Lobomycosis: epidemiology, clinical presentation, and management options

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Abstract: Lobomycosis is a subcutaneous mycosis of chronic evolution caused by the *Lacazia loboi* fungus. Its distribution is almost exclusive in the Americas, and it has a particularly high prevalence in the Amazon basin. Cases of lobomycosis have been reported only in dolphins and humans. Its prevalence is higher among men who are active in the forest, such as rubber tappers, bushmen, miners, and Indian men. It is recognized that the traumatic implantation of the fungus on the skin is the route by which humans acquire this infection. The lesions affect mainly exposed areas such as the auricles and upper and lower limbs and are typically presented as keloid-like lesions. Currently, surgical removal is the therapeutic procedure of choice in initial cases. Despite the existing data and studies to date, the active immune mechanisms in this infection and its involvement in the control or development of lacaziosis have not been fully clarified. In recent years, little progress has been made in the appraisal of the epidemiologic aspects of the disease. So far, we have neither a population-based study nor any evaluation directed to the forest workers.

Keywords: infection, *Lacazia loboi*, lobomycosis, lacaziosis, mycosis

Introduction

Lobomycosis is a fungal infection caused by *Lacazia loboi*. This disease affects primarily the subcutaneous tissue manifested by a chronic granulomatous reaction, full of parasites, in the dermis. Keloid-like lesions are the most common clinical presentation.¹⁻³

With a clear geographic distribution, lobomycosis affects exposed populations of endemic areas in Latin America, with few reports of exported cases.⁴⁻⁶ A new epidemiologic scenario is linked with dolphins that are prone to acquiring lobomycosis. This new context expands the possibility of lobomycosis to every coastal region in which those cetaceans are found, raising the need for clinicians to recognize this emerging fungal infection.

Etiology

The first case report of lobomycosis was done in 1931 by the Brazilian dermatologist Jorge Lobo. This report was about a 52-year-old man who lived in the Amazon region and who presented with sacral lesions resembling keloid. This “new” disease was named “blastomycose keloidiana” (keloid blastomycosis).¹

Since this first description, several names have been used to describe this entity: Jorge Lobo disease, Jorge Lobo mycosis, Jorge Lobo blastomycosis, amazonic pseudolepromatous blastomycosis, miraip or piraip (in the tupi language), Caiabi

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leprosy (Caiabi is an Indian tribe located in the state of Mato Grosso), and lacaziosis. Lobomycosis is the correct name for this disease.²

The taxonomy of this fungus is confusing and has changed several times since its first description. *Glenosporella lobo* was used by Fonseca Filho and Area Leao,³ *Blastomyces brasiliensis* by Conant and Howell,⁴ *Glenosporosis amazonica* by Fonseca Filho,⁵ *Paracoccidioides lobo* by Almeida and Lacaz,⁶ *Blastomyces lobo* by Langeron and Vanbreuseghem,⁷ and *Lobomyces lobo* by Borelli.⁸

The binomial *Loboa lobo* described by Ciferri et al is considered a “nomen nudum and illegitimate,” and should not be used.^{9–11} Most recently, Taborda et al proposed the binomial *Lacazia lobo*, arguing that previous designations were taxonomically invalid.¹²

Herr et al, after amplifying the 18SSU ribosomal DNA (rDNA) and 600 bp of the chitin synthetase gene, have contributed to the clarification of the taxonomic enigma of this agent, placing it in the group of the Onygenales order and Ajellomycetaceae family.¹³ Similarities between *Paracoccidioides brasiliensis* and *L. lobo* put both species in the same taxonomic complex.^{2,14} Electronic microscopy study showed similarities concerning cellular structure, although differences in reproduction could be demonstrated.¹⁵ Immunological similarities between these species have been described.^{2,11,16–19} Phylogenetic data strongly support the placement of *L. lobo* in its own species, separate from all known *P. brasiliensis* phylogenetic species.²⁰

Regular round-shaped yeasts, isolated or in a chain, are the typical presentation of *L. lobo* in tissues. The size is approximately $6 \times 13.5 \times 11 \mu\text{m}$, with a birefringent membrane and thick wall containing melanin. Reproduction with simple gemmulation, without exoporation, forms the blastoconidia and leads to the typical rosary bead figures.^{19,20}

The impossibility of cultivating the species *L. lobo* in culture medium is believed to be an adaptation to the parasitic life of the fungus.²⁰ Inoculations have been described in several animals, including hamster testis,²¹ hamster cheek pouch,²² armadillo (*Euphractus sexcinctus*), and turtles, but have produced no satisfactory response in mice.²³ Culture in chorioallantoic membrane of embryonic chicken eggs and disease after accidental inoculation in humans has also been described.^{24,25}

Pathogenesis

Lobomycosis can cause primary skin infection in humans and dolphins. Trauma is considered the pivotal event. It is believed that *L. lobo*, which is saprophytic in soil, vegetation,

and water, must be inoculated within the dermis to start an infection.²⁶ Some speculate transmission is related to insect or animal inoculation based in reports in which the symptoms occurred after snakebite, stingray accident, or insect bite.²⁷

In the dermis, the fungus starts its proliferative phase within the macrophages.²⁸ By direct influence of the micro-organism, transforming growth factor $\beta 1$ concentration increases. Transforming growth factor $\beta 1$ is a cytokine produced by macrophages and Th3 lymphocytes and is considered to be a potent immunosuppressive molecule. This cytokine is expressed in histiocytes and multinucleated giant cells and diffuses in the inflammatory infiltrate of patients with lobomycosis.²⁹ It suppresses the phagocytic activity of macrophages and has the capacity to inhibit nitric oxide and gamma interferon expression, consequently impairing the cell-mediated immunity.^{29–33} In addition, this cytokine can promote the proliferation of CD8 T lymphocytes, stimulating the production of immunoglobulin A antibodies by plasma cells and the process of fibrosis, including the formation of extracellular matrix, contributing with the keloid-like appearance of the clinical lesion.^{23,31,34}

Another cytokine found in the dermis of lobomycosis patients is interleukin 10 (IL-10). Together with transforming growth factor $\beta 1$, IL-10 acts by inhibiting the cellular immune response and, as a consequence, the activation of macrophages.²⁹ The negative effect on cellular immunity could create a localized environment of specific immunodeficiency, as demonstrated by the absence of a response to dinitrochlorobenzene, as well as delayed responses to Staphylococci, Streptococci, Trichophyton, and Candida antigens.^{28,35} Immunoglobulin and complemented characterization of the lesions are in agreement with the findings of a T helper 2 profile.³⁶

Quaresma, in 2010, created the hypothesis that Langerhans cells could modulate local infection, helping the fungus to evade the immune system.³⁷ The leukocyte and neutrophil functions, as well as complement activity, are preserved in patients with Jorge Lobo's disease.^{38,39} Studies of humoral immunity in patients with lobomycosis exhibit a Th2 cytokine profile with increased production of IL-4 and IL-6 and lower production of IL-2.^{28,35,40} Some authors believe in a protective factor caused by the presence of the melanin within the fungus wall.⁴¹

In spite of all defensive mechanisms, fungal viability indices range from 20%–50%.⁴² The mechanisms that lead to in situ *L. lobo* cell lysis are still unknown. It is possible that CD8 T lymphocytes or natural killer cells exert a cytotoxic effect by lysing macrophages infected with the

fungus through a mechanism dependent on exocytosis of granules containing perforin and granzyme, similar to what occurs in other infectious diseases.^{43–45} Another possibility is the participation of the complement system, as deposits of the C3c component on the fungal cell wall in histological sections obtained from patients with the mycosis could be demonstrated.³⁶

Molecular techniques identified eight antigens of *P. brasiliensis* (29–108 kDa) in sera of infected hosts with *L. loboi*.⁴⁶ Mendoza et al, in 2008, used specific *L. loboi* antigens extracted from mice as well as from dolphins with Jorge Lobo's disease. They demonstrated that an immunodominant antigen with a high molecular weight of ~193 kDa was recognized by antibodies in the serum, suggesting that the antigenic proteins of *L. loboi* have much higher molecular weight than the counterpart, gp43, of *P. brasiliensis*.⁴⁷

Preserved cellular immunity is probably necessary to hinder the progression of the disease, or in some cases, prevent its appearance. Nowadays it is not possible to identify sub-clinical lobomycosis due to lack of a specific and reliable antigen. Lobina, once used for this purpose, lacks specificity and may present cross reaction with other agents such as *P. brasiliensis* and some mycetoma agents. Because there is no way to correctly identify cases of lobomycosis infection, at this time it is not possible to know the exact number of infected people or the percentage of them that present with the disease.⁴⁸

After the proliferative phase in the dermis, there is a possibility of a dissemination phase through lymphatics. Reports of regional lymph node enlargement and lymphatic spread of the disease have both been described, and supports this hypothesis. It is not known, however, how many patients evolve with lymphatic disease.⁴⁹

Contiguous dissemination and/or autoinoculation have also been described. Repetitive traumatism cannot be discarded in many cases because the patient is still under the epidemiologic risk of being infected. There is only one reported case of systemic lesion caused by possible *L. loboi* where the testicle was involved, probably after hematogenous spread. Human transmission has never occurred, although experimental autoinoculation and accidental inoculation both have been reported.^{24,25,50}

Epidemiology and geographic distribution

The biogeographic complex of *L. loboi* is situated in areas of forests with dense vegetation and large rivers. The annual rainfall is usually more than 2,000 mm/year, with an average temperature of 24°C and relative humidity of 75%.

Those climatic characteristics are found in the tropical region of the Amazon basin, where most of the cases have been described.⁵¹

Since its first description, “keloid blastomycosis” was believed to be specific to areas of forests with high heat and humidity. Until that time, it mainly affected male forest workers.⁵² Jorge Lobo's disease was relatively frequent in the Amazon region,⁵³ with most cases originating from the Brazilian Amazon region.⁵⁴ By 1950, the first case of lobomycosis was described in Central America, and reports of the disease in Central and South America have been published regularly ever since. By 2000, only 3 of 465 human cases had been published outside the Amazon basin.²³

The ecological niche of the fungus is expanding. The identification of the disease in dolphins was first made in the bottlenose dolphin (*Tursiops truncatus*) from the Atlantic coast of the United States at the Gulf of Mexico;⁵⁵ it is also endemic in Florida coastal estuaries. The disease also affects the Guyana dolphin (*Sotalia guianensis*) from the Suriname River.^{55–60} Reports of photographic evidence of lobomycosis-like disease in dolphins from the Indian Ocean, the Japanese coast, the Brazilian South coast, the western Pacific, the Africa coast, the European coast, and the North Carolina coast show the regions where lobomycosis can be found.^{57,59,61–63}

The dolphins of the endemic areas, botos (*Inia geoffrensis*) and tucuxis (*Sotalia fluviatilis*), that inhabit the Amazon and Orinoco river basins of Brazil and Venezuela, respectively, where the human disease is endemic, do not present with lobomycosis.⁵⁸

To date, occurrences of Jorge Lobo's disease in humans were reported in nine countries of South America (Brazil, Colombia,^{26,64,65} Suriname,⁶⁶ Venezuela,^{58,67–71} Guyana, French Guiana,^{72–74} Ecuador,⁷⁵ Peru,^{76–78} and Bolivia⁷⁹), three countries of Central America (Panama,^{80,81} Costa Rica,⁸² and Mexico), and imported cases in the United States,⁸³ Canada,⁸⁴ France,⁸⁵ Netherlands,⁸⁶ Germany,⁸⁷ Greece,⁸⁸ and South Africa.⁶⁹

For some time, it was believed that genetic predisposition was crucial for acquiring the disease once it affected preferably indigenous populations.^{89,90} Baruzzi et al were the first to demonstrate the link between geography and lobomycosis. The authors showed that after transferring the Caiabi Indians from the Tapajos River region to the Indian Xingu National Park, there were no more new cases of lobomycosis detected. The same study⁸⁹ incisively reinforces the importance of location in the occurrence of lobomycosis.^{89,91,92}

Lobomycosis can now be included in different epidemiologic contexts: occupational or recreational infection in endemic areas, occupational hazard for professions dealing with dolphins, and emerging infection in many coastal regions. This disease is classically an opportunistic infection that affects vulnerable populations living and working in forest areas, especially extratropical forest workers, river dwellers, and the Indian population. Nowadays, there is an increasing interest in products and substances derived from the forest. The need to preserve the native vegetation during extraction leads to strategies of sustainable harvesting for a new market. Those workers must be protected from all the diseases related to the forest environment, including lobomycosis.^{65,89,91,93–97}

Since the description of natural disease in dolphins and the report of a zoonotic transmission in an aquarium worker after contact with a sick dolphin,⁸⁶ lobomycosis can be included in the list of zoonotic mycosis.⁶¹ It is an occupational hazard for veterinarians, marine biologists, and others who handle dolphins during health assessments, rescue operations, and rehabilitation efforts of stranded or injured animals. Direct and indirect human contact with dolphins have expanded because of the increased number of dolphins under managed care in aquarium and commercial exhibitions, as well as in swimming-with-dolphins programs for recreational or therapeutic benefit.^{86,87}

Zoonotic transmission from dolphins is presumed, the clearest evidence of which was described in an aquarium attendant with a hand lesion that occurred after managing a sick animal.⁸⁶ Other cases in which zoonotic transmission is suspected have been published. The first case was a patient from Suriname,⁹⁸ an area where lobomycosis occurs in Guiana dolphins (*S. guianensis*) that inhabit the Suriname River estuary,⁹⁹ and the second case developed in a young man from South Africa who was an avid swimmer and diver.¹⁰⁰ The third occurred in a fisherman from Venezuela who developed lesions on the ear after being pierced with a fishing hook in a coastal area where an affected dolphin was observed.⁶⁷ Most recently, lobomycosis was diagnosed in a female farmer with hypoglobulinemia and common variable immunodeficiency and hepatitis who lived on the Greek coast.⁸⁸

A report by a dermatologist who suffered an accidental laceration during a biopsy procedure of a dolphin with lobomycosis¹⁰¹ without subsequent development of lobomycosis suggest that transmission from dolphins to humans, even through direct inoculation, is unlikely in immunocompetent individuals.

Morphologically, the organisms found in dolphin differ when compared with human *L. loboi*. They are smaller and have morphometric and ultrastructural differences in the cell wall.¹⁰² Molecular sequencing of rDNA from an infected dolphin showed a novel sequence related more closely to *P. brasiliensis* than to *L. loboi* of human origin.¹⁰³

This recent evidence is supported by an earlier study that showed that ribosomal RNA gene sequences from an infected dolphin were 97% homologous with *P. brasiliensis*.⁵⁷ In contrast, serum from an infected dolphin recognized an immunodominant 193-kDa antigen from an extract of human *L. loboi* more strongly than the gp43 antigen of *P. brasiliensis* in western blotting analyses.⁴⁷

Experimental inoculation of a laboratory scientist with yeast-like cells from a human patient, as well as a report of an accidental transmission of lobomycosis in another laboratory scientist who collected and purified fungal cells from human skin biopsies,⁵⁰ imply that under unusual circumstances, *Lacazia* of human origin can be transmitted to other humans.²⁴

The epidemiologic data of lobomycosis in endemic areas is unknown. The largest casuistic comes from Acre, Brazil. A retrospective study identified 249 patients diagnosed with lobomycosis in a period between 1998 and 2008; the calculated prevalence was 3.05/10,000 inhabitants. This number is probably underestimated because the population at epidemiologic risk lives in the forest, with difficult access to the health system.¹⁰⁴

Clinical presentation

After an unknown incubation period, estimated to be between 1–2 years, lobomycosis affects predominantly exposed areas (pinna in 38%, upper limbs in 28%, lower limbs in 22%) of adult males who develop activities in the forest (Figure 1).^{2,105} Localized disease represents 61% of the cases.¹⁰⁴ The time between the first signs of the disease and the diagnosis varies from months to decades. In the Woods article, the average time was 19 years.⁸³

The initial lesion is a papule: depending on the level of the trauma, it may be superficial or deep. Slow progression in a period of months to years leads to the formation of a plaque or nodule. The primary lesion is covered by smooth and shiny intact skin. The surface color varies from the patient's color to erythematous-brownish or red-wine, with or without telangiectasia. Those characteristics give the typical presentation a fibrous appearance, resembling a scar or a keloid (Figure 2).²³

Chronic by nature, localized in trauma-prone areas, and exposed to a moist environment, the clinical lesions may suffer

Figure 1 Patient presents with multiple nodules in the right auricle, a typically affected area.

modifications leading to a more polymorphic clinical picture. Dyschromic changes are commonly described, varying from hyperpigmentation to hypopigmentation and achromia.^{7,9,23}

Ulcers are believed to be secondary to trauma, especially after maceration that occurs in the rainy season.

Figure 2 Typical primary fibrous appearance, with nodular plaques covered by smooth and shiny skin, with small exulcerated areas and visible telangiectasias.

Deeper lesions are probably related to recent inoculated lesions and are described as infiltrative. Continuous growth may bestow an exophytic appearance in some cases (Figure 3).^{13,23,93}

Some of these lesions may present with a wart-like surface leading to verrucous lobomycosis. This clinical picture typically affects the lower limbs and imposes differential diagnosis with chromomycosis.^{23,106}

Gummalike lobomycosis is rarely seen. It is described as occurring in macular lesions that evolve with turgid borders, followed by pustules and finally an exudation of a thick yellow material. Scar tissue eventually develops. This phenomenon can occur several times in the same lesion and is associated with spontaneous resolution, an extremely rare event.⁹⁶ There is only one report of spontaneous resolution, accompanied by cicatricial areas without fungal elements after an episode of lobomycosis.⁹³

Emergence of new wounds around the index lesion raises questions about autoinoculation or local lymphatic dissemination, although continuous exposure cannot be discarded. This picture may lead to confluent lesions forming big plaques or the presence of hundreds of lesions. Autoinoculation has been documented in a case where the donor site for skin graft evolved with a lobomycosis lesion; contaminated material was the probable cause.¹⁰⁶ Local

Figure 3 Local destruction of the left auricle, presenting exophytic erythematous-brownish lesion, with a pedunculated aspect and telangiectasias.

lymphatic spread of the disease has been reported with estimated occurrence of 10% to 25%.^{49,107} In one case, the testicle was affected, and hematogenous spread of the fungus was implicated as the cause.²⁶

Symptoms are rarely associated with lobomycosis lesions. Pruritus and dysesthesia are symptoms more often described in extensive cases. The progressive nature may lead to deformation, causing functional and aesthetic concerns.¹⁰⁴ Carcinomatous degeneration is a possible and feared complication (Figure 4).^{104,108}

Classifications have been proposed and are essentially based on clinical aspects of the disease. A morphologic classification subdivided the cases into infiltrative, keloid-like, in plaques, verruciform, and ulcerated forms (Figure 5).^{109,110} A classification based on the immunologic response to the fungus was proposed by Machado: hyperergic (macules and gumma) and hypoergic (keloid-like).¹¹¹ An operational approach proposed one classification based on the distribution of the disease as follows: localized or isolated disease, multifocal disease (restricted to an anatomical area), or disseminated disease (more than one anatomical segment).

Figure 4 Superimposed carcinomatous degeneration on typical fibrous Lacaziosis nodules.

Figure 5 Ulcerated presentation with small fibrous plaques and nodules at its borders.

This classification is aimed to program the therapeutic strategy.¹⁰⁴

Diagnosis

Diagnosis is primarily based on clinical aspects of the lesion. It should be confirmed by identifying the numerous agents within the lesion. Round and oval yeast-like structures with regular size, between 6–12 μm , and a birefringent membrane are found in the dermis. The fungal structures may be found isolated or with a simple gemmulation; the typical catenular or Rosario beads distribution is commonly found (Figure 6). Direct examination by scraping the lesions is the simplest way to visualize the fungus. Alternatively, techniques such as vinyl adhesive tape or exfoliative cytology may also be used.^{112–114}

Figure 6 Histological section showing round and oval yeast-like structures with birefringent membrane, with isolated and Rosario beads distribution, commonly found in Jorge Lobo's disease.

Note: Grocott methenamine silver-stained, 400 $\times$.

The histopathology of the lesions sent for biopsies are obtained by routine staining with hematoxylin-eosin, with the agents better visualized with silver stains. The characteristic histopathologic picture is composed by a dense and diffuse histiocytic infiltrate of the dermis, with an overwhelming number of parasites. Occasionally, the Unna band may be observed.²⁶

The epidermis is typically presented with rectification of the rete ridges or atrophic areas above a thin Grenz band.¹¹⁵ Acanthotic areas with the presence of hyperkeratosis, spongiolysis, and neutrophil collection may be observed.¹¹³ Those changes are probably elicited by the presence of the fungus in the epidermis.¹¹⁶ Hyperplastic infundibulum is associated with transepidermal elimination of the fungus.¹¹³ This phenomenon has already been documented and is the basis for the vinyl adhesive tape technic.¹¹²

The dense histiocytic dermal infiltrate is composed of a large number of epithelioid, multinucleated, and Langhans cells with or without the presence of granulomas (Figure 7). Sometimes, aggregates of large xanthomatous histiocytes with clear cytoplasm or finely granular eosinophilic cytoplasm, without parasites within, can be found. Those are called pseudo-Gaucher cells.¹¹³ A great number of fungal structures are found within the macrophages or in the dermis. Lymphocytes are present in discrete to moderate numbers, with a predominance of CD4 T lymphocytes and a CD4:CD8 ratio of approximately 3:2. Plasma cells and B lymphocytes are less frequent than T lymphocytes, with natural killer cells always present.^{29,117} Neutrophils are rarely found and are associated with ulcers or fungus within the epidermis. Fibrosis is a striking feature, and Asteroid bodies may be seen.²³

Figure 7 Histological section of a patient with lobomycosis.

Notes: Notice the inflammatory infiltrate with multinucleate giant cells, dispersed fungi, a large number of histiocytes, and a single asteroid body. Hematoxylin-eosin, 400×.

Treatment

The ideal treatment is wide surgical excision. It is worth noting that instruments contaminated during operation can lead to reinfection.¹⁰⁶

There is no optimal drug treatment for cases in which surgery is contraindicated or for disseminated infection. The only successful oral treatment with complete response was reported in a dolphin, using myconazol.¹¹⁸ Many anti-fungal agents have been tested with unsatisfying results: ketoconazole,^{79,119,120} amphotericin B,¹²¹ sulfa compounds,¹²² and 5-fluorocytosine¹²³ all have been proved inefficient. Itraconazole has been shown to be partially effective and can be used as an adjuvant to prevent recurrence of surgically removed lesions.¹²⁴ Itraconazole with cryosurgery has been successfully used to treat relapse of lobomycosis.^{123,124} Clofazimine, with dosages of 100–300 mg daily for up to 2 years, has been used in some reports, with unsatisfactory results.^{125–127} Interestingly, as per the experience of the Leprosy Elimination Programme of Acre, in Brazil, patients with lobomycosis and concurrent leprosy have been shown to respond to multibacillary therapy with reduction of pruritus and size of the mycotic nodules.¹⁰⁴

The new azoles with expanded spectrum may prove to be efficacious. Posaconazole has been used for 24 months and has achieved the cure of the lesion without remission in 5-year follow-up.⁷⁸

Because of the recurrence of lesions, in cases of surgical removal, patient follow-up is necessary for a long time before considering it cured. To date, there is no efficient drug treatment, and surgical removal is the most-used therapeutic procedure.

Disclosure

The authors report no conflicts of interest in this work.

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