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Lobomycosis. Literature Review and Future Perspectives

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Abstract. Lobomycosis is a cutaneous infection of tropical and subtropical regions caused by the fungus *Lacazia loboi*, which still has a controversial taxonomical position.
The first description of the disease and fungus was made in 1930 by Jorge Lobo. It is a chronic disease with predominance of lesions similar to keloids, in exposed areas, limited to skin and semimucosa. There is no systemic involvement and patients maintain a good general health. Diagnosis is confirmed by direct or histopathologic exam and, until present, the fungus has not been cultivated. Surgery is the treatment of choice for isolated lesions, but there are frequent recurrences. Good therapeutic responses have been reported with clofazimine, with or without itraconazole, and with 5-fluorocytosine.
This disease should be recognized by dermatologists worldwide because, although restricted to the Amazon region, it has been observed in other locations. Research development and achievement of new knowledge in molecular biology and genetic engineering of lobomycosis are of utmost importance because they may, in the future, lead to the culture of the fungus in the laboratory and to a better understanding of its pathogenesis, transmission mechanism, and new methods of diagnosis, prevention and treatment.

Key words: lobomycosis, fungus, *Lacazia loboi*, clofazimine, infection.

LOBOMICOSIS. REVISIÓN DE LA LITERATURA Y PERSPECTIVAS FUTURAS

Resumen. La lobomicosis es una infección cutánea de las regiones tropicales y subtropicales que está causada por el hongo *Lacazia loboi*, y cuya posición taxonómica continúa siendo controvertida.
Jorge Lobo realizó la primera descripción de la enfermedad y del hongo en 1930. Se trata de una enfermedad crónica con predominio de lesiones que se asemejan a queloides, en áreas fotoexpuestas, limitadas a la piel y a la semimucosa. No existe afectación sistémica y los pacientes presentan buen estado general. El diagnóstico se confirma por el examen directo o el estudio histológico y, hasta el momento, el hongo no se ha podido cultivar. La escisión quirúrgica es el tratamiento de elección para lesiones aisladas, pero las recurrencias son frecuentes. Se han descrito respuestas favorables con clofazimina, con o sin itraconazol, y con 5-fluorocitosina.
Aunque es una enfermedad propia de la región del Amazonas, los dermatólogos de todo el mundo deben reconocerla, ya que también se ha observado en otras regiones. El desarrollo de la investigación y la consecución de nuevos conocimientos en biología molecular e ingeniería genética sobre la lobomicosis son de gran importancia ya que, en un futuro, permitirán el cultivo del hongo en el laboratorio, lo que facilitará una mejor comprensión de su patogenia, mecanismo de transmisión y nuevos métodos de diagnóstico, prevención y tratamiento.

Palabras clave: lobomicosis, hongo, *Lacazia loboi*, clofazimina, infección.

Introduction

Lobomycosis was first described in 1930 by Jorge Lobo[1,2] and for that reason it is also known as Jorge Lobo disease or Jorge Lobo mycosis. Other names are keloidal blastomycosis, Jorge Lobo type blastomycosis, *miraip* or *piraip* (what burns, in the *Tupi* Indian language), leprosy-of-the-caiabi, false-leprosy, blastomycoid granulomatosis, Amazon blastomycosis and lacaziosis.

The first report was for a 52 year-old male, observed in the city of Recife, State of Pernambuco in the Northeast of Brazil; but the patient came from the Amazon region, where he worked as rubber tapper. The clinical picture

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showed nodular lesions in the lumbosacral and gluteal regions. Parasitic corpuscles, resembling *Paracoccidioides brasiliensis*, were seen in direct and histological examination[2].

Lobomycosis is a cutaneous infection caused by the *Lacazia loboi* fungus, by probable traumatic inoculation, with prevalent occurrence in tropical and subtropical regions[3]. This fungus has a controversial taxonomic classification, being genetically similar to *Paracoccidiodes brasiliensis*[4].

The clinical picture is chronic, localized, with predominance of keloidiform lesions in exposed areas, limited to skin and semimucosa. The regional lymph nodes may also be compromised. There is no systemic involvement and the overall patient's state is good. Dissemination of cutaneous lesions is rare, providing a good prognosis for the disease. The consequences include possible restriction of movements, significant aesthetic damage, secondary infection and carcinomatous degeneration[3,5-7].

Diagnosis is made by direct examination of the fungus or by histopathologic examination, and to present, the fungus is not subject to culture in laboratory[7].

The knowledge of this disease is extremely important, because, besides the already described situations, the differential diagnosis includes neoplastic diseases.

The treatment of choice for isolated lesions is surgery, with cryosurgery being also a treatment option. In extensive lesions, frequent recurrence occurs with surgical methods and the aesthetic result is often unsatisfactory. There are reports of good therapeutic results with clofazimine, clofazimine in association with itraconazole[8] and 5-fluorocitosine. Several medications and surgical methods were already tested with unsatisfactory results[3,5-7].

The development of new researches and knowledge of molecular biology and genetic engineering may, in the future, lead to the fungus cultivation in laboratory and a better knowledge of its etiopathogeny, its mechanism of transmission, and, above all, the proposition of new methods for diagnosis, prevention and therapy.

Etiologic Agent

The etiologic agent was initially described by Jorge Lobo in 1930 and has already received the following names: *Paracoccidioides loboi*[9], *Glensporella loboi*[10], *Blastomyces loboi*[9], *Glenosporopsis amazonica*[11], *and Loboa loboi*[4].

The phylogenic study of this fungus, using amplification of the 18S subunit of ribosomal deoxyribonucleic acid (DNA), recently classified it as belonging to the Onygenales order[12] and, therefore, taxonomically close to *Paracoccidiodes brasiliensis*.

Taborda et al[13], using Fontana-Masson staining, detected a different kind of melanin in the cell walls of *Lacazia loboi*, than that observed in *P. brasiliensis* and in ascomycetes, phylogenetically related to the Onygenaceae family. The authors concluded that no existing gender, not even the *Paracoccidioides*, could accommodate this fungus, and, for that reason, a new gender was proposed with the presently prevailing name, *Lacazia loboi*. The name "Lacazia" was given in honor of the Brazilian mycologist Carlos da Silva Lacaz, a researcher who significantly contributed to the present knowledge of that disease; while "loboi" was a reference to the Brazilian dermatologist Jorge O. Lobo, the first to describe the disease.

In some individuals with lobomycosis, the reaction against antigens of *Paracoccidiodes brasiliensis*, as glycoprotein (gp) 43, was positive, according to Villela[4]. According to these authors and based on molecular studies, the name *Lacazia loboi* is the current recommended name. As is common in medical mycology, the name of the disease is taken from the genus of the etiologic agent and, therefore, lacaziosis has been proposed for the disease name rather than lobomycosis.

In 1999, Opromolla et al[14] described the growth of *L. loboi* after inoculation in Swiss rats. Madeira et al[15], in 2000, experimentally reproduced lobomycosis after inoculation in BALB/c rats. Belone et al[16] carried out a study obtaining an experimental reproduction of the Jorge Lobo disease in BALB/c rats, using intradermal inoculation, with *Lacazia loboi* extracted from rats previously infected with material obtained from human lesions. The histopathological analysis and clinical picture of those two groups of rats were similar and compatible with that of lobomycosis. The BALB/c rats were submitted to a sequence of inoculations and sacrificed, in different time intervals, during 8 months. It was found that BALB/c rats are an excellent mode to maintain *Lacazia loboi* in laboratory and may help in new studies on the fungus.

Until present, the fungus has not been cultured in the laboratory, despite several trials. The reason for this remains unknown. Perhaps, in the future, the identification of this fungus as dimorphic, the elucidation of its antigenic properties, and biochemical and molecular constitution may be relevant for its culture in the laboratory.

Epidemiology

The disease prevails in tropical and subtropical regions with hot and humid climate, especially in the Amazon region (Brazil and Colombia)[5-7]. There are cases reported in Costa Rica, Venezuela, Peru, French Guyana, Suriname, Panama, Guiana, Ecuador, Bolivia, Mexico, Canada and the United States[13]. In Europe, one case was reported in Spain (Bay of Biscay)[17] in a dolphin caretaker. The first U.S. patient, described in 2000, had traveled to Venezuela[18]. Elsayed et al reported, in 2004, the first case in Canada, in a woman[19]. There was also an isolated case in

Bangladesh[20], but there are doubts if it really was lobomycosis[13], and two in South Africa[21].

Migaki et al, in 1971, described the disease for the first time in a *Tursiops truncatus* dolphin from Sarasota, on the Coast of Florida[22]. The cases of lobomycosis involve two dolphin species: *Tursiops truncatus* (marine dolphin) and *Sotalia fluviatilis* (river dolphin)[23,24]. De Vries described a sweet water dolphin affected in Suriname[24].

The fact that lobomycosis can be acquired from contact with infected dolphins leads to the hypothesis that water might be one of the fungus' reservoirs, and the geographic distribution, therefore, might be much wider than presently supposed, and vertebrate animals may also transmit it to humans. Transmission between humans is not possible[3], even among members of the same family[25] or between people with great conviviality[26-28].

Important studies on the disease were carried out with the Caiabi Indian tribe. In 1966, Machado et al[29] reported 12 cases among the Caiabi. Later, 22 new cases in the same tribe were described by Baruzzi et al[30] In the period of the 50's to the 70's the Indians were transferred from the area between the Arinos and Teles Pires Rivers, in the state of Mato Grosso, to the Indian Park of Xingu and, curiously, no new cases were detected in that population.

It is a disease of low overall prevalence, despite the number of notified cases being on the rise in locations of greater frequency[28]. It is probable that many cases are not reported, which emphasizes the importance of knowing this disease, mainly in tropical and subtropical countries, but also in the remaining countries of a globalized world.

It is more common in males, in a proportion of 10 men to 1 woman, between 20 and 40 years, working in forest and rural activities, as rubber tappers, gold and precious stones prospectors, forest exploiters and hunters[5]. An exception occurs in the Caiabi tribe, where women represent 32% of the affected, possibly for their greater participation in forest activities[30].

Etiology and Pathogenesis

The etiopathogeny of this disease is still unclear. The fungus probably lives as saprophyte in soil, vegetation and water, and is transmitted to man and dolphins by traumatisms. The incubation period remains unknown. The fungus is low pathogenic, proliferates intensely in the dermis, and invades the regional lymph nodes in some cases[3,5-7].

In the study by Marcos et al[31] 21 patients with Jorge Lobo disease were compared with healthy individuals of the same ethnic group, in order to assess a possible association of antigen specificities with human leucocytes (HLA) of class II. The HLA typifications were made by PCR (polymerase chain reaction) – SSP (sequence-specific primers). No association between HLA antigens and Jorge Lobo disease was found. Despite any statistical relevance, a reduction in the frequency of HLA-DR7 antigen was found in the affected group in relation to the controls (0% vs. 18%), suggesting a negative association (protective).

As in the case of paracoccidioidomycosis[32] and leprosy[33,34], HLA in lobomycosis seems to be more associated with clinical presentation of the disease than to susceptibility to infection[35].

The clinical variations of this disease also depend on innate immunity genes, while protective and susceptibility mechanisms depend, probably, on other involved genes and on the nature of the pathogen[35].

Xavier et al[36] analyzed the expression of TGF- in cutaneous lesions in lacaziosis. Their results suggest that the abundance of collagen bands, together with weak immunolabeling for CD68 seen in macrophages, indicate a concomitant effect of TGF- inhibiting macrophages and inducing fibrosis, which is responsible for the frequently observed keloid aspect of these lesions. The evolution of infection supports the hypothesis that TGF- plays a fundamental role in the etiopathology of *Lacazia loboi* infection, either by inhibiting the cellular immune response mainly mediated by macrophages or by inducing fibrosis.

Clinical Features

The clinical picture is variable with polymorphous lesions that can be single or multiple.

The most common clinical presentation is a nodular, solid lesion, with smooth surface, shiny and keloidal aspect (figs. 1 and 2), localized (fig. 3), especially, in the ears (fig. 4), and upper (fig. 5) and lower limbs (figs. 6 and 7). Other clinical forms are: infiltrative, gummatous, ulcerative, verrucous, tumoral, sclerodermiform, macular and in plaques. Manifestations include pain at touch, itching, burning, hypoesthesia, anesthesia[37] and involvement of semimucosa (fig. 8). Lymph nodes can be affected and, in such case, they will be hard and without fluctuation[3].

Evolution is slow, new lesions arise by contiguity or by lymphatic dissemination, and there is evidence of possible hematogenous dissemination. Restriction of movements, significant aesthetic damage, secondary infection and carcinomatous degeneration may occur[3,5].

The disease, therefore, has a wide spectrum of clinical manifestations. In the important work by Machado, in a study of the Caiabi Indians, a classification into two polar groups was suggested: the hyperergic (macules and gumma) and the hypoergic (keloidal)[38].

Lacaz et al[9] reported that some individuals presented disseminated disease prematurely, while others manifested only a localized isolated lesion, of chronic evolution, thus demonstrating the different clinical expressions of lobo-

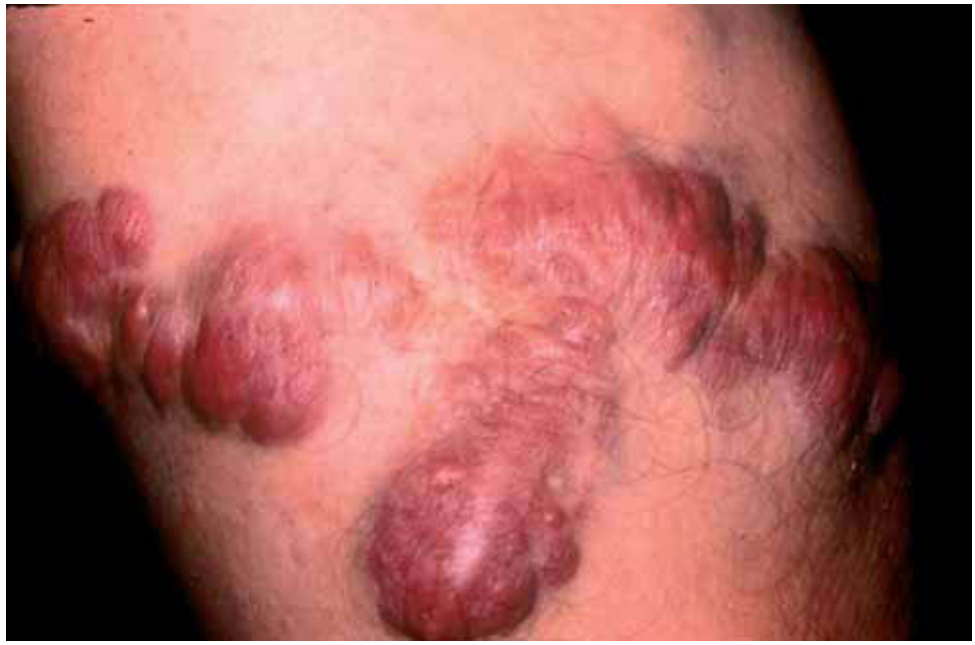

Figure 1. Lobomycosis on the thigh; keloidal lesion.

mycosis. Between those two clinical extremes, there would be a wide variation of the behavior and evolution of the disease. The form with dissemination of cutaneous lesions was described in the first case of lobomycosis in an HIV-positive patient by Xavier et al[39].

Differential Diagnosis

Because of its great clinical variation, lobomycosis may include the following diseases among its differential diagnosis: keloid; leprosy, including borderline tuberculoid (BT) leprosy[37]; mucocutaneous leishmaniasis, mainly its cutaneous diffuse anergic form; cutaneous tuberculosis; paracoccidioidomycosis; histoplasmosis; chromoblastomycosis; sporotrichosis; mycetoma; phaeohyphomycosis; blastomycosis-like pyoderma; Kaposi's sarcoma; sarcoidosis; keloidal forms of scleroderma; Ehlers-Danlos type IV syndrome; the sclerotic form of disseminated xanthoma; non-Langerhans cell histiocytosis; benign neoplasias of nodular expression; melanoma and non-melanoma skin cancer; dermatofibrosarcoma; lymphomas, especially mycosis fungoides, and cutaneous metastases.

Diagnosis

The diagnosis is obtained by direct mycological and histopathological examination.

Direct examination is carried out in the collected material from cutaneous lesions by scarification, scratching, curettage or use of adhesive tape[40].

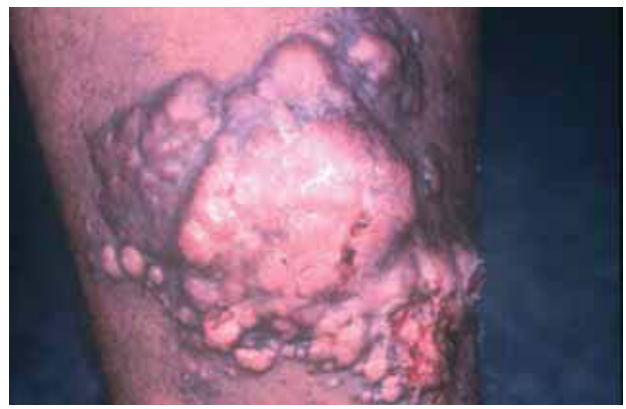

Figure 2. Lobomycosis on the thigh; keloidal lesion.

The direct examination reveals an abundance of fungi with thick refringent and double contour walls, measuring from 5 to 6 × 12 to 14 m and with reproduction by simple gemulation. Rosary or chain pattern is frequent. The fungus can be found in great numbers in direct examination and histological preparations and is better evidenced by periodic acid Schiff stain and methenamine silver stain (Grocott-Gomori) (fig. 9)[5].

Histopathological examination presents a normal atrophic, hyperplastic or ulcerated epidermis. Irregular hyperplasia, sometimes pseudo-epitheliomatous, is common in vegetating-verrucous lesions and on ulcer borders. *L. loboi* is present among the scales and scaly crusts of the stratum corneum, translated by black spots in the skin that cover the ulcerated-crusted lesions, as those of smooth aspect. There is transepidermal elimination of the fungus[5,41].

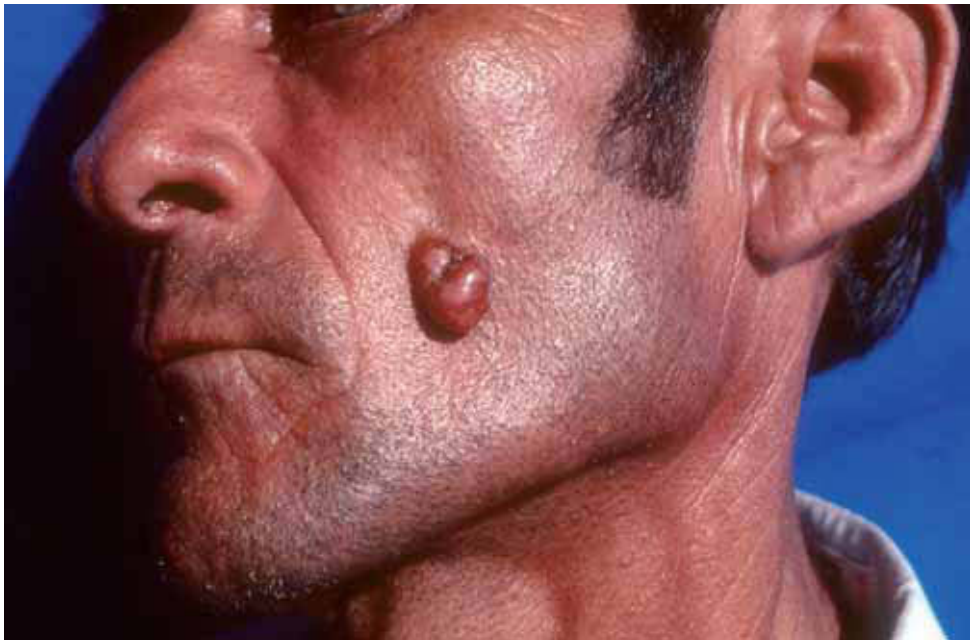

Figure 3. Lobomycosis on the cheek.

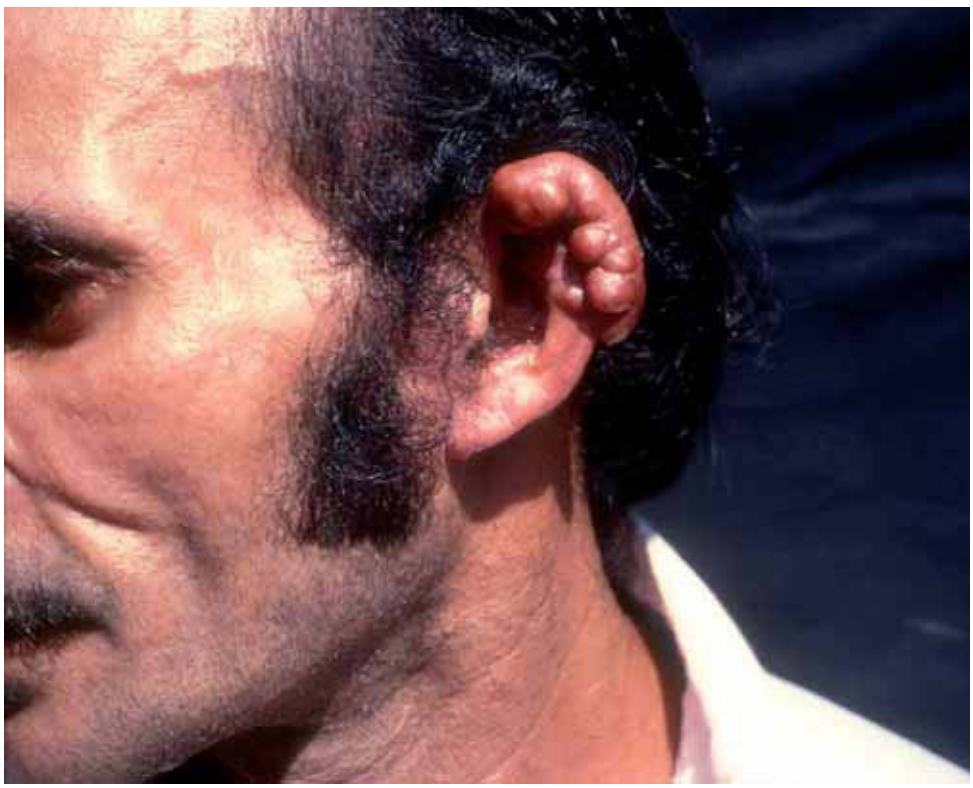

Figure 4. Lobomycosis on the ear; frequent location.

The dermal alterations are pathognomonic of the disease, easily disclosing its diagnosis. The inflammatory infiltrate is granulomatous, nodular and diffuse, comprising macrophages and numerous multinucleated cells, of Langhans and foreign body types. Histiocytes show a foamy aspect and large quantity of parasites. The infrequent exudative reaction is represented by dot aggregates of lymphocytes and plasma cells between phagocytic cells or in

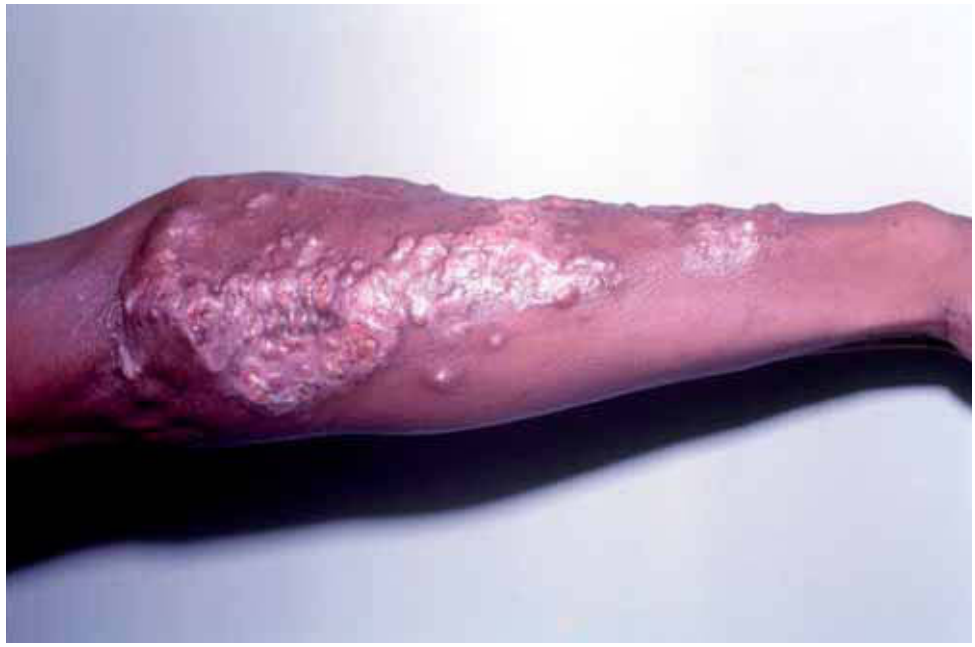

Figure 5. Lobomycosis on the elbow and forearm.

the perivascular space. Neutrophils, when present, occupy the upper dermis in ulcerated lesions. Necrosis is almost always absent. There is a light band (Grenz zone) separating the epidermis from the infiltrate, otherwise the productive reaction contacts the epidermis[5,41].

Few immunohistochemical studies exist. In the histological and immunohistochemical study by Vilani-Moreno et al[42], based on the high number of fungi found in infected tissues and in the disrupted granulomatous cell arrangements, it was hypothesized that a disturbance in immune regulation may be present in patients with lobomycosis.

An extraction method of *L. loboi* yeast cells from biopsies of skin lesions based on the proteolytic action of the dispase enzyme proved to be efficient and is an important tool for improving biological studies of this fungus[43].

Treatment

The treatment of choice for isolated lesions is surgery. Cryosurgery is also a treatment option. In extensive lesions, frequent recurrence occurs with surgical methods and the aesthetic result is, often, unsatisfactory[3,44-46].

Clofazimine was used for the first time by Silva in three patients with improvement of lesions[47]. Pradinaud and Talhari mentioned the use of 5-fluorocitosine[48]. The association of clofazimine and itraconazole during one year led to clinical and histopathological remission, according to Fisher et al[8].

Several other treatments were tested with unsatisfactory results[3,5], and the therapeutic difficulty for this myco-

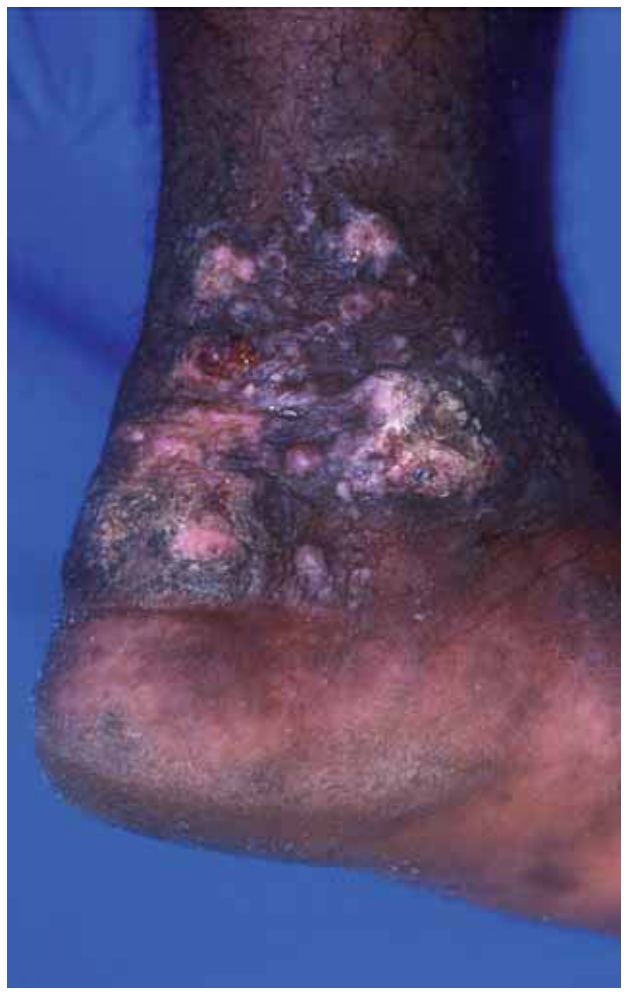

Figure 6. Lobomycosis on the ankle.

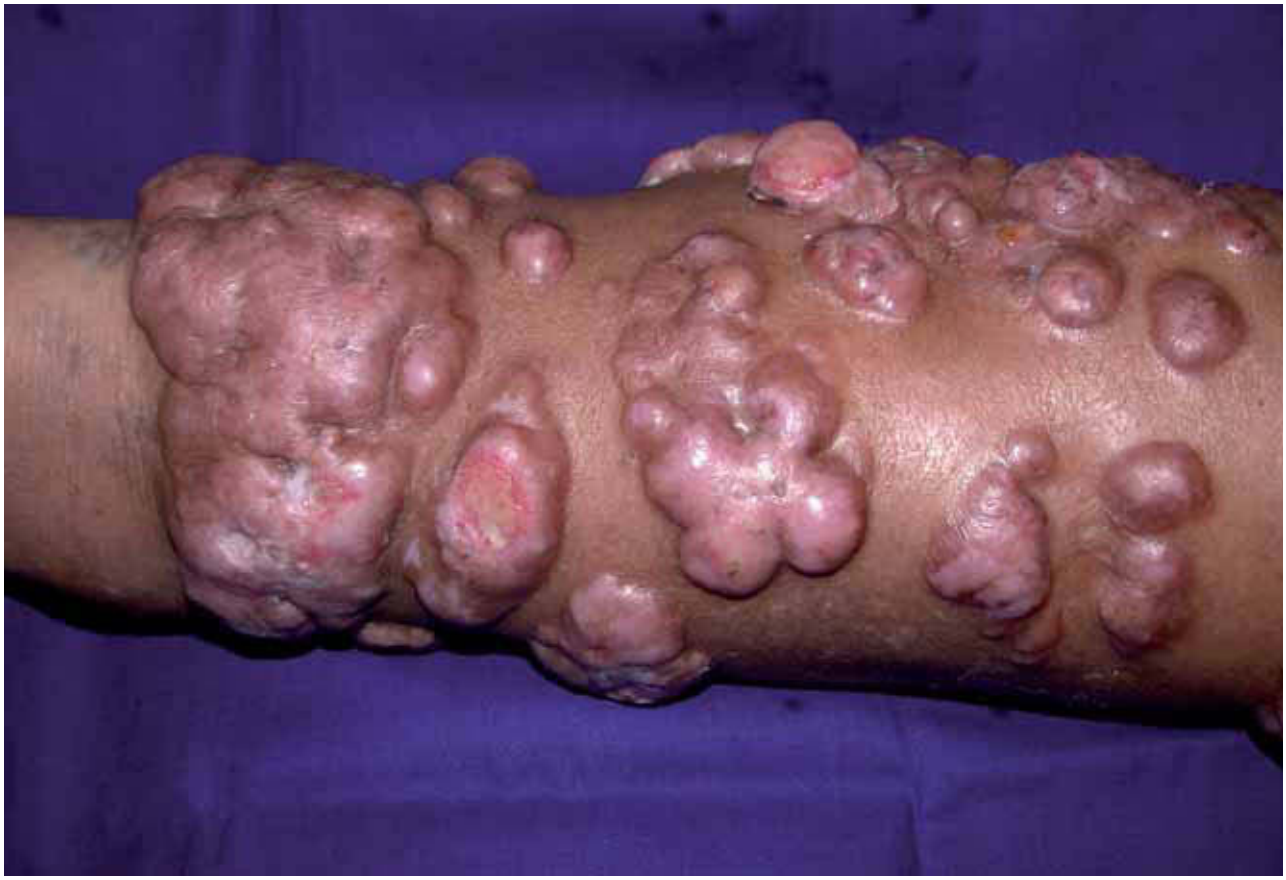

Figure 7. Lobomycosis on the thigh; numerous vegetating and ulcerative lesions (courtesy of Clivia Carneiro. Belém, State of Pará, Brazil).

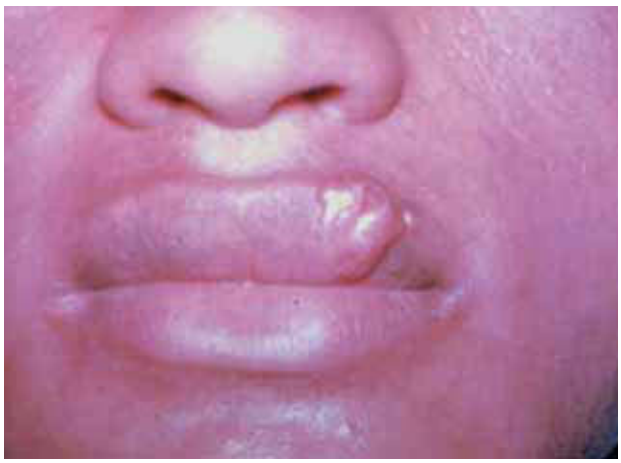

Figure 8. Lobomycosis on the lip; rare location.

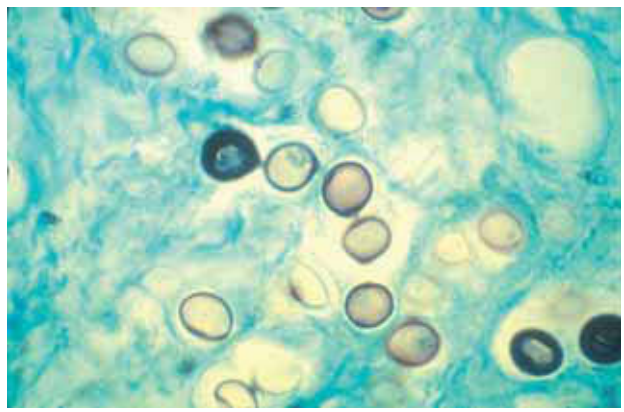

Figure 9. *Paracoccidioides loboi*; biopsy fragment with fungi showing simple gemulation in the typical chain aspect (methenamine silver stain Grocott-Gomori 100×)

sis lies in the disseminated forms, still without an effective medication that, besides efficiency, presents minimal side effects and low cost, with special emphasis on this last aspect since the disease prevails among poor population groups[5].

Conclusion

Despite having been discovered in 1930, lobomycosis, regardless of the progress in Dermatology and biomedical technologies, still remains an obscure disease.

In the future, new knowledge in molecular biology and genetic engineering may lead to a better understanding about this fungus, its etiopathogeny, and transmission, its culture in laboratory, and new methods for diagnosis, prevention and therapy. Likewise and especially, more effective treatments may be proposed, entailing an improved life quality and a psychosocial gain for those individuals.

In case the fungus is cultured in coming years, it is very likely that this will play a primordial role in research aiming at the discovery of more effective medications.

This disease, despite apparently being restricted to the Amazon region, has been observed outside that location, mainly in cases related to infections by contact with infected dolphins.

These data indicate the need for greater knowledge of the disease and its clinical aspects by dermatologists worldwide, who can diagnose, still in early phases, the disease in patients coming from the Amazon basin, or infections occurring outside of that geographic region.

Conflict of interest
Authors have no conflict of interest to declare.

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