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The advent of Paracoccidioidomycosis Ceti and new views on lobomycosis (Jorge Lobo's disease)

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Abstract

The disease caused by the fungus *Paracoccidioides lobogeorgii* – called lobomycosis – is an uncommon morbid condition that produces skin lesions in humans. Since its formal description in the 1930s, the disease has continued to be the subject of research, especially concerning a better characterization of its etiological, diagnostic, and therapeutic aspects. In addition to a series of questions about the disease's pathology that have persisted over the decades, the possible involvement of cetaceans, which have lesions similar to those described in Homo sapiens, must also be investigated. The debate about the etiology of the proliferative verrucous cutaneous lesions caused by non-cultivable yeast that has been reported in dolphins has been almost completely resolved in recent years, as all the evidence points to the etiological agent belonging to the genus Paracoccidioides. There is no molecular evidence of infection by *Paracoccidioides lobogeorgii* in cetaceans. Based on these preliminary considerations, the objectives of the present article are (1) to review the main etiological, pathogenic, clinical, diagnostic, therapeutic, and ecoepidemiological findings of human lobomycosis and (2) to present the most important aspects of the ceti PCM of aquatic mammals.

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Introduction

Jorge Lobo's disease (JLD) or lobomycosis is a non-debilitating chronic skin disease that affects human beings – mainly in the epidermis and dermis as well as, more rarely, in the hypodermis – in the tropical area of Central and South America. It is caused by the fungus *Paracoccidioides lobogeorgii*.[1] Pathogen access to Homo sapiens tissues often occurs after traumatic injury.[2]

The first reports of the disease, dating from 1915, refer to the involvement of the Kaiabi Indians, in Mato Grosso, Central Brazil, a region in which the disease was called "miriaip" or "piriaip", i.e. that which "burns".[3] Formally, however, the first description of mycosis was made in 1931, by the Brazilian physician Jorge Lobo, professor of dermatology at the Recife Faculty of Medicine (Pernambuco, Brazil), who examined a 52-year-old rubber tapper from the Amazon basin. The patient had confluent nodular lesions on the skin over the lumbosacral region for 19 years, which the biopsy revealed to be a yeast-like microorganism, currently called *Paracoccidioides lobogeorgii*[1], a causative agent of chronic localized cutaneous paracoccidioidomycosis – both of which are microorganisms belonging to the order of the Onygenales.[4]

An interesting aspect of lobomycosis – and reason for much debate over the years – concerns the involvement of cetaceans through a disease like the morbid condition produced by *Paracoccidioides lobogeorgii*.[1,5,6] This observation generated significant doubts about whether such attacks – in humans, and cetaceans – are the same nosological entity, or if they represent different morbid conditions. More recent studies have allowed the differentiation between the disease of *H. sapiens*, lobomycosis, and the disease described in non-human animals, which, as will be seen below, became known as *paracoccidioidomycosis ceti* (*PCM ceti*).[7] It is important to highlight the existence of paracoccidioidomycosis, a disease caused by *Paracoccidioides spp*. in humans, which has been described in other mammals (e.g., armadillos), but not in cetaceans.[8]

Furthermore, researchers have been attempting to define the exact genus and species responsible for Jorge Lobo's disease for more than 90 years (Table 1). Initially described by Jorge Lobo in 1931, the disease's causative agent was surrounded by taxonomic uncertainties, particularly due to its non-cultivable nature. Over the years, various names were proposed for this elusive pathogen, including *Loboa loboi* and *Lacazia loboi*.[2,6,9] However, molecular advances have clarified these ambiguities. Recent DNA sequencing and phylogenetic studies have conclusively determined that the etiologic agent in humans is *Paracoccidioides lobogeorgii*, which places this causative agent firmly within the *Paracoccidioides genus* that also includes species known to cause systemic infections, such as *Paracoccidioides brasiliensis*.

Based on those brief notes, this article presents the main aspects of JLD, with emphasis on: (i) the etiology and its controversial points; (ii) the pathogenesis and pathological findings; (iii) the clinic, diagnosis, treatment; and (iv) ecoepidemiology – addressing the findings in humans (JLD) and related conditions in aquatic mammals (*PCM ceti*).

Etiology

For many years, the taxonomic classification of the etiological agent of human lobomycosis and the corresponding disease in cetaceans was a major scientific challenge since the pathogens involved are fungi that, although abundant in the lesions, are not cultivable.[4,10,11]

Under microscopy, whether direct examination using potassium hydroxide (KOH) or evaluation of histological sections stained by Grocott, the pathogen morphology involved in lobomycosis can be identified: globular and multinucleated cells. The microorganism has a clear, well-refringing double membrane, thicker than that seen in *Paracoccidioides brasiliensis*, with an inner membrane free from irregularities or folds. In tissues, the etiologic agent presents a globoid shape with a thick wall. The size corresponds to approximately 8 to 12μm in diameter. The multiplication of this fungus occurs through continuous budding, whose structures are identified in numerous ways in the tissues. The formation of chains of several elements joined

characteristically, like a rosary, is common.[12] The proliferation of *L. loboi* is related to a decrease in mediated immunity due to the high expression of transforming growth factor cytokines (TGF-β); this leads to reduced macrophage activity, which contributes to the non-elimination of the pathogen.[13]

In 1971, Migaki et al.[14] described a lacaziosis-like disease identified in H. sapiens in a bottlenose dolphin, Tursiops truncates, off the coast of Florida.[14] Since then, similar cases have been reported, with the first record of the disease in dolphins in Brazil, also in *T. truncatus*, being described by Simões-Lopes et al,[15] in 1993, off the coast of Santa Catarina.[15] Due to the similarities in the macroscopic and microscopic characteristics of the disease in humans and dolphins — in addition to the inability to cultivate both etiologic agents responsible for each of the morbid conditions — some believed that *L. loboi*, the etiologic agent of lobomycosis in humans, also affects these animals.[10,11] This perception is also due to the existence of several human pathogens – such as *P. brasiliensis*, *Paracoccidioides lutzii* e *L. loboi* – which are grouped in the order Onygenales and are responsible for diseases that may present cutaneous manifestations similar to the disease described in the species *T. truncatus*.[10,11,16]

The morbid condition – very similar to lobomycosis – that affects cetaceans has been named by some authors as lacaziosis-like disease (LLD = lacaziosis-like disease or lobomycosis-like disease).[9,10]

However, preliminary phylogenetic analyses have already shown a greater proximity between LLD agents and *Paracoccidioides spp.*, when compared with the fungus *L. loboi*.[10] Therefore, the hypothesis that *Lacazia loboi* would be the fungus responsible for the disease, both in humans and in dolphins, was recently challenged following the DNA sequencing of the pathogen, which identified a fungus distinct from *L. loboi* named *Paracoccidioides lobogeorgii*.[6,11,17]

From these current findings of phylogenetic and/or molecular associations, the classification used to name the disease in dolphins is no longer sustainable. Thus, and also to minimize further divergences and confusion, the name *Paracoccidioidomycosis ceti* (*PCM ceti*) has been proposed for the disease present in cetaceans – compatible lesions have already been identified in *T. truncatus* (bottle nose dolphins), *Tursiops aduncus* (Indo-Pacific bottlenose dolphins), *Sotalia guianensis* (Grey dolphins) and *Lagenorhynchus obliquidens* (Pacific white-backed dolphins) – ,[18,19,9,20,11] which is triggered by a non-cultivable fungus of the genus *Paracoccidioides*,[11,17] for which the name *Paracoccidioides brasiliensis var. ceti*16 has been suggested.

One theory, based on phylogenetic data, associates the emergence of *PCM ceti* with infections in dolphins that swim along the coastal areas of South America. It is caused by an ancestor of *P. brasiliensis* (which, as mentioned above, is a cultivable fungus). The fact that *P. brasiliensis* var. ceti cannot be cultured suggests two hypotheses of/for infection: (i) through infected animals transmitting the pathogen by direct contact with uninfected dolphins; and/or (ii) through routine dolphin contact with the pathogen located in South American river estuaries.[21]

Despite comparable clinical manifestations, important distinctions exist between the human pathogen and the similar disease found in dolphins. Initially, dolphin disease was thought to be caused by the same agent as in humans. However, modern molecular techniques have revealed that the dolphin pathogen, now named Paracoccidioides ceti, forms a distinct species within the same genus. This species was also found to be non-cultivable, but its genetic material shares significant similarities with *P. lobogeorgii*. This confirms their close evolutionary relationship while also highlighting the differences between the human and dolphin variants of the disease.[22,23]

The identification of these species, despite their inability to grow in culture, was made possible through the extraction of DNA from infected tissues and the subsequent genetic sequencing. By comparing specific genetic markers, such as the Gp43 gene and other coding regions, researchers could place *P. lobogeorgii* and *P. ceti* within the *Paracoccidioides genus*. The construction of phylogenetic trees showed that these non-cultivable pathogens cluster closely with other cultivable Paracoccidioides species, thus solidifying their taxonomic placement (Table 1).[22,23]

In summary, the recent taxonomic review has resolved the long-standing confusion surrounding the causative agents of Jorge Lobo's disease by confirming that *Paracoccidioides lobogeorgii* is responsible for the human form, while *Paracoccidioides ceti* affects dolphins. This distinction underscores the unique evolutionary paths of these organisms, despite their shared genus and similar disease presentation.[22,23]

Table 1. Controversial points of the name of the agents that caused Jorge Lobo´s disease over the years.

PROPOSED NAME	YEAR OF PROPOSAL	AUTHOR(S)	REASON FOR REJECTION
Glenosporella loboi	1940	Fonseca OF, Leão AE.[24]	Later identified as *Paracoccidioides brasiliensis* due to contamination with a typical isolate. Not the true agent of Jorge Lobo's disease (JLD).
Glenosporopsis amazonica	1943	Fonseca OF.[25]	Identified as *Aspergillus penicillioides*, an environmental contaminant. Incorrect original identification.
Paracoccidioides loboi	1948-1949	Almeida F, Lacaz C.[26]	Molecular studies showed this was not a variety of *Paracoccidioides brasiliensis* but a different species. Name corrected to *Paracoccidioides lobogeorgii*.
Blastomyces loboi	1952	Langeron M, Vanbreuseghem R.[27]	Proposed as a new name but based on erroneous phenotypic comparisons with other Blastomyces species.
Loboa loboi	1956	Ciferri R.[28]	Later identified as a synonym of *Paracoccidioides brasiliensis* due to contamination. Rejected for not describing the true pathogen.
Lobomyces loboi	1958	Borelli D.[29]	Name did not follow botanical nomenclature rules and lacked a Latin description. Later deemed invalid.
Lacazia loboi	1999	Taborda PR, Taborda VA, McGinnis MR.[30]	Widely accepted for a time, but molecular analyses showed it was related to *Paracoccidioides genus*. Renamed as *Paracoccidioides lobogeorgii*.
Candida loboi	2015	Costa PF.[31]	Identified as *Candida tropicalis*, a contaminant, not the true etiologic agent of Jorge Lobo's disease.
Paracoccidioides lobogeorgii	2021	Vilela, de Hoog, Bagagli, and Mendoza.[22]	Confirmed by molecular analyses as the true etiologic agent of Jorge Lobo's disease in humans. The recent taxonomic review has resolved the longstanding confusion surrounding the causative agents of Jorge Lobo's disease, confirming that *Paracoccidioides lobogeorgii* is responsible for the human form, while *Paracoccidioides ceti* affects dolphins. This distinction underscores the unique evolutionary paths of these organisms, despite their shared genus and similar disease presentation.

Source: The authors (2024).

The disease in humans: pathogenesis, clinical aspects, diagnosis and treatment

Pathogenesis

After inoculation of the fungus in the skin, the appearance of the first symptoms and signs usually takes between three months and two years. The lesions' evolution generally occurs very slowly; such changes may be unique and localized or disseminated over large areas of the tegument.[12] Multiple lesions are presumed to arise from autoinoculation. The hypothesis of hematogenous dissemination, as in leishmaniasis, is considered for more distant manifestations[32] and is supported by observation of the fungus in an intravascular environment.[33] Lymphatic involvement is quite uncommon,[4] although it has been described in the Kaiabi Indians[33] and in cases from the 1970s.[34]

The histopathology of lobomycosis has enough typical characteristics to distinguish it from other lesions of paracoccidioidomycosis. The following aspects should be highlighted in the examination: richness of pathogens; intense histiocytosis, without the formation of individualized granulomas; and absence of yeasts with the typical “rudder wheel” morphology.[35] The epidermis normally shows atrophy, although vegetating and hyperkeratotic epithelial hyperplasia can be seen. In the dermis, a thin layer of subepithelial collagen, usually unharmed, like the “Unna band” of lepromatous leprosy, is present. The remainder of the dermis is filled along its entire length by a diffuse inflammatory granuloma with a fibrous but never necrotizing evolution. Histochemical analyses demonstrate a polysaccharide impregnation of the inflammatory granuloma, which usually extends to the contours of the hypodermis, but does not jeopardize it.[32]

No B lymphocytes and few T lymphocytes are found in lobomycosis granulomatous lesions.[32,36] Infiltrative-looking masses are formed, which contain granulomas composed of giant foreign body-type cells, each harboring numerous phagocytosed fungal elements in addition to quiescent macrophages in different proportions.[12,36] The characteristics of the tissues of the affected lymph nodes are similar to those described in granulomas.[34,37] In the intracytoplasmic region of some giant cells, asteroid-shaped bodies – of unknown nature – are observed. They have the appearance of solitary eosinophilic intracytoplasmic structures surrounded by a lipid layer. Under the electron microscope, these asteroid bodies consist of branches of dense, filamentous material, as well as myelin structures, which make the assembly resemble the image of asteroid bodies in sarcoidosis.[13,38] This appearance can be confused with the sporotrichosis findings. The fungus *L. loboi* (now known as *Paracoccidioides lobogeorgii*[22]) can also be found in the extracellular environment surrounded by histiocytes.[39,40] The viscera are not usually affected because of the poor thermotolerance of the fungus, which is confirmed by the presence of lesions mainly on the skin of the coldest regions of the human body.[12]

The possibility of malignant transformation of lesions, which have a chronic evolution to squamous cell carcinoma, also exists. This fact was verified in two Kaiabi Indians, one of whom had disseminated metastases.[3,33] Other cases of carcinomatous degeneration were also described in a Colombian indigenous person;[41] a 64-year-old farmer from the state of Pará;[42] an 83-year-old indigenous person residing in the state of Amazonas;[40] and an 87-year-old rubber tapper from the banks of the Purus River, Amazonas.[5]

Clinical aspects

Lobomycosis is a cutaneous mycosis (whose presence is almost entirely restricted to the skin; only one case on the labial mucosa has been reported),[43] that is, without visceral involvement (one reported case of testicular involvement).[44] Satellite adenopathy is not described, except in scarce circumstances. Most of the patients come from the Amazon Basin, and their general condition is satisfactory despite the long evolution of the process, since the disease can affect the individual for decades and presents a slow clinical course.[12,32]

Commonly reported symptoms include burning and itching near the lesions. The disease is characterized by dermal-epidermal nodules of various sizes or plaques resulting from the confluence of nodules. The lesion that most affects patients – and that gives rise to the diagnosis – is keloidiform nodular alteration. Plaques are formed, which can occupy a considerable area of the body and present polycyclic contours with prominent edges.[12]

In some patients, multiple lesions of different shapes are described, with numerous types of manifestations in the epidermis, such as macules, papules, infiltrated plaques, gums, keloid-like nodules, and even ulcerated lesions.[12,45] Atrophic skin lesions, which resemble tuberculoid leprosy in their clinical form, have also been reported.[32] Another form that has been detected includes verruciform disorders.[12,32] The appearance of the lesions generally varies with their topography: the points of support are unharmed, while the dorsum of the foot has hardened, polylobed, non-fistula-shaped vegetations with a shell-on-rock appearance. In addition to the other lesions mentioned above, those of the pseudokeloid type can be observed in the limbs and in the rest of the body.[33]

The habit of carrying straw and wood on their shoulders to build tents, as well as chestnuts and flour.[32] Manifestations in the distal extremities of the upper and lower limbs and in the gluteal region are also common; however, other parts of the body can also be affected, such as shoulders, back and abdomen (Figure 1).[12,16] In more severe cases, large areas of skin may be affected by dispersion or by clustered and confluent nodules. Disseminated skin lesions have been described in an HIV-infected patient.[46]

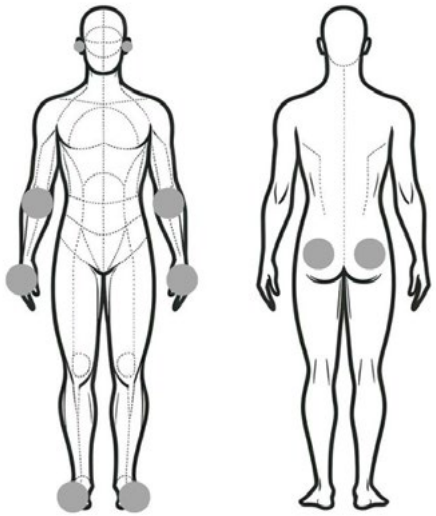

Figure 1. Regions of the human body, marked in gray circles, where skin changes. They are most commonly in cases of Jorge Lobo's disease.

Source: The authors (2024).

Complications include possible restrictions of movement, significant cosmetic damage, secondary infections, ulcerations, and carcinomatous degeneration.[14,19,5] Squamous cell carcinoma infiltration in long-term lobomycotic lesions has been described in some patients,[33,40,41,42,47,48] including cases of death.[40,47]

Differential diagnoses that must be established include: paracoccidioidomycosis, in its nodular and vegetative cutaneous form; vegetative chromomycosis;[3,41] histoplasmosis, in its African and American forms;[3] sporotrichosis;[49] cutaneous leishmaniasis, in its pseudo-lepromatous form;[3,32] keloid scar; dermatofibrosarcoma protuberans; fibroma and neurofibroma;[50] *lupus vulgaris*, in verrucoid forms;[51] nodular or reactional tuberculoid leprosy, especially ear lesions;[32] squamous cell epithelioma; skin metastases from deep squamous cell carcinomas;[3,32] Kaposi's sarcoma;[49] sarcoidosis; and lymphomas, mainly mycosis fungoides.[46] Cases of co-infection with *L. loboi* (now, known as *Paracoccidioides lobogeorgii*[22]) and *P. brasiliensis*, an association already described in the literature,[4] may also occur.

Diagnosis

Laboratory diagnosis can be performed by analysis of the material collected from the skin lesion (whether ulcerated or not) or the pus from gummy lesions, diluted in saline solution and examined between the slide and coverslip under an optical microscope. The material can be stained with hematoxylin-eosin (H&E) or Gomori's methenamine silver (GMS), which is specific for fungi.[12] The result of the analysis can be confirmed by the finding of characteristic globular cells in the shape of a lemon, alone or grouped in small chains.[1]

Treatment

The recommended therapy is conservative surgical extirpation of non-extensive or disseminated lesions, with clinical follow-up of up to three years.[52] Cryosurgery is an alternative and presents good results for this type of injury.[12,53]

Lobomycosis is normally resistant to antimicrobial treatment; in rare cases, clinical improvement is observed with the use of azole derivatives – such as ketoconazole (at a dosage of 400mg/day) –, but the fungi always persists.[32,33,54] Due to its anti-inflammatory action, another therapeutic option that has been put forward involves the use of clofazimine (with or without itraconazole) at a dosage of 200mg/day for three months, followed by 100mg/day for a variable period. Furthermore, a recent study conducted in Acre (Brazil) showed that the treatment used in leprosy (clofazimine, dapsone, and rifampicin) can also be relatively effective in treating lobomycosis. Pharmacological treatment is appropriate, especially for extensive and disseminated forms of the disease.[12,32,33,49,53]

One possible treatment option is posaconazole, which has shown good results – in an individual who had lesions on the face, trunk, and limbs since childhood – by generating a reduction in keloids and even scarring. Although this is the first report in the literature of treatment with posaconazole in the extensive form of the disease, the results were satisfactory and may indicate a possible therapeutic alternative.[55]

The early diagnosis and treatment of lobomycosis are hampered by many factors, such as the similarity in the pattern of lesions with other diseases already mentioned, resulting in the need to exclude differential diagnoses, in addition to the long incubation period of the disease.[56] The general health of individuals affected by lobomycosis is not usually impacted; how-

ever, late or incorrect diagnoses can worsen the disease and/or leave the patient susceptible to co-infections.[56]

The disease in aquatic mammals (Pcm Ceti): clinical aspects, diagnosis and treatment

Pathogenesis

The fact that the alterations caused by *P. brasiliensis var. ceti* in dolphins are confined to subcutaneous tissues suggests that the pathogens are most likely introduced in this region by traumatic implantation of fungal elements. Upon reaching the subcutaneous tissues *P. brasiliensis var. ceti* changes to a yeast-like form and successfully establishes itself inside the host.[16]

After entering the animal's organism, the pathogens increase in size very slowly and may take months or even years to produce large parakeloid granulomatous lesions, with rare dissemination to other organs. Yeast cells trigger a slowing of immunity, via a Th2 response pattern, when they proliferate inside inflammatory cells and affect macrophages. Transforming growth factor β1 (TGF-β1) is released, blocking the release of nitric oxide and inhibiting the production of interferon gamma (IFN-γ). Adaptive immunity is compromised due to a dramatic decrease in the number of circulating helper B and T cells. Antibodies against *P. brasiliensis var. ceti* cross-reacted with the antigens of cultivable P. brasiliensis isolates.[16,44]

The presence of melanin in the cell wall of *P. brasiliensis var. ceti* is believed to protect pathogens from the host's immune response. The viability of yeast cells is reduced to about 40% of viable cells in the tissues of the infected host.[57] Subcutaneous granulomas, present in infected dolphins, show numerous branched yeast cells of uniform size, arranged in chains and surrounded by inflammatory cells and significant fibrosis44. The proliferation of CD8 T cells believed to be promoted by TGF-β1 is also responsible for producing immunoglobulins and other factors that promote the fibrosis process, causing the paracheloid external appearance of skin lesions.[16]

Clinical aspects

The PCM ceti lesions described in dolphins are generally similar to the changes produced by lobomycosis in humans. The disease usually has a chronic course and takes time to develop into large, characteristic monomorphic or multimorphic lesions.[16] In fact, nodular, ulcerous-crusted, verrucous skin lesions with colors ranging from white to pink are identified. The changes described in dolphins may be more pronounced and reach the lymph nodes, but without the involvement of internal organs.[14,51,58] Lesions in these animals can cover large somatic areas, predominantly in the cephalic region and with a possibility of extension to the back and tail. In addition, they may be associated with scarring from previous injuries, such as collisions and shark bites.[59]

The dolphins affected by the disease are older and usually show evidence of immune deficiency. In fact, these animals are often found to be very debilitated and/or carry multiple associated comorbidities.[28,60,61] Furthermore, in dolphins, a substantial decrease in CD4+ helper T lymphocytes, B cells, CD19+ and CD21+ associated with the morbid condition has been described.[39] Indications also exist that the presence of the fungus predisposes to co-infections,

as occurred in a bottlenose dolphin in Kinko-wan, Japan, which presented bronchopneumonia with the isolation in culture of *Enterobacter cloacae*, *Klebsiella pneumoniae* and *Aeromonas hydrophila*. Indeed, areas where reports of the disease are more frequent may harbor populations of immunocompromised dolphins.[21,58]

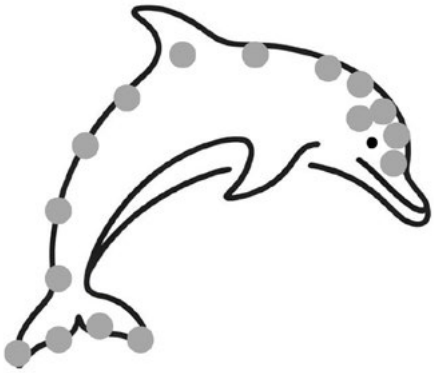

Figure 2. The regions of the dolphin's body, marked by gray circles, where skin changes most commonly appear in cases of Paracoccidioidomycosis ceti.
Source: The authors, 2024.

Diagnosis

The investigation of this disease in cetaceans can be a genuine challenge since they are protected species and the collection of material from them for histopathology is strictly regulated. For a long time, cases were diagnosed only by photographs and macroscopy, without histopathological, serological, or molecular data.[62] Subsequently, a presumptive diagnosis was made from the observation of the yeast structures detected in the lesions of these animals by means of histopathology, including procedures of yeast staining with Gomori's methenamine silver (GMS). This process revealed the presence of numerous dark ovals, 2 to 10µm wide, connected by short isthmuses. Such findings were considered a diagnosis of cases of the disease in dolphins.[16,63] Currently, detection of the disease is based on molecular techniques, as well as on observation of the yeast cells, which are characteristic of the disease, either by cytology or histopathology.[64]

Many of the cases reported as being LLD – "lobomycosis-like disease", currently called *PCM ceti* – were classified as such without pathological examinations or without evidence of fungal bodies. This classification was based solely on external observations of skin lesions that resemble those described in humans.[7]

Treatment

The paucity of experiences in capturing dolphins for treatment is the reason for the lack of data on the effectiveness of drugs in the literature. When these animals are treated with strategies used in humans, the responses obtained are usually similar.[61]

So far, in attempts to treat *PCM ceti*, no antifungal agent has been proven effective, except for one case of apparent improvement reported by Dudok Van Heel,[35] based on the use of miconazole and a supposed remission of the disease in a dolphin of the *T. truncatus* species.[9,35]

Esperón et al.[63] reported ineffective treatment of a dolphin with topical itraconazole and ketoconazole. Subsequently, the same animal received 2.5mg/kg of oral itraconazole and 2.0mg/kg of terbinafine. The skin lesions were reduced to small nodules, and subsequently disappeared and did not recur. Surgical removal of small lesions may be an option; however, surgery in large or multicentric lesions is not recommended.[16]

Ecoepidemiology: lobomycosis and *Pcm Ceti*

Up to 1996, 418 cases of the disease had been reported in humans, of which 255 were in Brazil and 50 in Colombia.[32] In 2020, after epidemiological studies of the Kaiabi tribes, Florian et al.[32] identified 63 occurrences of lobomycosis between the years 1965 to 2019, of which 60 had already been diagnosed and three were new cases. Among the 63 patients, 39 (61.9%) were male and 24 (38.1%) were female. Most of the reports originated from Central and South America, mainly in the Amazon region;[56] in Brazil, all cases came from the Amazon, which is an endemic area for *P. lobogeorgii*. Six Colombian soldiers who served in the Amazon region had nodular and cheilodian lesions on the face, trunk, and limbs, which took two to 15 years to become noticeable.[36,65] Sporadic and isolated cases of the disease have been reported in Europe, the United States, and Canada. All such patients reported previous travel to Central or South America. Recently, two cases of lobomycosis were reported in South Africa.[49] The geographic distribution extends between the Tropic of Cancer and the Tropic of Capricorn, especially near the Equator. The climate and regions conducive to the development of the fungus are tropical and subtropical humid forests, with an average annual temperature of 24°C and rainfall greater than 2000mm per year.[3,33,51]

The humans most commonly affected are aged between 21 and 40 years. No single ethnic group predominates, since all populations appear to be equally susceptible.[49] Men are affected in 92% of cases, which can be explained by their carrying out of professional activities in a rural environment, as is the case of rubber tappers, foresters, prospectors, hunters and farmers. Early exposure in a hyperendemic environment, probably associated with occupational activities, could clarify this occurrence of cases. The Kaiabi Indian tribe, who inhabited Mato Grosso, Central-West Brazil, constitutes a different epidemiological model for this disease. In a span of 30 years, the tribe accounts for 32% of Brazilian cases and 21% of the total number of cases.[32] In this setting, the affected group is aged between 10 and 25 years. Furthermore, among the Kaiabi, agricultural activities are more developed than in other tribes in the locality. No reports of cases of lobomycosis in adjacent villages have been filed.[47,52] No new cases of lobomycosis among the Kaiabi have appeared since they migrated to the Xingu National Park (southeastern Pará), which is in the Amazon.[3,33]

Possible reservoirs and transmission routes are still not well clarified. The etiological agent was detected in the soil of Argentina and Venezuela, and also in vegetables in Brazil; while speculation about an aquatic reservoir is based on the existence of a similar disease (*PCM ceti*) in cetaceans. The entry point of the fungus is probably the skin, and local trauma usually precedes the skin injury. A wound over a pre-existing lesion can cause a local recurrence.[3,33] Interhuman transmission has never been confirmed, but two cases stand out as possible instances of non-human animals participating in the disease of *H. sapiens*.[33,66,67,68,69]

The first case was reported in Europe in 1983, when a granuloma, as well as supratrochlear lymphadenitis, was observed on the skin of one hand of an aquarium attendant three months after occupational contact with a bottlenose dolphin (*T. truncatus*). This specimen had been

captured in the Bay of Biscay and showed the presence of skin granulomas, whereas biopsied specimens showed morphologically indiscriminate organisms of *L. loboi*[66] (now, known as *Paracoccidioides lobogeorgii*[22]). Analogous pathogens were also present in the patient's skin lesions and in the supratrochlear lymph nodes66. Based on these findings, one cannot conclude with certainty that the microorganism infected the aquarium attendant. The second case was described in São Paulo, Brazil – an area where the disease is not endemic – and involved a veterinarian who handled mice in a laboratory, which had been experimentally infected with *L. loboi* (now, known as *Paracoccidioides lobogeorgii*).[22] Thus, the transmission of lobomycosis from a non-human animal to a human has been documented.[68]

Despite scant evidence of zoonotic behavior – from lobomycosis? from *PCM ceti*? –, the possibility of such an occurrence raises concern in areas that are endemic of the disease in cetaceans, especially in those cases where such animals are used for recreational purposes, such as, for example, in the Indian River Lagoon, Florida.[9,19,59,69]

Until the present moment, no registered cases of paraccidioidomycosis ceti in porpoises exist. All the confirmed reports relate to Delphinidae. The disease in cetaceans has been diagnosed in: (1) *T. truncatus* (bottle-nosed dolphins), in Brazil, in Cuba, on the east coast of the United States (histologically and microbiologically indistinguishable from JLD), in Europe and Japan;[10,11] (2) *T. aduncus* (Indo-Pacific bottlenose dolphins), in the Indian Ocean, between Mozambique and Madagascar;[9,18] (3) *Sotalia guianensis* (Guiana dolphin - Delphinidae), in Suriname;[19] and (4) *Lagenorhynchus obliquidens* (Pacific white-backed dolphin), in Japan.[11,20] Similar cases of *PCM ceti* have not been described in the boto, *Inia geoffrensis*, and the tucuxi, Sotalia fluviatilis, which inhabit the Amazon and Orinoco rivers.[19,59]

Dolphins are more sensitive to environmental changes, whether of natural or anthropogenic origins. Therefore, the increased incidence of disease in these animals may also be related to responses to environmental changes, such as exposure to pesticides and other contaminants or variations in temperature, salinity, vegetation, and even increased survival of the pathogen in the marine environment.[69] Furthermore, the molecular confirmation of the disease in *L. obliquidens*, in Japan, suggests a possible geographic expansion of the etiologic agent, in addition to raising the hypothesis that other cetacean species may be infected. In this context, the possible spread of the pathogen by ballast water from ships or other floating media (oil platforms, for example) is a subject of discussion; meanwhile, the disease could be expanding.[17]

Final considerations

After almost one hundred years of its recognition among the Kaiabi Indians and seventy years of its more systematic clinical description, lobomycosis continues to raise questions for clinicians and mycologists. Similarly, many gaps remain in our understanding of *PCM ceti* in aquatic mammals, a disease once confused with lobomycosis. Scientific advances have increased our knowledge of the areas of molecular biology and genetic engineering of etiological agents and the respective diseases in humans and cetaceans. However, further research is required into aspects of etiopathogenesis, transmission, diagnosis (including the possibility of cultivation in the laboratory) and prevention. Similarly, more effective treatments may be proposed, which can lead to improvements in the quality of life for the different animal species affected by these diseases as well as psychosocial gains.

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