Lucio's Phenomenon: A Comparative Histological Study[1]

Thomas H. Rea and Dennis S. Ridley[2]

Lucio and Alvarez described a necrotizing skin reaction in non-nodular leprosy which has subsequently received an eponymic designation, Lucio's phenomenon, and a descriptive name, erythema necroticans. Latapi and coworkers recognized that histopathologically, Lucio's phenomenon was a dermal vasculitis and that clinically it was restricted to patients with a diffuse non-nodular form of lepromatous leprosy, pure and primitive diffuse lepromatosis (PPDL) ([5]). Lucio's phenomenon is common in Mexico and Central America but evidently rare in other ethnic groups, a circumstance which has led to uncertainty regarding the distinctiveness of this syndrome among leprologists outside of North and Central America. In studies at the Los Angeles County/University of Southern California Medical Center, the clinical findings reported by Latapi and Zamora have been confirmed ([11]), and evidence has been presented that Lucio's phenomenon, like *erythema nodosum leprosum* (ENL), may be mediated by immune complexes ([10]).

In an attempt to elucidate further the pathogenesis of Lucio's phenomenon and its restriction to patients with PPDL, we have made a comparative histologic study of Lucio's phenomenon and ENL in Mexican-born patients. The results confirm the features which separate the two reactions but point to a distinctive, endothelial habitat of *M. leprae* as the probable pathogenic cause.

PATIENTS AND METHODS

Tissue specimens were obtained from 11 patients with Lucio's phenomenon and 12 patients with ENL. All patients were Mexican-born or of bilateral Mexican-American ancestry. Of the patients with Lucio's phenomenon, eight had received no antileprosy chemotherapy; of the three with prior chemotherapy, none had received treatment for at least one year prior to presentation, and the initial episode of Lucio's phenomenon had occurred while they were off treatment. Of the patients with ENL, none had received antileprosy chemotherapy prior to the onset of ENL.

The diagnosis of Lucio's phenomenon was established by the presence of a clinically typical hemorrhagic infarct in a patient with diffuse, non-nodular lepromatous leprosy. The diagnosis of ENL was established by the presence of clinically typical, painful and tender nodular lesions in a patient with diffuse or nodular lepromatous leprosy, a consistent histologic pattern and a favorable response to thalidomide therapy.

All specimens were processed routinely and stained with hematoxylin and eosin and by the Fite-Faraco technic. One specimen was stained by the Verhoeff-van Gieson method.

Following an initial review, all tissue sections were systematically examined, and the findings recorded in tabular form.

Recorded as present or absent were epithelial necrosis, necrosis of vessel walls in the superficial (papillary and subpapillary) dermis, severe passive congestion of vessels of the superficial dermis and changes in the vessels of the mid or deep dermis or subcutis.

The following changes were estimated semiquantatively on a scale of zero (0) to three plus (+++):

a) Dermal granuloma development: no granuloma evident, 0; histiocytes arranged as small perivascular cuffs, +; large but discreet perivascular granulomas, ++; confluent granulomas, +++.

b) Endothelial proliferation: less than 50% reduction in vascular lumen, +; more than 50% reduction in lumen but still patent, ++; complete occlusion, +++.

c) Parasitization of endothelial cells: isolated AFB without aggregation, +; focal aggregation of AFB but involving less than half the endothelial cells in a particular vessel, ++; aggregated AFB in more than half of the endothelial cells in a particular vessel, +++.

[1]Received for publication 22 September 1978.

[2]T. H. Rea, M.D., Section of Dermatology, Department of Medicine, University of Southern California School of Medicine, and the Department of Dermatology, Los Angeles County, University of Southern California Medical Center, Los Angeles, California; D. S. Ridley, M.D., Hospital for Tropical Diseases, London, United Kingdom.

d) Neutrophilic infiltration: arbitrarily, the neutrophilic infiltration found in the dermis of the earliest lesion of Lucio's phenomenon was taken to be ++; less severe, +; and more severe, +++.

Furthermore, changes (a) through (d) were tabulated for the superficial and mid-dermis separately, and also for the deep dermis if subcutis was present in the specimen.

The overall severity of a vasculitic process was graded on a scale of 0 to +++. Also the BI was determined in ENL lesions in the area of the severest neutrophilic infiltration.

RESULTS

All of the patients in this study were classified histopathologically as lepromatous leprosy (LL) in the Ridley system ([14]). The presence of either ENL or Lucio's phenomenon made it impossible to differentiate between subpolar lepromatous (LLs) and polar lepromatosis (LLp) with reasonable accuracy. The Mexican patients with ENL exhibited a higher biopsy index (LIB 3.8—5.6) and a less intensive neutrophilic infiltrate than had been found in patients with ENL from Africa and Asia ([3, 12]). (Although of considerable interest, these differences were tangential to the purpose of this study and will not be expanded upon in this paper.)

A number of well marked differences, summarized in Table 1, served to delineate quite sharply the Lucio and ENL groups. The majority of Lucio cases were characterized by a necrotizing process affecting mainly the small vessels of the subpapillary plexus with associated infarction of the overlying area of epidermis (Fig. 1). In the advanced cases the necrosis might extend to parts of the superficial dermis or granuloma. Passive venous congestion was severe (Fig. 1). Another important finding was the colonization by AFB of endothelial cells, occasionally in necrotic vessels but more readily observed in vessels in the parts of the lesion that were less

TABLE 1. *A comparison of the most well developed differences between Lucio's phenomenon and ENL.*

Findings	Lucio's phenomenon	*Erythema nodosum leprosum*
Epidermal necrosis	9 of 11	0 of 12
Necrosis of vessel walls in superficial dermis	8 of 11	0 of 12
Severe passive congestion of vessels of superficial dermis	8 of 11	0 of 12
Vascular endothelial swelling and proliferation in mid-dermis	0 in 0	0 in 7
	+ in 1	+ in 4
	++ in 2	++ in 1
	+++ in 8	+++ in 0
Overall severity of vasculitis	0 in 0	0 in 4
	+ in 4	+ in 4
	++ in 1	++ in 3
	+++ in 6	+++ in 1
Parasitization of endothelial cells by AFB in normal appearing mid-dermal vessels	0 in 0	0 in 5
	+ in 3	+ in 6
	++ in 7	++ in 1
	+++ in 1	+++ in 0
Granuloma development in superficial dermis	0 in 2	0 in 0
	+ in 7	+ in 2
	++ in 1	++ in 9
	+++ in 1	+++ in 1
Severity of neutrophilic infiltration	0 in 1	0 in 0
	+ in 6	+ in 0
	++ in 2	++ in 3
	+++ in 2	+++ in 9

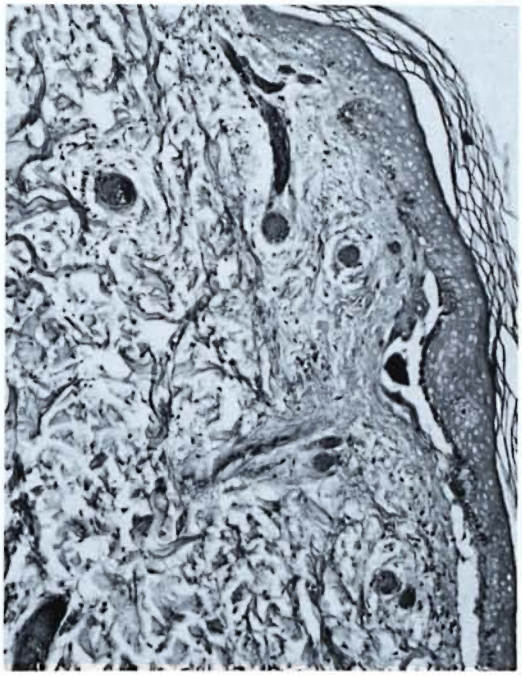

FIG. 1. Epidermal necrosis and vessel wall necrosis is demonstrated by the loss of nuclear staining. Intense passive congestion of vessels is present. Note early epidermal regeneration, originating from a sweat duct. No granuloma is evident. Hematoxylin and eosin stain, X 150.

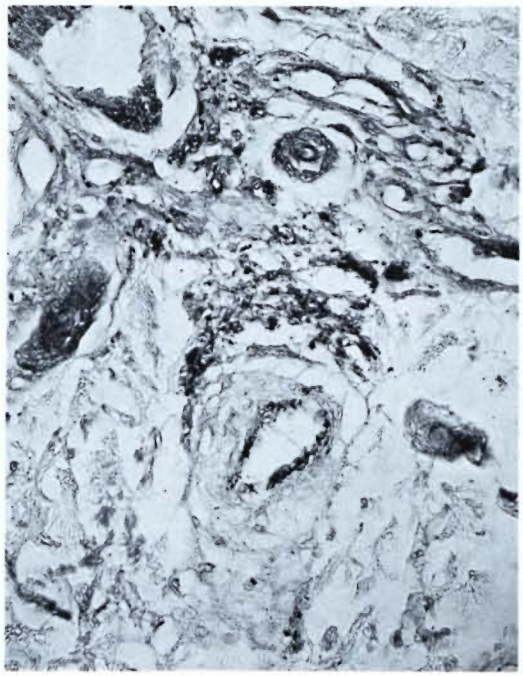

FIG. 2. AFB in endothelial cells of an apparently normal vessel in "normal" dermis 3 mm from the margin of an infarct. The density of the bacilli in these endothelial cells is similar to that in the histiocyte of the adjoining, small granuloma. Fite-Faraco stain, X 300.

directly involved in the reaction process. These vessels (up to 150μ in diameter) were found mainly in the mid-zone of the dermis, but colonization of endothelium, swollen or normal, was observed also in the more superficial vessels alongside the infarcted area (Fig. 2). It was found, too, in some of the ENL group of Mexican patients, and though here it was less marked than in the Lucio group, it was more than would have been expected in Asian or African patients. The endothelial proliferation and swelling, most fully developed in the mid-dermis, was focalized but was sufficient to cause complete occlusion of the vessel in some places (Figs. 3a-b).

In mild cases Lucio's phenomenon was primarily a reaction in superficial tissues, especially blood vessels. In general the reaction was centered in blood vessels rather than granulomas which, in the superficial zone of the dermis, were less well-developed than in the ENL group. Neutrophil infiltrate was not so heavy in the Lucio cases as in ENL, though this might have been due to the severe karyorrhexis of neutrophils as a result of the necrotizing mechanism. ENL was more a deep zone reaction, centered primarily in granulomas. However, in severe reaction these distinctions became clouded. There was endothelial swelling or vasculitis in the relatively large vessels of the deep dermis or subcutis in many of the ENL cases, vessels evidently not involved in the Lucio process.

Lucio reactions occurred usually in untreated patients, and the bacilli were notably more solid staining than in ENL.

DISCUSSION

The present results are in agreement with those of other workers ([1, 2, 4, 5, 8]). Lucio's phenomenon was distinguished histologically from ENL by the presence of ischemic epidermal necrosis and a necrotizing vasculitis of the small blood vessels of the superficial and mid-zone dermis with passive venous congestion. Though vasculitis sometimes occurs also in ENL, mainly in the deep vessels ([3, 7, 9, 15]), the vasculitis of our Lucio cases appeared to be primary and was seen in most cases and in the

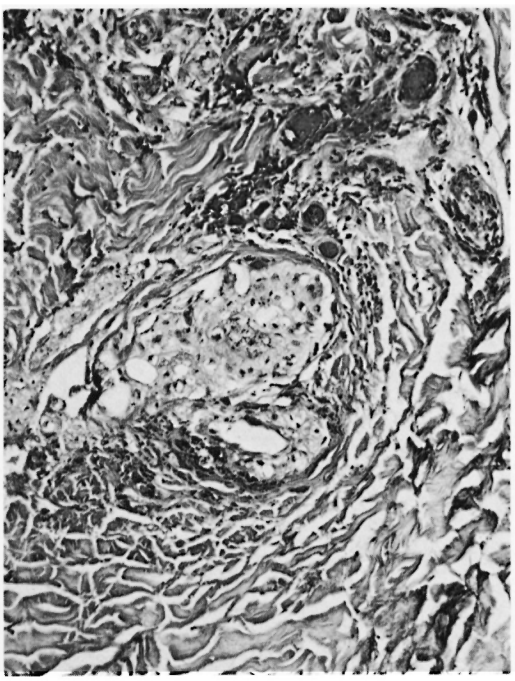

FIG. 3a. Severe endothelial proliferation in a mid-dermal vessel with only a sparse inflammatory infiltrate. Granuloma development is scant. Hematoxylin and eosin stain, X 150.

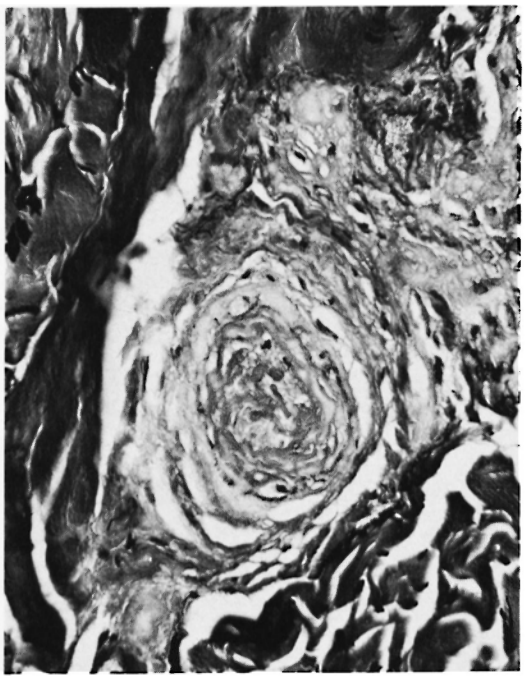

FIG. 3b. The fragmented remainder of the internal elastic lamina demonstrates that the structure is a vessel and that endothelial proliferation has been extensive in this mid-dermal vessel. Verhoeff - van Gieson stain, X 300.

earliest stage of the lesions. On this basis, 9 of our 11 Lucio biopsies were diagnostic. (In the two cases not showing epidermal necrosis we think it likely that comparatively old lesions were biopsied and that the superficial necrotic epidermis was exfoliated during tissue processing.) Another important point of distinction was the finding of endothelial swelling and colonization of endothelial cells by solid-staining AFB in non-necrotic vessels though it is thought that this may be a feature of diffuse lepromatous leprosy rather than of the Lucio phenomenon that is associated with it. This also has been emphasized by previous workers ([1, 2, 4, 8]).

These results suggest a hypothesis as follows. Diffuse lepromatous leprosy is diffuse because in patients of this type *M. leprae* is permitted to develop freely in vascular endothelium in the mid-zone dermis and subpapillary plexus. The region of this plexus was found to be optimum site for multipication of *M. leprae* though this only came about when the disease was well established or resistance was low ([13]). However, widespread and preferential colonization of endothelial cells seems to be peculiar to diffuse leprosy, in people of only a few ethnic groups, and may indicate that the defense mechanism in such people is exceptionally deficient. This is supported by Leiker's study of lepromin responsiveness ([6]). From the endothelium of this plexus diffuse dissemination throughout the skin would be unhindered and almost universal in a low immune patient. At the same time contact between bacterial antigen *in situ* and circulating antibody would be facilitated. When a reaction developed, the primary site would be the habitat of the bacilli in the small blood vessels of the skin, and infarction would follow. The points of similarity between the Lucio reaction and ENL suggest that the mechanism may be fundamentally similar. In line with this is the finding of circulating immune complexes in Lucio cases ([10]).

There is need for a histologic study of a control group of diffuse lepromatous cases prior to reaction (Lucio or other). Unfortunately, such patients seldom present themselves until the onset of a reaction. It was likewise impossible to obtain a control group of diffuse leprosy in non-Mexican patients;

among thousands of skin biopsies we were unable to trace a single suitable case. The phenomenon appears to be restricted to only a few groups of people.

In view of the relationship of Lucio's phenomenon to other forms of reaction in leprosy, especially ENL, it would seem more consistent to call it Lucio's reaction.

SUMMARY

To study further the pathogenesis of Lucio's phenomenon, we have made a comparative histological study of 11 patients with Lucio's phenomenon and 12 with ENL.

Confirming the findings of others, Lucio's reaction could be distinguished from ENL by epidermal necrosis and by necrotizing vasculitis manifesting necrosis in the walls of superficial vessels and severe, focal endothelial proliferation of mid-dermal vessels. Furthermore, in Lucio's phenomenon large numbers of AFB were found in evidently normal and in swollen or proliferating endothelial cells.

We hypothesize that patients with Lucio's phenomenon have an exceptionally deficient defense mechanism, allowing unrestricted proliferation of AFB in endothelial cells, facilitating contact between bacterial antigen and circulating antibody and leading to infarction; also, this nadir of resistance allows unimpeded dissemination of AFB, accounting for the clinical features of diffuse non-nodular leprosy. Thus, an explanation is offered for the restriction of Lucio's phenomenon to patients with diffuse non-nodular lepromatous leprosy.

RESUMEN

Con la intención de conocer mejor la patogénesis del fenómeno de Lucio, hemos hecho un estudio histológico comparativo de 11 pacientes con fenómeno de Lucio y 12 con ENL.

Confirmando los hallazgos de otros, la reacción de Lucio pudo distinguirse del ENL por la necrosis epidermal, por la vasculitis necrozante en las paredes de los vasos superficiales y por la proliferación endotelial focal y severa de los vasos en dérmis media. Además, en el fenómeno de Lucio se observaron grandes números de bacilos resistentes al alcohol acidulado (BRAA) tanto en células endoteliales aparentemente normales como en aquellas células edematosas o proliferantes.

Proponemos la hipótesis de que los pacientes con fenómeno de Lucio tienen un mecanismo de defensa excepcionalmente deficiente, lo cual permite la proliferación ilimitada de BRAA en las células endoteliales, facilitando el contacto entre los antígenos bacterianos y los anticuerpos circulantes y generando cambios inflamatorios. Este bajo estado de resistencia permite, también, la libre diseminación del bacilo de la lepra que caracteriza a la lepra lepromatosa difusa. Asi, se presenta una explicación a la asociación del fenómeno de Lucio con la lepra difusa no nodular.

RÉSUMÉ

Afin d'approfondir la connaissance de la pathogénèse du phénomène de Lucio, il a été procédé à une étude histologique comparative de 11 malades atteints du phénomène de Lucio et de 12 malades souffrant d'*érythème noueux lépreux* (ENL).

Ceci a permis de confirmer les observations faites par d'autres, à savoir que la réaction de Lucio peut être distinguée de l'ENL sur la base de la nécrose épidermique et de la vasculite nécrosante qui traduit la nécrose des parois des vaisseaux superficiels, de même qu'une prolifération importante et focale de l'endothelium des vaisseaux situés dans les couches intermédiaires du derme. De plus, dans le phénomène de Lucio, on constate la présence d'un grand nombre de bacilles acido-résistants dans les cellules endothéliales qui sont, soit normales, soit gonflées et en prolifération.

On fait l'hypothèse que les malades souffrant du phénomène de Lucio présentent une déficience exceptionnelle dans les mécanismes de défense, ce qui permet une prolifération non contrôlée des bacilles acido-résistants dans les cellules endothéliales, facilite le contact entre l'antigène bactérien et les anticorps circulant, et conduit dès lors à un phénomène d'infarcissement. De plus, cette manifestation extrême d'absence de résistance permet la dissémination, sans aucun obstacle, des bacilles acido-résistants, ce qui explique les caractéristiques cliniques de la lèpre diffuse non nodulaire. Cela fournit dès lors une explication au fait que le phénomène de Lucio est limité aux malades atteints de lèpre lépromateuse diffuse non nodulaire.

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