Lucio's Phenomenon Is a Necrotizing Panvasculitis: Mostly a Medium-Sized Granulomatous Arteritis

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Abstract: Lucio's phenomenon (LPh) is a vasculitis clinically described in 1852 and microscopically documented in 1948 in patients with diffuse lepromatous leprosy; however, at present, there is no a clear concept about the pathogenesis of the necrosis, or about the type, size, and site of the damaged vessel. The objective of this study was to elucidate the type, size, site, and form of vessel damage in LPh in a retrospective, clinical, and histopathological study. Clinical information was obtained from the charts and records and/or from the histopathology request. Slides stained with hematoxylin and eosin, Ziehl–Neelsen, and Fite–Faraco were retrieved from our files. Direct immunofluorescence had been performed in 6 cases. Twelve cases fulfilled clinical evidence to make unequivocal diagnosis of diffuse lepromatous leprosy with LPh. All of them had necrotic, irregular, purpuric, and/or ulcerative lesions, which under the microscope showed medium-sized arteries, with their walls involved by clusters of macrophages containing large amounts of bacilli, distortion of the structure of the vessel wall, narrowing, and obliteration of their lumen. Smaller vessels showed changes of the leukocytoclastic type. LPh is a distinctive type of granulomatous and necrotizing panvasculitis; the involved vessels are mostly medium-sized arteries, located deeply in the skin, at the base, and within the hypodermis, but any other vessel is likewise involved, their occlusion leads to ischemic necrosis of the whole skin, frequently with detachment of the epidermis. These changes explain clearly and logically the clinical features observed more than 150 years ago.

Key Words: Lucio's phenomenon, panvasculitis, granulomatous vasculitis, leprosy

(*Am J Dermatopathol* 2008;30:555–560)

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The data and figures in the manuscript are original and the paper is not under consideration elsewhere, and all of us have worked and read the final version of it.

This paper is dedicated to: Professor Ruy Pérez-Tamayo, MD.

We do have any conflict of interest and there are no founding sources. There is no source of support other than the author's themselves.

With a grant from the Direction of Investigation of the Hospital General de Mexico.

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INTRODUCTION

Among the protean clinical and histopathological features of leprosy, the polar form known as lepromatous leprosy, the systemic presentation of the disease, usually manifest itself with papules and nodules all over the body, this is the nodular form. However, there is another well-known form of lepromatous leprosy, which presents itself without papules or nodules, that is, as a diffuse form or diffuse lepromatous leprosy (DLL), in which there is a widespread and dense infiltration of the whole skin by bacilli, without papules or nodules and commonly in association with alopecia of eyebrows and eyelashes.

In addition, patients with lepromatous leprosy may develop the reaction known as type II, which is in fact an acute immune complex disease of 2 kinds, which clinically may expressed as erythema nodosum (characterized by tender nodules) usually complicating the nodular lepromatous leprosy or as a necrotizing form, also known as Lucio's phenomenon (LPh) (actually *Lucio's and Alvarado phenomenon*), in which cutaneous infarcts are the hallmark and develop almost only on DLL.

This peculiar and distinctive type of reaction was clinically described in detail by Lucio and Alvarado in 1852 in an article entitled "Opúsculo sobre el Mal de San Lázaro o Elefanciasis de los Griegos," in which they studied and described the diffuse form of leprosy (Saint Lazaro disease) in 41 adult patients, 21 women and 20 men. This form of the disease is today recognized as Lucio leprosy. These authors observed in 6 men and 7 women that at some moment "... any patient afflicted with Saint Lazaro's disease will manifest, most probably the spotted form ...."[1] This is the way they saw how skin infarcts develop and what we today know as Lucio's phenomenon.

Almost a century later, in 1948, Latapí and Chévez studied again this peculiar form of leprosy and recognized that histopathologically it was a vasculitis and that it was restricted to patients with diffuse, nonnodular lepromatous leprosy. They called this necrotizing skin reaction as "erythema necroticans" or LPh and the diffuse nonnodular lepromatous form of the disease as "pure and primitive diffuse lepromatosis" or DLL, an eponym and a name that actually they coined in the literature.[2]

Even when Latapí and Chévez made a very important contribution to our knowledge of the disease, they were unable to precise the kind and size of the vessel involved or which type of vasculitis was occurring. Probably because in those days, the scientific study of the vasculitic process in general was just starting.[3]

Our hypothesis is that LPh is not only a leukocytoclastic vasculitis, as some authorities state,[4] but also a distinct kind of

vasculitis, which has an excess of antigen, leading to ischemic necrosis of the depending tissues, and it is responsible for the clinical findings, that is, cutaneous hemorrhagic infarcts.

With the objective of identifying and elucidating which are the pathological changes that occur in the LPh, what kind and which size of vessel is the one involved in this process, and how these changes could explain the clinical features and the pathogenesis of such changes, we have performed this retrospective, clinical–pathological study.

MATERIALS AND METHODS

Leprosy cases studied during 15 years at the Department of Pathology, Hospital General del Centro Médico Nacional IMSS, and those assisted at the Service of Dermatology, Hospital General de México in Mexico City, with unequivocal clinical diagnosis of DLL according to the clinical criteria emphasized by Latapí and Chévez[2] and with one or more events of LPh, according to Lucio and Alvarado's original description,[1] which is widely accepted: one or more serrated hemorrhagic infarcts arising in crops in association with DLL were included in this study.

The clinical information was obtained from the charts and records and/or from the histopathology request, and clinical pictures were collected. Slides of tissue stained with hematoxylin and eosin, Ziehl–Neelsen, and Fite–Faraco stains were retrieved from our files; direct immunofluorescence had been performed with immunoglobulin (Ig) G, IgA, IgM, C3, C4, and fibrin in 6 cases. All that material was studied individually and then analyzed and compared together by a dermatologist and by 2 pathologists–dermatologists.

RESULTS

Twelve cases fulfilled with all clinical evidence to make unequivocal diagnosis of DLL in coexistence with LPh, with slides of tissue suitable for study. All patients (7 men and 5 women) were adults, ages from 29 to 72 years. All of them had ischemic lesions in different evolution stages: from red or violaceous spots to necrotic areas to ulcers, which were from a few millimeters up to 6 cm in diameter and serrated or irregular in shape, always involving the legs at the beginning, to the thighs to the trunk, sometimes also the neck and head. Only 3 of them had been found to have the disease, which were their second or third acute event; others presented as leprosy patients by this reaction (Figs. 1, 2).

The histopathological analysis in all of them showed foci of ischemic necrosis of the epidermis, frequently with detachment from the dermis; areas of ischemic necrosis in the dermis and hypodermis were seen too. Besides necrosis, other epidermal changes were hyperplasia in 5 and ulceration in 6 cases.

In the dermis, those changes characteristic of DLL were seen, such as diffuse infiltration by foamy histiocytes or Virchow cells with abundant bacilli inside their cytoplasm (globi), evident with Fite–Faraco stains; these histiocytes were mostly in and around adnexal, nerves, and follicle–sebaceous complexes, including erector muscle. A careful analysis of every skin sample showed that all kinds and all sizes of blood vessels are also involved by the process in the form of

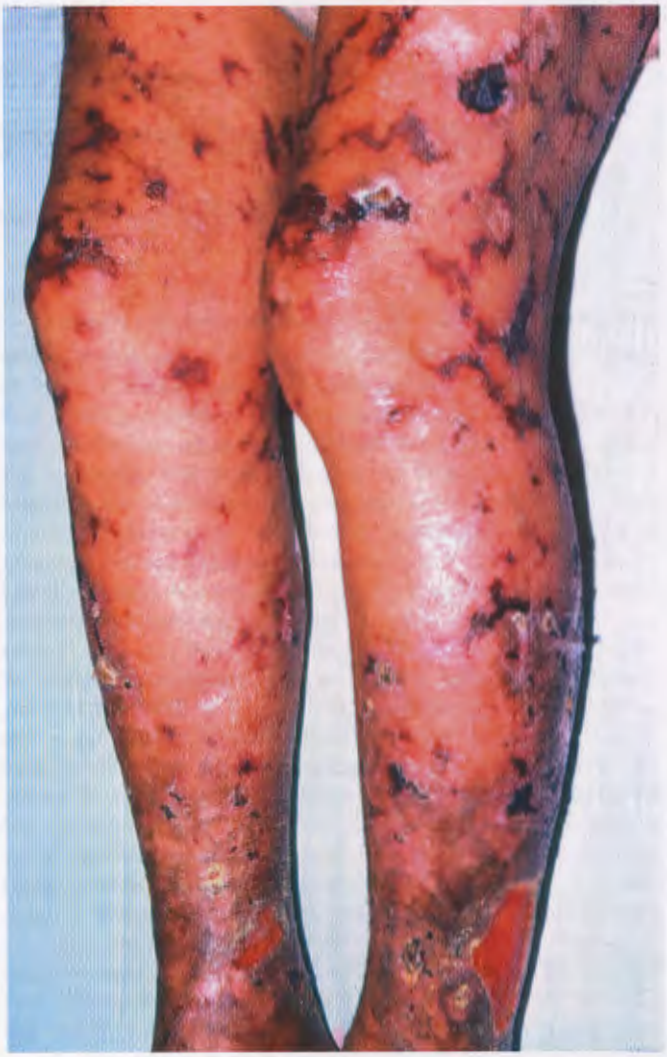

FIGURE 1. Characteristic clinical picture of Lucio's phenomenon involving the limbs of a man with Lucio's leprosy, note the angulated borders of the ulcers, a very characteristic sign of this disease.

infiltration by macrophages and/or damage to vessel walls (Figs. 3–5). Small vessels such as venules developed leukocytoclastic vasculitis.

However, the most outstanding and distinctive changes were found in the muscular or medium-sized arteries, of which walls were widely infiltrated by macrophages plenty of bacilli, usually as globi but also as solitary units (Fig. 3).

Nevertheless, other vessels, such as veins (Figs. 4, 5), venules, and arterioles, also showed their walls more or less densely infiltrated by foamy macrophages arranged in groups and filled with bacilli of *Mycobacterium leprae*, usually in association with lymphocytes. Such infiltration, by definition, is considered as a granulomatous one[5] and distorts the normal morphology of the vessel, with thickening and dissecting of their walls and narrowing of their lumens, usually with its occlusion and the consequent ischemic changes. These are constant findings in all cases.

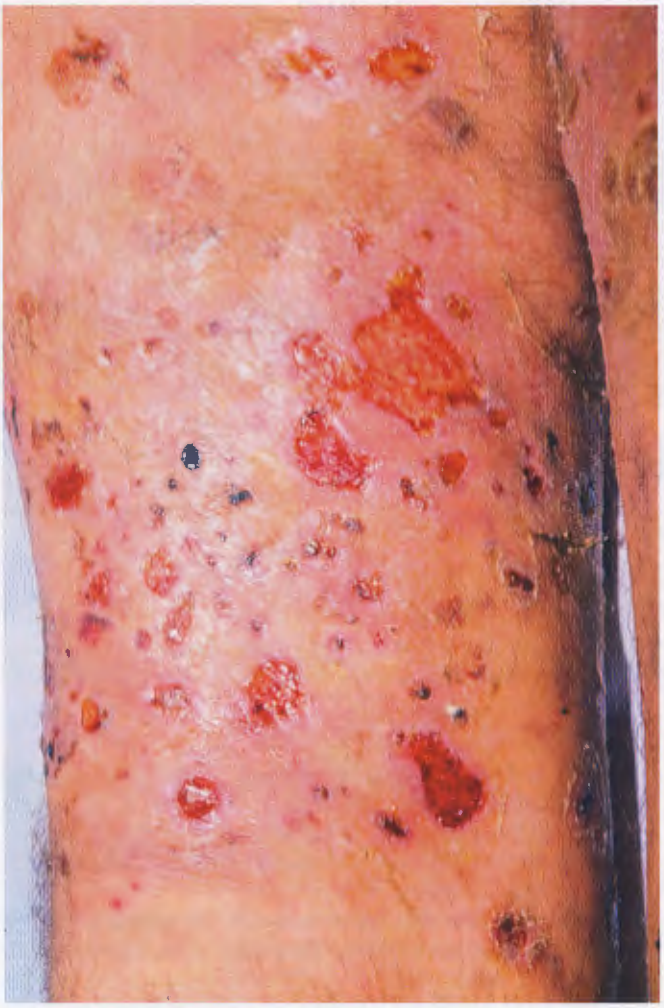

FIGURE 2. A 35-year-old man with asymptomatic diffuse lepromatous leprosy who suddenly developed Lucio's phenomenon showing infarcts and ulcers.

It should be mentioned that in smaller vessels in the dermis, such as venules, a leukocytoclastic vasculitis was seen; we were able to perform direct immunofluorescence for IgG, IgM, C3, C4, and fibrin in their moment for 6 cases, which shown to be positive in the walls of those venules. Therefore, the anatomopathological substratum in LPh involves small- and medium-sized blood vessels.

Also, a constant and repetitive change was seen in the hypodermis, which developed mostly a lobular panniculitis, but sometimes a panpanniculitis was also present.

DISCUSSION

In spite of the many chapters in books and articles published about LPh, there is no clear concept regarding the type, kind or size of vessels involved and about the pathogenesis of the vasculitic process. After the study by Latapí and Chévez,[2] other authors have clinically recognized this distinctive phenomenon.[6–15] Among them, a 46-year-old man had DLL and developed LPh. Interestingly, the histopathological study of his skin showed "intense vasculitis involving blood vessels of all sizes in the corium and subcutaneous fat."[16] Therefore, even when the kind of vessel damage was not mentioned, it seems that the author observed a wide vascular involvement, similar to what we have found in our cases.

In 1978, Rea and Levan reported an interesting study of 10 cases of DLL with LPh: in 8 patients, this acute reaction was the first manifestation of the disease, and in 2 patients, the diagnosis of leprosy had been established for several years, but the patients had received chemotherapy only sporadically. They mentioned vascular changes as "prominent, with dense aggregates of acid-fast-bacilli (AFB) found within the walls and endothelium of normal appearing vessels"[17]; however, the cells containing AFB, according to their photomicrographs, seem to be macrophages.

In a comparative histological study between 11 cases of LPh and 12 cases of erythema nodosum leprosum, it was found that necrosis of epidermis and vessel walls was greater in LPh, and the overall severity of vasculitis, the parasitization of "endothelial cells" (in most of the vessels) by AFB, and granuloma development were much more severe than in erythema nodosum leprosum. These authors also noted the "finding of endothelial swelling and colonization of endothelial cells by solid-staining AFB in non-necrotic vessels"[18]; however, a careful study of their microphotographs suggests very strongly that those cells are macrophages.

In 1980, Pursley et al found changes very much like ours when they studied a 38-year-old woman with LPh, whose several previous skin biopsies were interpreted as "periarteritis nodosa," but a detailed observation of more sections revealed infiltration of foamy histiocytes (Fite stain positives) around and in the walls of a medium-sized artery in the reticular dermis with narrowing of their lumen.[19]

Therefore, it seems that up to this point, those articles by Rea and Levan[17] and by Pursley et al[19] were the first ones to mention that the vasculitic process in LPh is actually an infiltration by macrophages. In addition, although Rea and Ridley[17] interpreted the cells filled with bacilli as endothelial ones, in our view those cells may actually be macrophages too.

These articles support our observations and hypothesis in the sense that in LPh macrophages are the target cells of *M. leprae* involving also blood vessels.

In a review of the subject matter,[20] it is interesting that a careful study of their microscopic pictures numbered from 7 to 10 shows medium-sized vessels; although the authors interpreted them as "arterioles," their size and morphological features are not similar to those of arterioles but of muscular or medium-sized arteries in the hypodermis, which demonstrates that vessels of diverse type and shape participate in the process of LPh.

In more recent reports about LPh, unfortunately, there is no mention about the vasculitic process.[21–24] Books of pathology, dermatology, and dermatopathology do not tell much about the precise changes or the kind of the pathological vascular process that develops in LPh.[25–30]

Rodríguez seems to be the one who has realized that LPh is a vasculitic process caused by macrophagic infiltration of vessels walls[31] and concurs with us in the sense that this process is actually a granulomatous necrotizing vasculitis.[32]

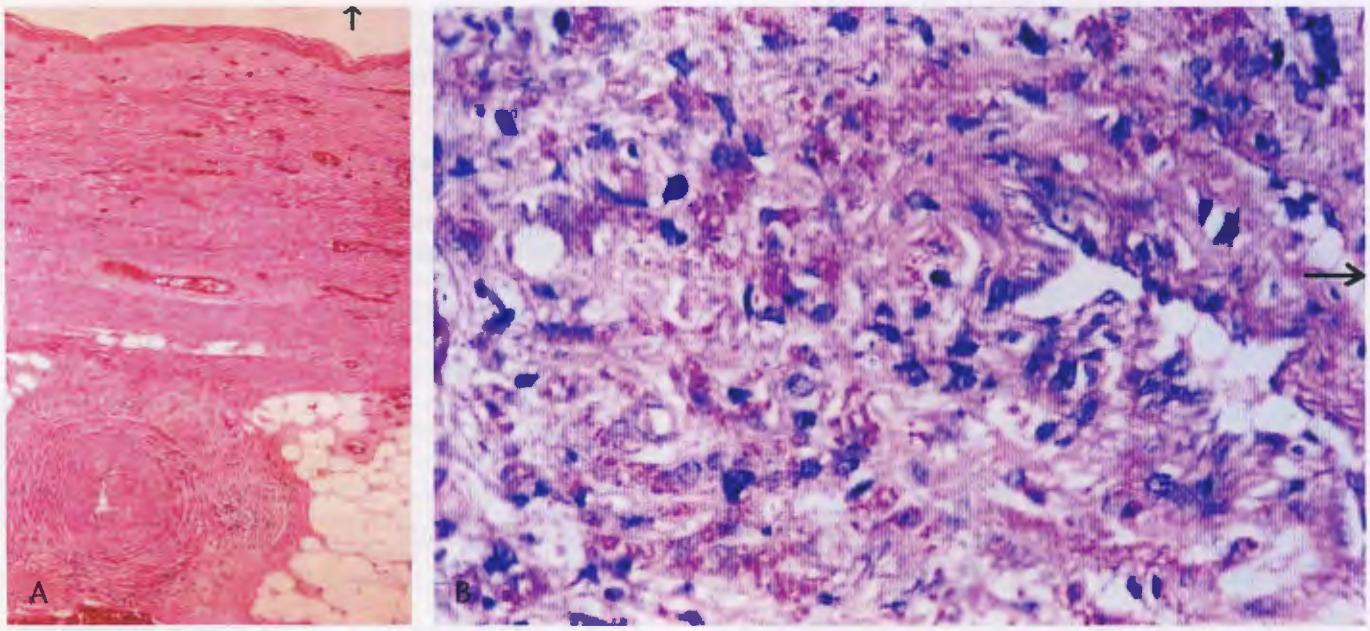

FIGURE 3. Histopathology of Lucio's phenomenon: medium sized necrotizing arteritis, which is clearly shown because of a good in depth biopsy (H&E stain, 10X) (A). High power shows macrophages with globi inside infiltrating the wall of this artery, endothelial cells do not show bacilli inside (Ziehl-Neelsen stain, 400X) (B).

According to a most trusted reference in basic pathology, granulomatous inflammation is characterized by focal accumulation of activated macrophages.[5] Therefore, if we accept that definition, it is valid to classify this vasculitic process as a granulomatous one, even without obvious necrosis. Other cells, such as lymphocytes, are usually part of the infiltrate; however, it is well known that in leprosy, it is usual to see macrophages without other cells or necrosis.

Turkel et al[33] have studied the ultrastructure of dermal microvasculature in 18 cases of leprosy and demonstrated bacilli inside the cytoplasm of cells, which they interpreted as endothelial cells; however, Weibel–Palade bodies, the ultrastructural marker of endothelial cells, are not present in their microscopic pictures. In addition, endothelial cells are not precisely phagocytic cells; according to several recent studies regarding the many properties of endothelial cells, there is no mention about their phagocytic capability to engulf mycobacteria.[34–40] Therefore, the cells very nicely observed by Turkel et al could very well be macrophages too.

Parasitism of endothelial cells by *M. leprae* has been well demonstrated in epineurial and perineurial blood and lymphatic vessels in the armadillo,[41] and endothelial cells are considered in the pathogenesis of lepromatous neuritis by some authorities in the field.[42]

Not only macrophages and endothelial cells interact with *M. leprae* but also Schwann cells and dendritic cells, and many molecules.[43] Therefore, our interpretations, made on routine histopathological observations, regarding the macrophage as the principal cell plenty of bacilli inside the walls of blood vessels of human skin in LPh as causative of narrowing of the lumen to the point of obliteration and the ischemic changes (with and without thrombosis), make sense. Analogous changes have been published recently.[44]

We concur with Rea and Jerskey,[45] who also observed that vascular changes in LPh and LLD are the result of the infiltration of macrophages filled with globi within the vessel walls, and properly named these changes lepromatous granulomatous vasculitis.

In short, LPh is a necrotizing panvasculitis due to an excess of antigen, not only as entire bacilli or its fragments but also as globi, which can be easily seen inside macrophages (and not only inside the endothelial cells) that infiltrate the vessels' walls, mostly of muscular or medium-sized arteries (which explains the cutaneous infarcts) but also those of arterioles, venules, and medium-sized veins. Smaller and more superficial vessels exhibit a leukocytoclastic vasculitis with immune complex deposition.

Therefore, the main changes are those of a granulomatous necrotizing vasculitis not only because of the morphological evidence shown here—the massive infiltration (if active or passive is unclear yet) by macrophages (with bacilli inside) of blood vessel walls—but also because of the evidence demonstrated by other authors.[31,32,45] Endothelial cells may be involved as phagocytic cells in peripheral nerves[41,42] and in other tissues of the patient with DLL, but these cells can also be easily identified as normal ones and different from macrophagic cells in our cases (Figs. 3–5) and in those of others.[16–19,31])

The possibility of a new species, *Mycobacterium lepromatosis*, is found to be raised in patients with DLL and LPh by Han et al (in press), which could explain the distinct clinical–pathological features and the peculiar host reactions of a proportion of patients to a particular etiologic agent. Recognizing this etiology may explain the endemic nature of DLL in Mexico and some other areas.

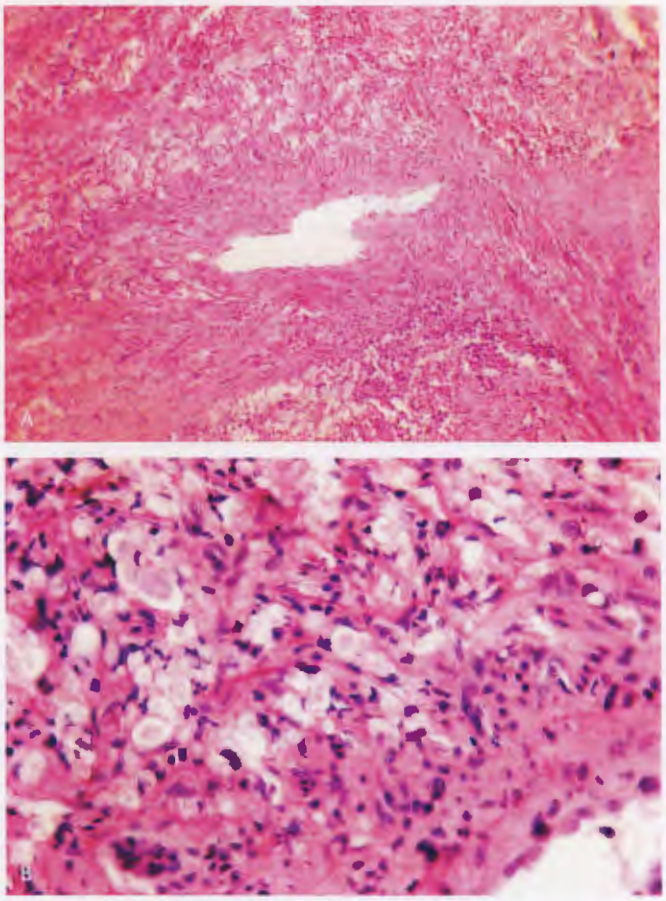

FIGURE 4. This is a medium-sized vein widely infiltrated by macrophages filled with globi (H&E stain 100X) (A). At higher magnification macrophages with globi appear clearly inside the wall while endothelial cells are obviously not involved by the granulomatous process (H&E stain, 400X) (B).

It is also true that leukocytoclastic vasculitis develops in LPh as it can be seen in smaller vessels such as capillaries and venules in the upper dermis,[4] but if the biopsy specimen is good enough to see epidermis, dermis, and hypodermis, it is possible to identify that the medium-sized granulomatous arteritis is the responsible for the severe ischemic process in this disease.

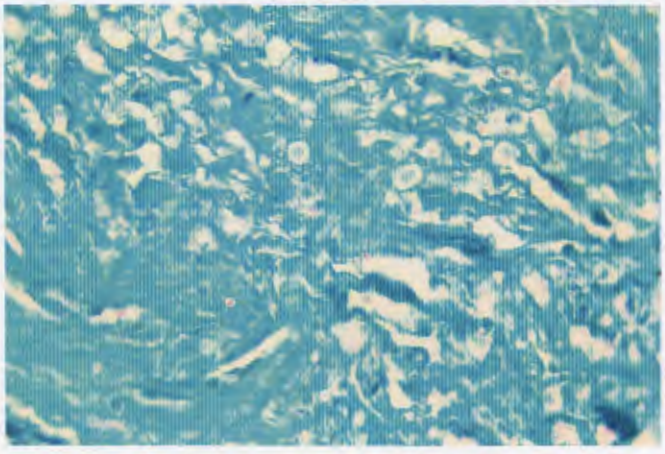

FIGURE 5. Bacilli arranged in globi inside macrophages in the medium layer of the wall (Fite-Faraco's stain 100X).

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