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Lobomycosis: A case from Southeastern Europe and review of the literature

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Abstract

Background: Lobomycosis, also known as Jorge Lobo's disease, represents a rare chronic subcutaneous mycosis caused by the fungus *Lacazia loboi*, an organism that is found within lesions but has not been cultured to date. The natural reservoir of *L. loboi* is unknown but it is believed to be aquatic, or associated with soil and vegetation. More than 550 human cases have been reported, especially in patients with a history of travel or residence in endemic areas (Central and South America, particularly Brazil) or in communities along rivers.

Main observations: We describe a 64-year-old Greek female farmer living in a coastal region, who presented with an erythematous plaque on her left inner thigh resembling a keloid. The diagnosis was based on the triad: 1) absence of fungal growth in cultures, 2) positive direct microscopic examination of the lesion and 3) histopathology, all consistent with lobomycosis. Particularly, skin biopsy showed deep cutaneous fungal infection with granulomatous reaction. Fungal cells were found inside giant cells. The fungi were thick-walled with some budding, isolated or in short chains. Dermal fibrosis was present. Our patient had a medical history of common variable immunodeficiency but no history of travel to South or Central America. She probably acquired this rare infection by injury during her agricultural works.

Conclusion: Our case represents probably the first documented case of human lobomycosis in Southeastern Europe. This case is unusual due to the rarity of lobomycosis in Mediterranean countries, particularly in Southeastern Europe. (*J Dermatol Case Rep*. 2012; 6(3): 65-69)

Introduction

Lobomycosis, also known as Jorge Lobo's disease, represents a rare chronic subcutaneous mycosis caused by the fungus *Lacazia loboi*,[1-4] an organism that is found within lesions but has not been cultured to date.[1-5] The natural reservoir of *L. loboi* is unknown but it is believed to be aquatic, or associated with soil and vegetation.[1-4,6-8] Lobomycosis is described in dolphins and humans, particularly adult hunters, fishermen, miners and rural workers.[1,2,9]

The lesions are pleomorphic and usually located on exposed and cooler areas of the body, particularly on limbs and ears.[1,2,7] They appear mainly after traumatic events such as cuts while working, or after insect or animal bites.[10,11] They are characterized as papules, nodules or plaques of various sizes which appear as isolated or aggregated, multiple forms.[1,2] At first they have a smooth, shiny surface and appear to be movable, elastic and firm. They can also be verrucous or ulcerated.[1,2,11] The lesions are usually painless, hypo or hyperchromic with slight or absent pruritus and

dysesthesias whereas secondary nodules may appear.[1-3,11] *L. loboi* presents a prolonged incubation period, suggesting a chronic evolution of the disease.[1,2,11] There are cases with a 30 to 40 years history of lesion appearance indicating that the disease is typically slow progressive.[1,2] Transformation of an old lesion to squamous cell carcinoma has been described.[12]

As the organism has not yet been cultured, the diagnosis is based upon the macro- and microscopic examination of the lesions,[1,2,5,13,14] demonstrating the presence of round or oval, thick walled yeast-like cells ranging from 5 to 12 μm diameter in lesions exudate or tissue sections.[1,2,13,14] The organism multiplies by budding, and thus mother cells with single buds are often observed.[1,2] Characteristic sequential budding leads to the production of cell chains linked to each other by a tubular connection. Budding may occur at more than one point in a cell, giving rise to branched or radiating chains of cells. These thick walled, hyaline, spherical cells in chains interconnected by tubular connections are the basis on which a diagnosis of lobomycosis is made.[1,2,13,14] The histological picture is dominated by a granuloma accompanied by accentuated fibrosis.[1,2]

At present, there is no effective treatment for lobomycosis. The optimal therapy for localized lesions is cryosurgery or wide surgical excision in health margins to avoid recurrence.[1,2,15,16] In cases where lesions are disseminated treatment with itraconazole, clofazimine or combination of both drugs is recommended.[15,16] Unfortunately, the disease has no tendency to heal spontaneously whereas none of the above treatments are proved to be satisfactory.[1,2]

We present herein a 64-year-old female patient with common variable immunodeficiency, who developed lobomycosis. This is according to our knowledge the first documented case of human lobomycosis in Southeastern Europe.

Case report

In August 2006, a 64-year-old woman was admitted to the hospital with backache, anemia and hypoglobulinemia. She had a 6-year history of hypoglobulinemia and cholestatic hepatitis treated with corticosteroids and a consequent 4-year history of diabetes mellitus. Physical examination was unremarkable apart from a 3 cm discoid erythematous infiltrative plaque with a smooth brilliant surface resembling a keloid located at the left inner thigh (Fig. 1). This was present for 7 months. She was anemic (hemoglobin 10.1 gr/dL), with white blood cells 3.75x109/L (42% neutrophils, 51% lymphocytes, 5% monocytes, 1% baseophils, 1% eosinophils) and platelets: 117x109/L. Her biochemical profile showed elevated alkaline phosphatase: 871 mg/dL and γ- glutamine transferase 495 mg/dL. Hypoglobulinemia was verified (IgG: < 138 mg/dL, reference range: 700-1600, IgA: < 24.5 mg/dL, reference range: 70-400 and IgM: < 16.5 mg/dL, reference range: 40-230). Blood cultures were negative. Viral testing and serology for HSV-1, HSV-2, CMV, HBV, HCV, HAV, and HIV-1 and 2 were negative. Thoracic and abdominal CT scan showed no pathological findings except one enlarged lymph node (1.5 cm) at the anterior mediastinum and a slight splenomegaly (14 cm). Bone marrow aspiration was negative for any malignant infiltration. Immunophenotyping of peripheral blood revealed a high percentage of CD3+, CD8+ T lymphocytes (69.2%, reference range: 22- 30%) and decreased CD3+ CD4+T and B lymphocytes (14.3%, reference range: 42-58%). Duodenal biopsy showed follicular hyperplasia characteristic of common variable immunodeficiency.

Biopsied tissue specimens of the lesion were submitted for pathological and microbiologic examination. The tissue culture was negative for fungal growth. Direct microscopic examination by scraping the lesions with KOH yielded round or oval yeast-like cells, measuring approximately 5-12 μm in diameter, isolated or in chains and connected by a short tubular projection. Skin biopsy showed deep cutaneous fungal infection with granulomatous reaction and in a lesser degree neutrophilic infiltrate of dermis with small necrotic foci surrounding fungal yeasts. Fungal cells were found inside giant cells (Fig. 2). The excised tissue was also stained with Periodic Acid-Schiff stain. The fungi were thick-walled with

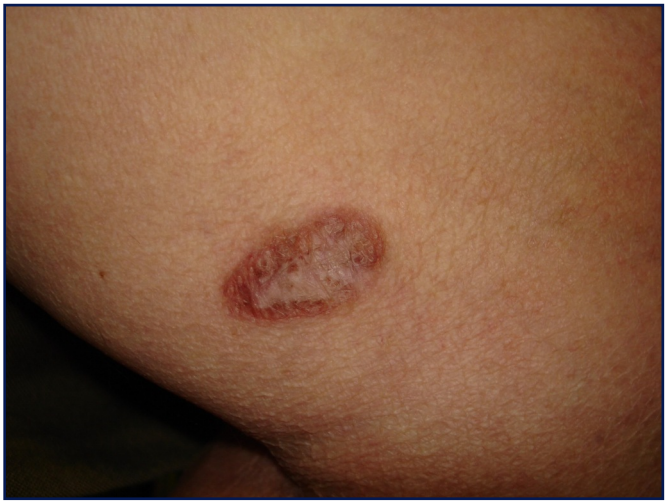

Figure 1
Discoid keloidal plaque on the thigh.

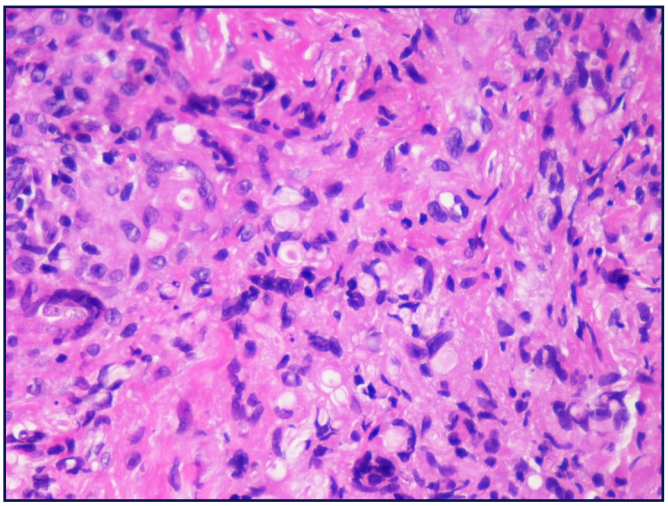

Figure 2
Fungal cells inside giant cells. Dermal fibrosis. HE x 200.

some budding, isolated or in short chains (Fig. 3, 4). Dermal fibrosis was present. The overall histological features of the lesion were consistent with lobomycosis.

Complete excision of the plaque was planned. This was cancelled due to severe aggravation of the underlying disease, for which she had intravenous therapy with immunoglobulin. During her admission, she developed renal failure and submitted to hemodialysis. The patient suffered from several infections and died 2 years later from septic shock.

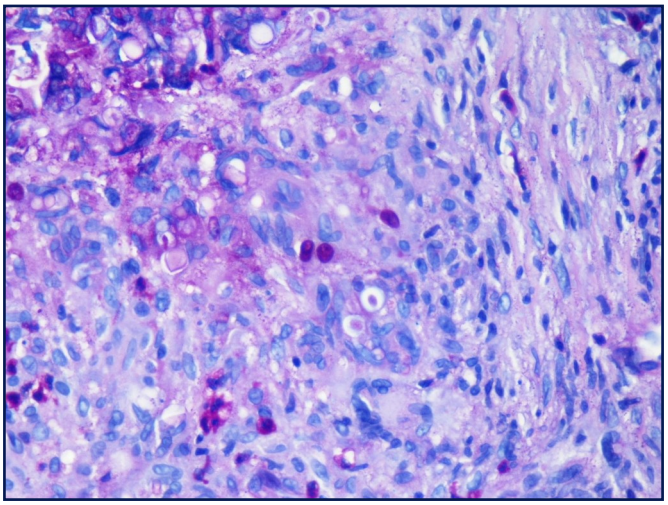

Figure 3

Thick-walled fungi with some budding, isolated or in short chains. PAS x 400.

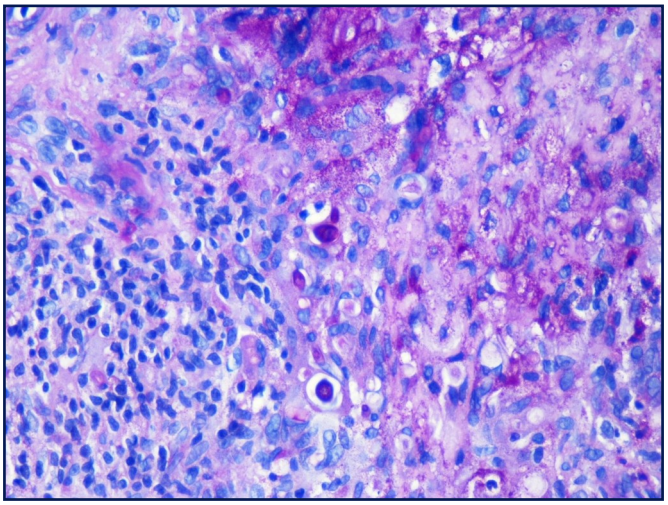

Figure 4

Thick-walled fungi with some budding, isolated or in short chains. PAS x 400.

Discussion

We present an extremely rare case of lobomycosis in a 64-year-old Greek female farmer living in a coastal region in Southeastern Europe.

In our case, the clinical appearance of the dermal lesion was an infiltrative plaque with a smooth brilliant surface resembling a keloidal plaque. In humans, the dermatologic lesions are pleomorphic being single or multiple.[2,7,8] Although a common clinical presentation is a nodular, solid lesion with smooth surface, shiny and keloidal aspect,[7] lesions may occur also as papules, ulcers with a smooth brilliant aspect, sclerodermiform, verrucous and in plaques.[2,5-8] Although a specific dermatologic pattern may dominate in any given case, lesions are rarely monomorphous.[2,14] Based on the lesion morphologic appearance, Silva and de Brito proposed a classification with five subtypes: infiltrative, keloidal, gummatous, ulcerative and verrucoid.[2,17] The clinical differential diagnosis included deep mycoses as lobomycosis, chromoblastomycosis and paracoccidiomycosis, keloids, dermatofibrosarcoma protuberans, leprosy and Kaposi's sarcoma.[1,2,7,11]

The diagnosis was based on the triad: 1) absence of fungal growth in cultures, 2) presence of yeast-like organisms in direct microscopic examination of the lesion and 3) histopathology features consistent with lobomycosis. Although other fungi may resemble *L. loboi* microscopically, none of them form the characteristic chains of uniform sized, thick-walled fungi connected by tubular projection. Furthermore, in contrast to *L. loboi* the mothercell of *Paracoccidioides brasilensis* forms multiple buds and remains larger than the daughter cells, giving the characteristic "ship's wheel" appearance.[1,2,4,18,19] Additionally, paracoccidiomycosis is a disease affecting also the oronasal mucous membranes and lungs which were unaffected in our case. On the other hand, regarding chromoblastomycosis cases, histopathology shows the characteristic sclerotic cells, or Medlar bodies, which appear as single, or clustered thick-walled rounded brown cells found in giant cells in the dermis and extracellularly.[20] In our case, histopathology revealed neither "ship's wheel" nor Medlar bodies. Many yeast-like thick-walled fungi arranged singly or in small chains and connected by tubular connections were found; which is a typical morphology of *L. loboi*.

Lobomycosis was first described in 1931 by Jorge Lobo in a Brazilian patient.[1,3,5] The human disease appears to be endemic in Central and Western Brazil, Bolivia, Colombia, Costa Rica, Ecuador, Guyana, Mexico, Panama, Peru, Suriname and Venezuela.[1-6,8,11,13,21] However, there have been isolated cases in the United States,[22] Canada,[16] Africa,[23] the Netherlands,[24] France[25] and Germany.[15] More than 550 human cases have been reported to date, especially in patients with a history of travel or residence in the areas of endemicity or in communities along rivers.[1-6,26,27]

Our case represents the first documented case in Southeastern Europe (and Greece) and one of the rare cases in the Mediterranean countries. Our patient referred no history of travel to any of the above countries. We have no evidence of how this patient was infected by *L. loboi*. However, we can express the following hypotheses. The first nonhuman infection was described in 1971 concerning a bottle-nose dolphin from Florida.[28] Since then a significant number of sea and river dolphins inhabiting the coasts and rivers of the United States, South America and Europe were found being infected by *L. loboi*.[9,28-31] This fact explains satisfactory the geographical distribution of the disease and could justify the identification of *L. loboi* in our country as well. The natural

reservoir of *L. loboi* is unknown, but it is believed to be aquatic or associated with soil and vegetation.[1,2] As new reported cases of lobomycosis in Delphinidae and in people living in coastal environment are emerging, the aquatic environment may also represent a habitat for this fungus and a probable source of transmission. Most human cases in medical literature are linked to geographical regions with an important hydrographic component. Furthermore, rubber workers, farmers, miners, fishermen and hunters are particularly at risk due to outdoor exposure.[2-5] The history often reveals the cause being a trauma, i.e. a sting, a snake bite, a cut from an instrument or a wound acquired while cutting vegetation.[2-5] Our patient was a farmer living in a coastal Greek region. Although not confirmed by her, most probably as a result of her agricultural profession, injury is the most possible triggering factor. Infection may be acquired from contaminated vegetation or soil through injuries or traumas.[11] Finally, the fact that our patient suffered from common variable immunodeficiency could be a potential risk factor but not proven yet as one case of lobomycosis coexistent with immunodeficiency may not imply a pathogenic correlation. However, a relative hypothesis was expressed from Reif *et al* suggesting that lobomycosis may represent an opportunistic infection in an immunocompromised host.[31] In fact, significant impairment in adaptive immunity characterized by a significant decrease of the total number of CD4+ T cells and B lymphocytes, and a decrease in the expression of molecules belonging to type II Major Histocompatibility Complex were described in dolphins suffering from lobomycosis.[31] In humans, the slow incubation period and development of lesions may be attributed to the suppression of macrophagic activity through the cytokine TGFβ that inhibits nitric oxide and γ-interferon expression, impacting cell mediated immunity, leading to an antigen-specific cell mediated immune deficiency and inducing fibrosis.[32,33] Langerhan's cells may be implicated in modulating the local immune system to evade antigen presentation by those cells.[33] However, neutrophil function and complement system activity are normal as *L. loboi* may activate the alternative pathway of the complement system.[2,34] Humoral immunity studies have shown that lobomycosis patients present a predominantly Th2 lymphocyte subpopulation cytokine profile which might also negatively regulate its Th1 cellular counterpart.[2,34]

Conclusion

In summary, we report for the first time a case of lobomycosis in a 64-year-old Greek female farmer suffering from common variable immunodeficiency with no history of travel to remote countries. This case is unusual due to the rarity of lobomycosis in Mediterranean countries, particularly in Southeastern Europe.

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Note: Authors EP and MD have contributed equally to this paper.