).

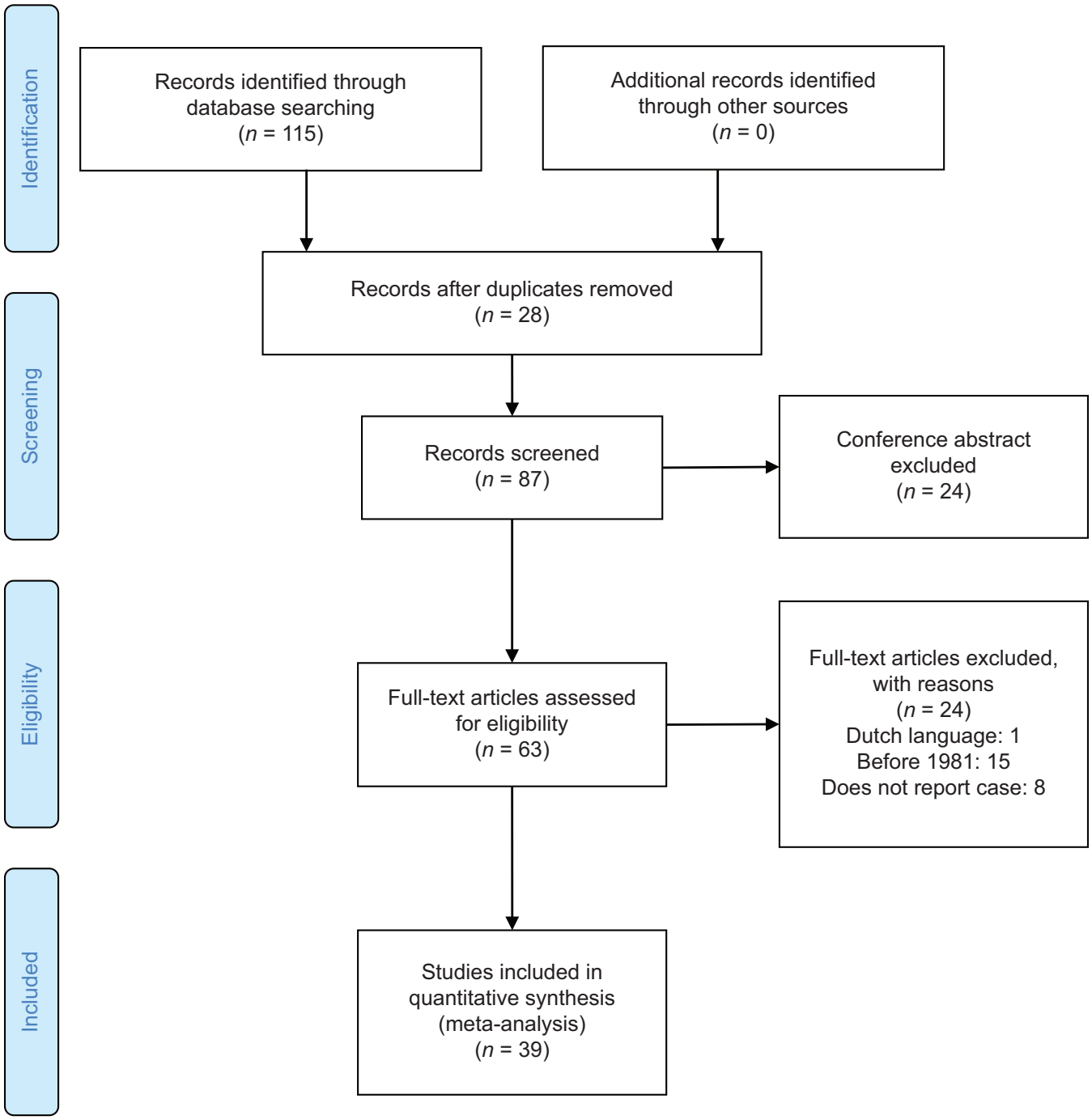

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram

Only 4 (8.2%) cases were positive for phenolic glycolipid-I antibody titration, while the other reports did not mention it. The polymerase chain reaction of the tissue revealed *Mycobacteria* in 9 (18.4%) patients, *M. leprae* in 5 (10.2%) and 4 (8.2%) showed the presence of *M. lepromatosis*. All four reported cases of *M. lepromatosis* were from Mexico, with one living in Minnesota for ten years and the other in Texas for seven years. While 31 patients (63.3%) had anemia with hemoglobin levels ranging from 5 to 11 g/dL (average: 9.1 g/dL), there was no information regarding the hemoglobin levels in eight cases. Leukocytosis was reported in 16 patients (32.6%) with leukocyte counts ranging from 11,230 to 69,000 cells/mm^3 (mean: 26,648 cells/mm^3), while nine patients (18.4%) had counts in the normal range, four (8.2%) had leukopenia and 20 (40.8%) cases did not report the white blood cell counts. Erythrocyte sedimentation rate and/or C-reactive protein levels were increased in 25 (51%) patients. IgM anti-cardiolipin was positive in four cases, negative in two and not described in 43 (87.7%) cases. Bone marrow examination was performed in three patients, of which two were positive for AFB.

Table 1: Demographic, clinical and laboratorial characteristics and outcome of patients

Reference	*n*	Sex	Age	Clinical form	Bacilloscopy of SSS	Start of LP (Pre, During or Pos)	PGL-I antibody titer	PCR of tissue for *Mycobacterium leprae*	Outcome
10	1	M	60	LL	6+	Pre	NR	NR	Most of the ulcers healed slowly, leaving depigmented atrophic scars
11	2	F	64	LL	5+	Pre	Positive	Positive	General condition and skin lesions improved; antileprosy drugs will be continued for 2 years
12	3	F	20	LL	NR	During	NR	NR	MDT planned to be given for 24 months
13	4	M	65	LL	6+	Pre	NR	NR	The patient was followed up for 2 months; initially, he showed improvement but was later lost to follow-up
14	5	M	38	DLL	4+	Pre	NR	NR	The ulcers healed slowly with depigmented scars after 10 weeks
15	6	F	28	LL	NR	Pre	NR	NR	MDT was prescribed for 12 months, but as after this period, biopsies of infiltrated skin on left knee and right elbow still disclosed +/6+granular and well-preserved bacilli, MDT was prescribed for 1 year more
16	7	M	65	DLL	6+	Pre	NR	NR	MRSA septicemia and died on the 16th day of hospitalization
17	8	M	53	LL	2+	Pre	NR	NR	Regression of the ulcers within 2 months
18	9	F	29	LL	6+	During	NR	NR	The ulcers started regressing over the following 2 weeks and healed completely in 4–6 weeks with scarring. MDT was continued until smears were negative
19	10	F	69	LL	NR	Pre	NR	NR	After 4 weeks of inpatient treatment, the patient was discharged and the actual leprosy therapy with dapsone and rifampicin continued
19	11	M	64	LL	NR	Pre	NR	NR	The patient died due to sepsis 17 days after admission
20	12	M	76	LL	NR	Pre	NR	NR	NR
21	13	M	65	DLL	5+	During (abandon)	NR	NR	The patient died from an undetermined cause
22	14	M	37	LL	6+	Pre	NR	NR	Death
23	15	F	31	LL	6+	Pre	NR	NR	Improvement of skin lesions 45 days after the start of treatment
24	16	M	49	LL	Positive	Pre	NR	NR	NR
25	17	M	64	LL	4+	Pre	NR	NR	Satisfactory response to treatment with resolution of secondary local sepsis and visible clinical recovery was also seen with the onset of healing of ulcers due to Lucio's phenomenon
26	18	F	76	DLL	6+	Pre	NR	Positive	At a 2-month follow-up the patient was still under MDT without side effects
27	19	F	22	LL	3+	During (irregular MDT)	NR	NR	NR
28	20	M	52	NR	Positive	Pre	NR	NR	Died
28	21	F	57	NR	Positive	Pre	NR	NR	Died of sepsis
28	22	M	74	NR	Positive	Pre	NR	NR	Died
28	23	F	59	NR	Positive	Pre	NR	NR	Died of sepsis
28	24	M	71	NR	3+	Pre	NR	NR	Alive
29	25	M	63	LL	5+	Pre	NR	NR	Marked improvement in the cutaneous signs and symptoms after 1 month
30	26	F	24	LL	Positive	Pre	NR	Positive	NR
31	27	M	32	LL	NR	Pre	NR	Positive	NR

(*Contd...*)

Table 1: (*Continued*)

Reference	*n*	Sex	Age	Clinical form	Bacilloscopy of SSS	Start of LP (Pre, During or Pos)	PGL-I antibody titer	PCR of tissue for *Mycobacterium leprae*	Outcome
31	28	F	50	DLL	NR	Pre	NR	Positive	The patient was cured at Carville; she died in 1998 at the age of 85
32	29	M	61	LL	NR	During (irregular MDT)	NR	NR	The patient was discharged after 15 days of hospitalization with significant improvement demonstrated both clinically and in laboratory tests. Outpatient clinic follow-up was done at 30, 90 and 120 days post hospital discharge monitoring and returned to the original Basic Health Unit using only MDT, following the multibacillary scheme and without any sign or symptom of reaction recidivation
33	30	M	13	DLL	Positive	Pre	NR	NR	NR
34	31	F	23	LL	4+	Pre	NR	NR	She was discharged well 7 weeks later
34	32	M	34	LL	2+	Pre	NR	NR	Lesions healed after a further 2–4 months, leaving atrophic scars
34	33	M	45	LL	3+	Pre	NR	NR	He succumbed to sepsis 20 days after first presentation
35	34	M	32	LL	5+	Pre	NR	NR	The patient recovered very well and now, after more than 1 year of specific drugs, he is in a very good health
36	35	M	51	DLL	0	Pos	NR	NR	Outcome was favorable after 1 month of treatment
37	36	F	34	LL	NR	Pos	NR	NR	The patient subsequently developed pulmonary thromboembolism which culminated in death
38	37	F	33	LL	NR	Pre	NR	NR	Died at the 35th day of admission because of severe sepsis
39	38	M	54	LL	NR	Pre	NR	NR	NR
40	39	M	61	LL	5+	Pre	NR	NR	The patient died 2 weeks after hospital admission (sepsis, shock, disseminated intravascular coagulopathy and renal and respiratory failure)
40	40	M	72	LL	5+	Pre	NR	NR	Died approximately 2 months after admission (sepsis, renal impairment from fluid loss, disseminated intravascular coagulopathy and shock)
41	41	F	37	DLL	3+	Pre	Positive	Positive	After 2 months of hospitalization and medical management with antiretrovirals, he was discharged due to favorable clinical evolution and improvement of HIV viral load
42	42	F	43	LL	Positive	Pre	NR	NR	Died of sepsis
43	43	F	27	LL	1+	Pre	NR	NR	The gestation developed to term for a normal childbirth, without concurrent disease. The newborn was of appropriate weight for gestational age and without malformations
44	44	M	30	LL	6+	Pre	NR	NR	He was discharged with the advice to continue MB MDT for 2 years under monthly follow-up
45	45	F	86	DLL	NR	Pre	NR	Positive	Died at home 3 months later of unknown cause
46	46	M	53	DLL	NR	Pre	Positive	Positive	Died of presumed septic shock
46	47	M	31	DLL	NR	Pre	NR	Positive	Died
47	48	M	71	LL	NR	Pre	NR	NR	The patient died due to sepsis 7 days after admission
48	49	F	17	NR	NR	Pre	Positive	NR	NR

LL: Lepromatous leprosy, DLL: Diffuse LL, LP: Lucio's phenomenon, MB: Multibacillary, MDT: Multi drug therapy, NR: Not reported, SSS: Slit-skin smear, PGL-I: Phenolic glycolipid-I, PCR: Polymerase chain reaction, MRSA: Methicillin-resistant *Staphylococcus aureus*

Table 2: Clinical manifestations and histopathology of patients

Reference	*n*	Clinical diagnosis (pattern)						Histopathology			
		Skin	Madarosis	Nodule	Systemic symptoms	Glove-and-stocking anesthesia	Nerves	Epidermis, dermis, and/or subcutaneous fat	Grenz zone	AFB in endothelial walls	Capillary thrombosis
10	1	Multiple stellate purpuric patches, angular infarcts and gangrene, few with overlying hemorrhagic bullae and deep jagged necrotic ulcers, purpuric patches	Yes	No	Fever	Yes	Symmetrically thickened peripheral nerves	Diffuse infiltration of solid staining and granular bacilli in epidermis and dermis, including endothelial cells. Dense neutrophilic and lymphocytic infiltrate	NR	Yes	Yes
11	2	Painful erythematous macules, papules, nodules and multiple necrotic crusts; atrophic scars of old lesions	Yes	Yes	Fever	Yes	The great auricular, ulnar, radial cutaneous and superficial peroneal nerves were slightly enlarged	Papillary dermal oedema, vascular proliferation and multiple granulomas in dermis and subcutaneous fat. The noncaseous granulomas had infiltration of foamy macrophages and neutrophils	NR	Yes	Yes
12	3	Multiple elevated plaque to nodule-like tender rashes, necrosis	NR	Yes	Fever	NR	Thickening of both common peroneal and right ulnar nerves	Unremarkable epidermis, foam cells with numerous lepra bacilli in dermis	NR	Yes	Yes
13	4	Multiple punched-out ulcers of various sizes; margins of ulcers varied from round to irregular in shape; scarring and atrophy were noted over healed ulcers	Yes	No	No	Yes	Moderate thickening of the ulnar, radial and common peroneal nerves	Ischemic necrosis in the epidermis with varying degrees of atrophy and loss of rete ridges. The dermis showed foamy histiocytes containing fragmented bacilli with necrotizing vasculitis of vessels in the dermis	NR	NR	NR
14	5	Multiple hemorrhagic bullae, purpuric macules, scattered angular purpuric macules, large deep irregular ulcers with angulated margins	NR	No	No	Yes	Peripheral nerves were symmetrically thickened and nontender	Atrophic epidermis. Necrotizing leukocytoclastic vasculitis of papillary dermal vessels with thrombosis, numerous AFB in macrophages and macrophage granulomas extending up to subcutis	Yes	NR	Yes
15	6	Diffuse infiltration of the skin, more pronounced on the face, elbows, and knees and irregular and purpuric maculae, some covered by hemorrhagic vesicles and hematic crusts	Yes	Yes	No	NR	Ulnar and tibial painful nerve thickening	Normal epidermis. Patchy and nodular perivascular, periadnexial, and perineural inflammatory infiltrate of vacuolated histiocytes, lymphocytes and plasma cells; and some neutrophils in the dermis and extending to hypodermis	NR	Yes	Yes
16	7	Dark, irregular-shaped, bizarre, erythematous, purpuric spots and angulated ulcers, multiple deep ulcers covered with a blackish eschar, superficial atrophic scars of old, healed lesions, face was diffusely infiltrated	Yes	No	Fever	Yes	Bilaterally, the ulnar, radial, lateral popliteal, posterior tibial and great auricular nerves were moderately thickened	Ulcerated epidermis and dermis. Infiltrate of foamy macrophages	NR	Yes	Yes
17	8	Erythematopurpuric, irregularly-limited spots appeared, hemorrhagic blisters and resulting necrotic ulcers	Yes	No	No	Yes	NR	NR	NR	Yes	Yes
18	9	Multiple deep ulcers, atrophic scars	Yes	No	Fever	Yes	Bilaterally, the ulnar, radial, lateral popliteal, posterior tibial and great auricular nerves were moderately enlarged	Ulcerated epidermis and dermis along with foamy macrophages, ischemic necrotizing vasculitis, fibrinoid necrosis and new vessel formation. Clumps of AFB periadnexally, perivascularly, and within macrophages and endothelial cells	NR	Yes	Yes
19	10	Disseminated polygonal necrotic foci and some mummified areas	Yes	No	No	NR	Peripheral nerves were not thickened	Necrosis of the upper dermis. Inflammatory infiltrate around multiple vascular walls with concomitant degeneration	NR	Yes	Yes
19	11	Disseminated polygonal purpura, necrosis, saddle nose	Yes	No	No	NR	Retroauricular nerves on the left were thickened	Necrosis; infiltrates of epithelioid cells, lymphocytes, plasma cells and neutrophils	NR	Yes	Yes
20	12	Necrotizing lesions with large polygonal scars	NR	No	No	NR	NR	NR	NR	Yes	Yes

(*Contd...*)

Table 2: (*Continued*)

Reference	*n*	Clinical diagnosis (pattern)						Histopathology			
		Skin	Madarosis	Nodule	Systemic symptoms	Glove-and-stocking anesthesia	Nerves	Epidermis, dermis, and/or subcutaneous fat	Grenz zone	AFB in endothelial walls	Capillary thrombosis
21	13	Purpuric macules, dysesthesias, necrosis		No	Fever	NR	NR	Moderate infiltrate of foam cells which followed the linear paths of the blood vessels and nerves, in some areas that had occlusive vasculopathy and neutrophilic nuclear dust. Fite Faraco staining: positive for *Mycobacterium leprae* in the foam cells, interstitial cells, and endothelial cells	NR	Yes	Yes
22	14	Multiple irregular dark violaceous purpura with angular, ragged margins and scabs	Yes	Yes	Fever	NR	NR	Atrophic epidermis with an intact epidermis	Yes	Yes	Yes
23	15	Shallow polygonal ulcers with fibrinonecrotic base and irregular erythematous edges, bilateral necrosis on the ear, elbows, buttocks and toes, left ankle revealed tendon exposure	NR	No	Fever	NR	NR	Superficial and deep inflammatory perivascular lymphohistiocytic infiltrate, with Virchow's cells	NR	Yes	Yes
24	16	Ulcerations, hypopigmented macules, leonine facies	Yes	Yes	Fever	NR	NR	Epidermal necrosis	NR	Yes	Yes
25	17	Necrosis	NR	No	Fever	NR	Bilateral thickening of the ulnar nerves	Focal necrosis. Foamy macrophages within the dermis	NR	Yes	Yes
26	18	Polymorphous necrotic-haemorrhagic macules with irregular shapes, angulated or 'stellar'; the collapse of the nasal pyramid, atrophy of both auricular lobes, diffuse infiltration of the skin of the trunk, atrophy of both thenar and hypothenar eminences of both hands, with flexion of the proximal interphalangeal joints and claw fingers of both hands; blue discoloration of the right big and second toe with distal gangrene	Yes	No	Fever	Yes	Superficial peripheral nerves did not appear enlarged or painful on palpation	Epidermis was necrotic. Perineural and periadnexal infiltrate with foamy macrophages	NR	Yes	Yes
27	19	Ulcers, necrosis	Yes	No	NR	Yes	Superficial cutaneous nerves were thickened	NR	NR	NR	NR
28	20	Palpably nodular purple-reddish lesions (nonpainful); diffuse infiltrate in the face; vesicles, blisters and necrosis	Yes	Yes	Fever	NR	NR	Polymorphonuclear infiltrate with plasmocytes, eosinophils, lymphocytes and fibrinoid necrosis	NR	NR	NR
28	21	Plaques and nodules (nonpainful, nontender); pustules and ulcers	Yes	Yes	Fever	NR	NR	Necrotizing vasculitis (polymorphonuclear infiltrate with foamy histiocytes, plasmocytes, eosinophils and lymphocytes in the dermis and hypodermis and fibrinoid necrosis in the vessel wall	NR	NR	NR
28	22	Necrotic ulcers in both hands	Yes	No	Fever	NR	NR	Necrotizing vasculitis	NR	NR	NR
28	23	Necrotic ulcer lesions, erythematous-violaceous plaques in both arms and legs	Yes	No	Fever	NR	NR	Necrotizing vasculitis	NR	NR	NR
28	24	Macular and atrophic scarring skin lesions on the ear lobule and both lower extremities with alteration of thermalgesic sensitivity on these lesions	Yes	No	Fever	NR	NR	Vasculitis septal and lobulillar hypodermitis	NR	NR	NR
29	25	Infiltrated face, besides ulceronecrotic geometrically shaped lesions	Yes	No	No	NR	Bilaterally thickened fibular nerves, which were painless to palpation	Ulcerated epidermis. Dense histiocitary infiltrate with peri-adnexal and interstitial distribution; the presence of vascular fibrinoid necrosis with neutrophilic infiltrate and associated edema	NR	Yes	Yes

(*Contd...*)

Table 2: (*Continued*)

Reference	*n*	Clinical diagnosis (pattern)						Histopathology			
		Skin	Madarosis	Nodule	Systemic symptoms	Glove-and-stocking anesthesia	Nerves	Epidermis, dermis, and/or subcutaneous fat	Grenz zone	AFB in endothelial walls	Capillary thrombosis
30	26	Multiple nodules, hemorrhagic crusts, necrotic crusts with surrounding areas of irregularly-shaped purpura on swollen legs	Yes	Yes	No	NR	NR	Epithelial necrosis with re-epithelization, subjacent neutrophils, fibrin and occlusion of superficial dermal vessels. Diffuse granulomatous dermatitis without panniculitis and presence of plasma cells, lymphocytes and foamy histiocytes, many of them with globi	NR	Yes	Yes
31	27	Crops of painful, tender and erythematous macules and papules spread over the body	Yes	Yes	Fever	No	No, however, the patient complained of paraesthesias and dysesthesias in both forearms	Abundant vacuolated histiocytes within parafollicular areas and sinuses; Fite stain demonstrated innumerable AFB	NR	NR	NR
31	28	Flat infiltrative, confluent, deeply livid, sharply outlined and in variable sizes and shapes; left earlobe was indurated, the forehead subcutaneous tissue was swollen and the sclerae and conjunctivae were injected	Yes	No	Fever	NR	NR	Foci of necrosis in the dermis and epidermis, vasculitis and lymphohistiocytic infiltration of the appendages. A Fite stain further revealed AFB in histiocytes in the dermis and subcutaneous tissue, around nerves and arteries, and in the endothelial cells of blood vessels	NR	Yes	Yes
32	29	Livedoid maculae and painful, polymorphic ecchymotic maculae, some of them topped by whole and tense blisters with hyaline content. There were infiltrated ulcerated plaques, with irregular outlines and ill-defined borders, in addition to small erythematous subcutaneous nodules. Most of the lesions presented an ulcerated surface covered by scarce granulation tissue, purulent fibrin material, sometimes hemorrhagic and honeycolored crusts	NR	Yes	Fever	NR	NR	Extensive areas of necrosis and suppuration in the dermis and subcutaneous regions, with thrombosed blood vessels in their midst. By means of Fite Faraco staining were detected AARB in the neighborhood of these vessels, within their walls, invading endothelial cells and the vascular lumen, besides focal areas of histiocyte proliferation, with ample xanthomatous cytoplasm	NR	Yes	Yes
33	30	Numerous, nonpalpable, thread-like and blanchable blood vessels; face was "swollen and puffy," "diffuse central facial edema;" ear lobes were enlarged; hands and fingers, as well as his feet and toes, were described as having a nontender, nonpitting edema; toes had a "red-purplish discolouration"	Yes	No	No	NR	NR	Heavy infiltrate of macrophages in the dermis and subcutis. AFB were numerous	NR	Yes	Yes
34	31	Confluent, sharply marginated, purpuric patches, bullae, gangrenous and ulcerated; multiple, irregularly shaped, angulated, purpuric macules; face and ears were diffusely infiltrated	No	No	Fever	NR	NR	Extensive necrotizing leukocytoclastic vasculitis and numerous foamy histiocytes with globi of AFB in the dermis and subcutis	NR	NR	NR
34	32	Diffusely infiltrated waxy skin, flattened nasal bridge. Both ears were grossly enlarged with hemorrhagic blisters. There were widely disseminated, bizarrely shaped, purpuric macules and patches of varying sizes affecting all four limbs and the lower half of the trunk	Yes	No	Fever	NR	Thickened ulnar nerves	Multiple perivascular and periadnexal, poor to moderately formed granulomata in the dermis and subcutis, composed of a few foci of epithelioid histiocytes, abundant foamy macrophages, lymphocytes and occasional plasma cells. Wade–Fite stain showed numerous masses of AFB in macrophages, endothelial walls and sweat glands	NR	Yes	No

(*Contd...*)

Table 2: (*Continued*)

Reference	*n*	Clinical diagnosis (pattern)						Histopathology			
		Skin	Madarosis	Nodule	Systemic symptoms	Glove-and-stocking anesthesia	Nerves	Epidermis, dermis, and/or subcutaneous fat	Grenz zone	AFB in endothelial walls	Capillary thrombosis
34	33	Progressive gangrene affecting all four limbs; collapsed nasal bridge; multiple, bizarrely shaped, purplish papules and plaques; necrotic ulcers; scrotal skin was also gangrenous	Yes	No	No	NR	NR	Endothelial proliferations, as well as interstitial, perivascular and periadnexal infiltrates of foamy macrophages, with globi of AFB admixed with acute inflammatory cells and prominent leukocytoclasia in both the dermis and subcutis	NR	NR	NR
35	34	Cutaneous ulcerations, purpuric erythematous cutaneous lesions, diffusely infiltrated "myedematous" xerotic skin	Yes	No	Fever	NR	Bilateral swelling of ulnar and radial nerves	Necrotizing vasculitis of dermal vessels with AFB in endothelial cells	NR	Yes	Yes
36	35	Inflammatory livedo, several infiltrating maculo-papular lesions and painful erythemato-pupuric lesions	Yes	No	No	NR	NR	Epidermic necrosis with aspects of leukocytoclastic vasculitis	NR	NR	NR
37	36	Diffuse skin infiltration, saddle nose, necrotic, dark, irregular-shaped lesions	Yes	No	No	NR	NR	Epidermal necrosis; intense macrophagic infiltration in the adipose tissue	NR	Yes	Yes
38	37	Leonine face, extensive ecchymotic patches in association with deep ulcerative lesions	Yes	No	Fever	NR	NR	Atrophic epidermis with focal necrosis, swollen endothelial cells with fibrinoid necrosis and a mixed inflammatory infiltrate with nuclear dusts	NR	Yes	Yes
39	38	Multiple superficial non-healing ulcers with hyposthetic margin, large thick nose and ears giving appearance of somewhat Leonine face	NR	No	Fever	NR	NR	NR	NR	NR	NR
40	39	Deep and irregular ulcers, areas of purpura and a few bullae	NR	No	No	NR	NR	Foamy macrophages and occasional neutrophils in the edematous dermis. There was leukocytoclastic vasculitis, and AFB were seen with the modified Fite stain. The direct immunofluorescence showed IgM, C3, and C1q in the walls of superficial and deep dermal blood vessels	NR	Yes	Yes
40	40	Deep necrotic irregular ulcers, purpura and earlobes and gangrene of the toes	Yes	No	No	NR	NR	Dense infiltrate of neutrophils with lymphocytes	NR	NR	NR
41	41	Skin ulcers with burning pain associated with local oedema and serous-hematic and purulent discharge	Yes	No	Fever	Yes	Thickening and pain on palpation of the auricular, ulnar, median, radial, posterior tibial and common fibular nerves	NR	NR	NR	NR
42	42	Skin ulcers, necrosis, livedo	Yes	No	No	NR	NR	Infiltrate of histiocytes and polymorphonuclear cells, numerous intact and fragmented AFB, isolated and in globi	NR	NR	NR
43	43	Infiltrated facies, edema and extensive erythema in the members, with disseminated and confluent erythematous-purpuric lesions, topped by blisters with well-defined borders, some with ulcerated and necrotic areas	Yes	No	No	NR	NR	Leukocytoclastic vasculitis with fibrinoid necrosis, foamy histiocytes occupying the lobular portion of the hypodermis and presence of numerous granular bacilli determined by Fite Faraco. This pattern is compatible with Virchow's leprosy and Lucio's leprosy phenomenon	NR	NR	NR
44	44	Ulceration of the skin, swelling of the feet, erythematous acral lesions, triangular and bizarre purpuric and necrotic lesions, necrosis of pinnae and nasolabial folds, diffuse infiltration of the face	Yes	No	No	Yes	Thickening of the right radial cutaneous and both ulnar nerves	Necrotizing vasculitis of the small vessels in the upper dermis and endothelial proliferation of medium-sized vessel in the mid dermis; periappendageal and perivascular lymphohistiocytic infiltrate containing foamy macrophages; The infiltrate extended up to the subcutaneous fat	NR	Yes	Yes

(*Contd...*)

Table 2: (*Continued*)

Reference	*n*	Clinical diagnosis (pattern)						Histopathology			
		Skin	Madarosis	Nodule	Systemic symptoms	Glove-and-stocking anesthesia	Nerves	Epidermis, dermis, and/or subcutaneous fat	Grenz zone	AFB in endothelial walls	Capillary thrombosis
45	45	Purpuric appearance, with necrosis and ulceration in some of the areas, leading to sloughing in acral sites such as fingers and toes	Yes	No	No	NR	NR	Vasculitis with thrombosis and perivascular and periadnexial lymphocytic infiltrates as well as numerous AFB	NR	Yes	Yes
46	46	Multiple, tender, well demarcated, purpuric skin lesions with scabs on all 4 extremities	Yes	No	Fever	NR	NR	Necrosis, vasculitis and innumerable AFB; nerve invasion, vasculitis and panniculitis with AFB invasion that caused skin ulceration and massive AFB burden (globi) in internal organs	NR	Yes	Yes
46	47	Extensive skin necrosis evidenced by ulceration and gray to black discoloration	NR	No	Fever	NR	NR	Invasion of nerves and subcutis (deeply located) by numerous AFB-laden macrophages diagnosed LL, and vasculitis with endothelial proliferation and AFB infiltration	NR	Yes	Yes
47	48	Ulcers, necrosi	Yes	No	No	NR	NR	Necrosis; AFB positive	Yes	Yes	Yes
48	49	Facial malar flush, deep ulcerative lesions in both pretibial areas and palpable purpuric lesions	NR	No	No	NR	NR	Prominent dermal vascular changes with endothelial proliferation leading to luminal narrowing. A sparse to moderate inflammatory infiltrate consisting mainly of round cells with a polymorphonuclear admixture, in some areas, was present. Inflammatory cells were found primarily around and only occasionally in the wall of the vessels. Thrombosis and fibrinoid necrosis were absent. Dense aggregates of AFB were readily revealed after Ziehl-Nielsen staining in endothelial cells of even normal appearing vessels. In some places of one of the skin biopsies small aggregates of foamy histiocytes containing AFB were observed	NR	Yes	No

NR: Not reported, AFB: Acid-fast bacilli, AARB: Alcohol-acid resistant bacilli, AFB: acid-fast bacillus

Among 49 cases reported, only six patients used standard MDT exclusively, to treat Lucio's phenomenon, of which three (50%) died; two by sepsis and one from an undetermined cause. Thirty two (65.3%) patients were given steroids as anti-inflammatory treatment with different outcomes. When this steroid treatment (n = 32) was given along with bactericidal drugs (MDT, ofloxacin and/or clarithromycin; n = 25), 17 patients (68%) survived, while eight (32%) died. When given along with bacteriostatic drugs (dapsone and/or clofazimine; n = 4), only one (25%) patient survived while three (75%) died. Besides the standard adult treatment regimen for MB leprosy, use of ten alternative drug schemes (substitute schemes) was reported [Table 3].

Fifteen patients used systemic antibiotics for sepsis, 14 (93.3%) with bactericidal antileprosy drugs and 10 (66.7%) with steroids. Nine (60%) of these patients survived, all using bactericidal antileprosy drugs, while seven (46.7%) cases survived in the steroid group. Five (33.3%) patients died, four (80%) by sepsis (three using bactericidal antileprosy drugs and one steroid exclusively) while one died of pulmonary thromboembolism.

Nine (18.4%) cases were prescribed thalidomide and eight (88.9%) steroids. Only two (4.1%) patients had used acetylsalicylic acid and, two (4.1%), pentoxifylline.

Among the 49 cases reported, debridement was performed in five patients and one of them underwent skin grafting.

Overall, improvement in the general condition and skin lesions was reported in 23 (46.9%) patients. Eighteen (36.7%) patients died, 11 due to sepsis, one due to pulmonary thromboembolism and six from unknown causes. The outcomes for eight cases were not reported.

Discussion

Despite the high number of patients with leprosy in the world, Lucio's phenomenon is seen mostly in untreated patients and rarely reported.[11-14] It is restricted to particular geographic areas of South and Central Americas and rarely reported from other parts of the world such as Africa and Asia. It may not be easily recognized, even in endemic countries which leads to delay in diagnosis and loss of treatment time.[10,12,15] Several previous reports show how leprosy has been neglected, as

Figure 2: Distribution of LP cases reported in the literature in Brazil and around the world. (Plotted using Google Maps)

only a few reported cases of Lucio's phenomenon had a previous diagnosis of leprosy.

In our view, Lucio's phenomenon is defined as a specific kind of leprosy reaction manifested by severe necrotizing lesions that can occur in Lucio–Latapi leprosy and other forms of lepromatous leprosy. The initial pathogenesis begins in the vascular endothelium, since the *M. leprae* parasitizes here, leading to the occlusion of deep-vein plexus veins and subcutaneous tissue, progressing to a cutaneous hemorrhagic infarction.[16-18]

Clinically, many authors related that Lucio's phenomenon can resemble the necrotic variant of erythema nodosum leprosum,[20,21,22,50] though there are certain differentiating features. It is characterized by a transient or persistent, blotchy, reddish-blue to purple and net-like cyanotic pattern with a burning sensation. These macular areas are sharply delineated and have a characteristic center which turns purpuric and necrotic leaving stellar atrophic scars [Figures 3 and 4].[22-49] In our experience, Lucio's phenomenon is characterized by erythematous-violaceous macular and slightly infiltrated plaques on the skin, which subsequently lead to central necrosis and ulceration, affecting mainly the limbs but also the trunk and face in the severe cases, without significant systemic involvement initially. Erythema nodosum leprosum, 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 Lucio's phenomenon.[15,16]

Table 3: Anti-leprosy drug schemes and number of reported cases according the literature review

Anti-leprosy drug schemes	Number of cases	Death outcome
MDT	25	7
MDT+OFL	3	1
MDT without DDS and with OFL	1	0
DDS+CLF	3	2
DDS+RFP	1	1
DDS	1	1
(RFP+DDS) 4 years+DDS monotherapy	1	0
(RFP + DDS + CLZ)/day	4	1
(RFP + OFL + MIN + CLA)/day	1	0
RFP/m + DDS/day	1	0
(RFP + DDS + CLF + OFL)/day	1	1

MDT: Multidrug therapy; OFL: Ofloxacin; DDS: Dapsone; CLF: Clofazimine; RFP: Rifampicin; MIN: Minocycline; CLA: Clarithromycin

Histopathologically, Lucio's phenomenon is characterized by a large number of AFB aggregates in the vascular endothelium, areas of fibrinoid necrosis,[18] leukocytoclastic vasculitis[50] and ischemic epidermal necrosis [Figures 5 and 6].[18,22] Acute erythema nodosum leprosum, on the other hand, is marked by a polymorphonuclear leukocyte inflammatory infiltrate in the deeper layers of the dermis and subcutis, within pre-existing lepromatous lesions, often associated with vasculitis. Edema of the dermis is another frequent finding.[16] Lucio's phenomenon presents less neutrophil infiltration compared to erythema nodosum leprosum and confirmed colonization of endothelial cells by solid-staining AFB [Figure 7].

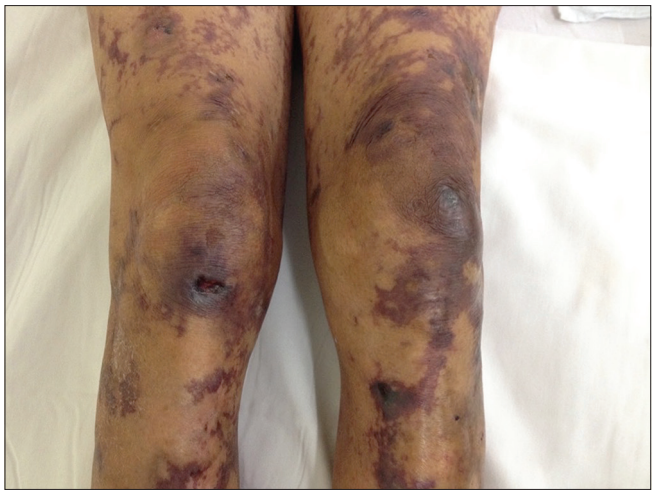

Figure 3: Diffuse erythematous-purpuric and ulceronecrotic lesions over the lower limbs

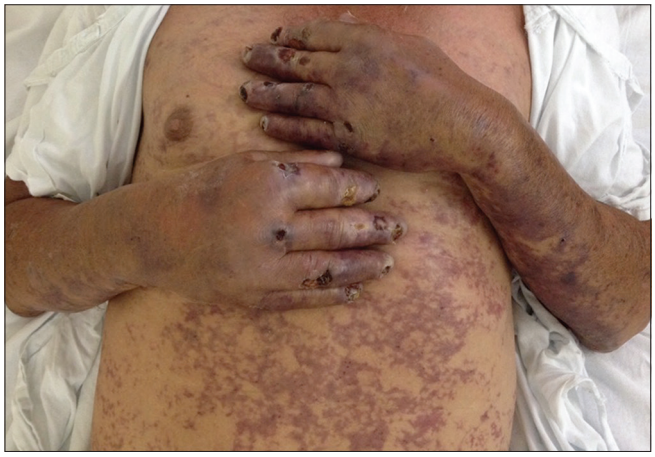

Figure 4: Diffuse polymorphous necrotic-hemorrhagic lesions with irregular shapes over upper limbs and trunk

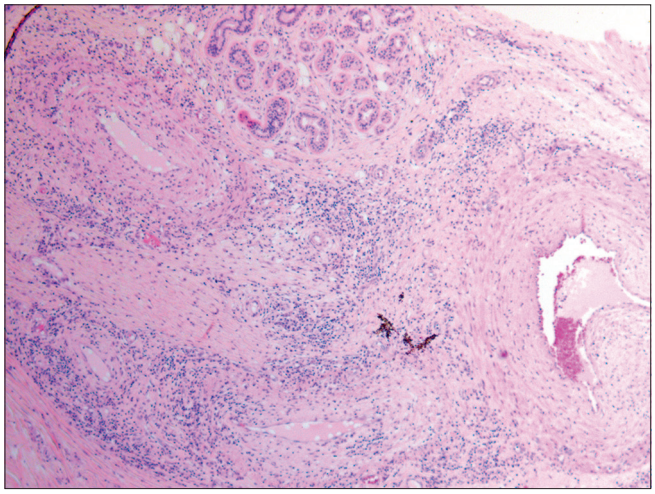

Figure 5: Neutrophilic inflammatory infiltrate with the presence of lymphocytes and vacuolated histiocytes with areas of vascular wall aggression (vasculitis) and thrombi (H and E, ×50)

Involvement of bone marrow and lymph nodes has been rarely described.[19,32]

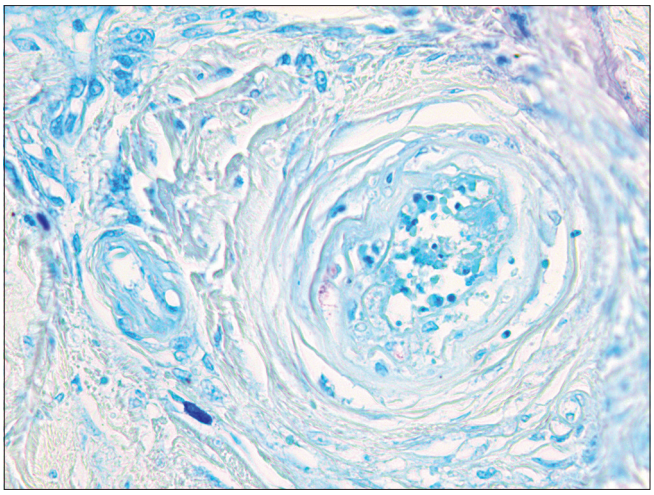

Figure 6: Presence of moderate bacillary load in xanthomatous histiocytes of the inflammatory infiltrate and vascular wall involvement (Fite Faraco stain, ×400)

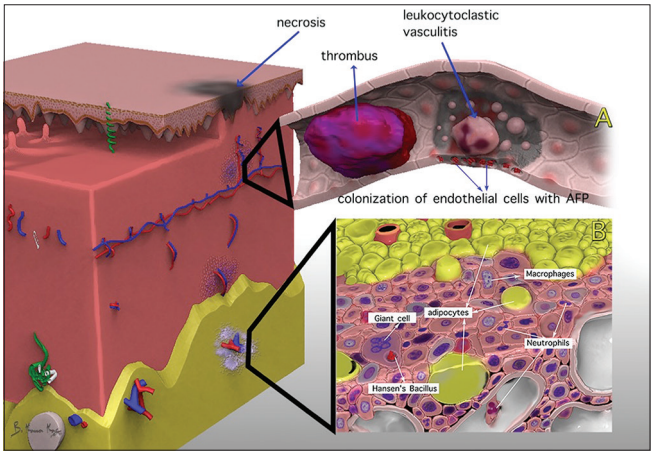

Figure 7: Diagrammatic illustration showing the differences between Lucio's phenomenon and erythema nodosum leprosum respectively. a - A large number of acid-fast bacilli aggregate in the vascular endothelium, areas of fibrinoid necrosis, leukocytoclastic vasculitis and ischemic epidermal necrosis b - Polymorphonuclear leukocyte inflammatory infiltrate in the deeper layers of the dermis and subcutis, often associated with vasculitis

On correlating the clinical and histopathological findings, we corroborate the findings of Pursley and Jacobson, that in Lucio's phenomenon, ulceration is the rule, general symptoms are scarce or nonexistent and in histopathology, there is endothelial proliferation, thrombosis, ischemic necrosis and a discrete mononuclear infiltrate along with the infiltrate of lepromatous leprosy, while in erythema nodosum leprosum, ulceration is rare, systemic signs and symptoms are common, and there are only a few bacilli present.[51]

Our literature review corroborates previous reports indicating that Lucio's phenomenon and late diagnosis of leprosy are associated with madarosis, generalized skin infiltration, a high degree of disabilities and several signs and symptoms of systemic inflammation. Lucio's phenomenon is an acute reactional clinical episode of leprosy, considering the high number of patients with anemia, leukocytosis,

an acute increase in systemic markers of inflammation associated with devastating cutaneous necrosis, sepsis and the consequent high risk of death. Recent reports[5,6] on the disparity between the official data and the actual incidence of leprosy highlight the hidden endemic nature of leprosy in many parts of the world,[1,52,53] reports that should alert us in relation to underdiagnosis of leprosy around the world and to the possibility of the disease load increasing, and consequently in the number of Lucio's phenomenon cases. In fact, only the early diagnosis and proper management of the leprosy patients can reduce the high morbidity and mortality of Lucio's phenomenon, which are as worrying as the spread of infection epidemiologically, considering the high bacillary load of these lepromatous leprosy patients.

According to the reviewed literature, we would highlight that there is no consensus about the treatment of Lucio's phenomenon. In addition to specific MDT, steroids, anticoagulants, systemic antibiotics, surgical debridements and skin grafting were described with variable outcomes. In summary, regarding treatment, three points deserve to be emphasized: the use of multibacillary MDT due to the patients' high bacillary load, the use of immunosuppressant and anticoagulants due to vascular aggression and necrosis, and the care of multiple cutaneous ulcers and consequent risk of infection and sepsis.

Limitations

The major limitation of our study is the low number of case reports reviewed which is due to the low incidence of Lucio's phenomenon and difficulty in its diagnosis.

Conclusion

There are only a few articles on Lucio's phenomenon, most of them being case reports. Clinically, it is characterized by crops of wine–red colored irregular macules with a characteristic center, turning purpuric, and then necrotic, leaving behind stellate atrophic scars after healing. In general, it is associated with clinical signs of advanced leprosy such as diffuse skin infiltration and madarosis. Furthermore, it is characterized by a high bacterial index and histopathologically by the presence of AFB in the vascular endothelium associated with thrombosis and/or leukocytoclastic vasculitis. Although there is no consensus, most reports suggest that the treatment of Lucio's phenomenon should use bactericidal antileprosy drugs (MDT or alternatives schemes) and systemic steroids. All should be aware of the risk of sepsis, which should be treated immediately if it occurs.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

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