Case Report: Sclerosing Orbital Inflammation Caused by *Leishmania braziliensis*

Antonio Augusto V. Cruz,^{1*} Eliza V. C. Alves-Ferreira,² Gherusa Milbratz-Moré,¹ Fernando Chahud,³ Patricia C. Ruy,² Maria Irma Seixas Duarte,⁴ and Angela Kaysel Cruz^{2*}

¹Department of Ophthalmology, School of Medicine of Ribeirão Preto, University of São Paulo, Ribeirão Preto, Brazil; ²Department of Cell and Molecular Biology, School of Medicine of Ribeirão Preto, University of São Paulo, Ribeirão Preto, Brazil; ³Department of Pathology, School of Medicine of Ribeirão Preto, University of São Paulo, Ribeirão Preto, Brazil; ⁴Department of Pathology, School of Medicine of University of São Paulo, São Paulo, Brazil

Abstract. Orbital biopsy of nonspecific orbital inflammation, commonly referred to as “orbital pseudotumor,” typically shows a combination of polyclonal lymphocytes, plasmacytes, leukocytes, macrophages, and variable degrees of collagen deposition. Herein, we report a patient with a positive history of mucocutaneous leishmaniasis who presented with an orbital mass with a histological profile of idiopathic orbital inflammation. Immunohistochemical and molecular analysis of the orbital specimens demonstrated that the orbital inflammation was associated with the presence of antigens of *Leishmania braziliensis* and DNA from the parasite.

INTRODUCTION

The orbit is a frequent site of inflammatory processes of unknown etiology. Since these conditions usually have a marked mass effect similar to that of tumors, they are commonly referred to as “orbital pseudotumor.”¹ A wide range of cellular components are seen in the inflammatory infiltrate of idiopathic orbital inflammations. An orbital biopsy of an orbital pseudotumor typically shows nonspecific combinations of polyclonal lymphocytes, plasmacytes, leukocytes, macrophages, and variable degrees of collagen deposition.²

Herein, we report a patient with a positive history of mucocutaneous leishmaniasis (MCL) who presented with an orbital mass with a typical histological profile of idiopathic orbital inflammation. Immunohistochemical and molecular analysis of the orbital specimens demonstrated that the orbital inflammation was associated with the presence of antigens of *Leishmania braziliensis* and DNA from the parasite. To our knowledge, this is the first report of “idiopathic” orbital inflammation associated with the presence of antigens and DNA from *L. braziliensis* in the orbital tissues.

CASE REPORT

A 74-year-old farmer was sent to the hospital for evaluation of right eye proptosis which had progressed slowly over a 9-year period. The patient reported that 23 years ago he had been treated for lesions on the lower eyelid and nose caused by an *L. braziliensis* infection. On examination, the right eye was grossly proptotic (Hertel exophthalmometric readings were 23 oculus dexter and 16 mm oculus sinister). There was a mild lacrimal ectropion with medial conjunctival hyperemia. Right eye motility was limited on abduction. There was also a typical nasal saddle deformity (Figure 1A). Magnetic resonance imaging of the orbits and paranasal

sinuses showed a posterior nasal septum defect and an inferomedial orbital mass displacing the medial rectus muscle and optic nerve superiorly (Figure 1B).

The lesion was surgically debulked. During surgery, the orbital mass was found to be firmly adherent to the medial orbital wall. Histopathological examination of the surgical specimens revealed diffuse fibrosis and a chronic granulomatous inflammatory infiltrate with several multinucleated giant cells and a preponderance of CD3+ lymphocytes (Figure 1C). The whole picture was compatible with idiopathic sclerosing orbital inflammation.

Since the orbital lesion was intimately associated with the ethmoid sinus and taking into account the medical history of the patient, the tissue samples were stained with a custom-made pool of antibodies against *L. braziliensis*. Diffuse positivity was then revealed in the tissue macrophages (Figure 1D). DNA was extracted from the biopsy and submitted to a polymerase chain reaction to test for the presence of kinetoplast DNA (kDNA) of the parasite (Figure 2A). kDNA amplification was detected in the patient's biopsy sample and in the positive control, a *L. braziliensis* promastigote culture sample.^{3,4} To certify that the amplified DNA obtained from the biopsy was kDNA, the DNA was recovered from an agarose gel band and sequenced. A similarity sequence search (BLAST) confirmed the presence of minicircle kDNA (Figure 2B, Supplemental File 1).⁵ All results were consistent with MCL.

DISCUSSION

The identification of *Leishmania* DNA in an orbital lesion morphologically classified as a nonspecific inflammation strongly supports the concept discussed by Harris that “idiopathic orbital inflammation” is not a specific disease but rather a process that can be elicited by a variety of triggering agents including parasitic antigens.⁶

MCL occurs in 1–10% of cases of a primarily cutaneous disease caused by *Leishmania* species from the subgenus *Viannia*, which includes *L. braziliensis*.⁷ This severe and life-threatening form of leishmaniasis is characterized by migration of the parasite from the primary cutaneous site of inoculation to the oronasopharyngeal mucosa, where it provokes a strong inflammatory reaction months or even years after the initial infection, leading to progressive destruction of the affected tissues. Since *Leishmania* is an intracellular

*Address correspondence to Angela Kaysel Cruz, Departamento de Biologia Celular e Molecular, Faculdade de Medicina de Ribeirão Preto (FMRP), Universidade de São Paulo (USP), Av Bandeirantes, 3900, Predio Central, São Paulo, Brazil, E-mail: akcruz@fmrp.usp.br or Antonio Augusto V. Cruz, Departamento de Oftalmologia, Hospital das Clínicas-Campus, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, Av Bandeirantes, 3900, São Paulo, Brazil, E-mail: aaveacruz.fmrp@gmail.com.

FIGURE 1. (A) Clinical aspect of the patient: nasal saddle deformity and right eye proptosis. (B) Coronal view of T1 weighed magnetic resonance disclosing a mass along the medial orbital. The mass displaces the optic nerve medial rectus muscle upward. (C) Focal granulomatous inflammation with multinucleated giant cells in a dense collagenous stroma (hematoxylin and eosin stain, 400x). (D) *Leishmania*-specific immunohistochemistry image from biopsies of patient using polyclonal mouse anti-*Leishmania* (1:1,000).

parasite in the mammalian host, it has been postulated that migration occurs through infected macrophages, although the mechanisms involved in the preferential location of the disease on the nasal mucosa are not known.⁸

We believe that histiocytes or other inflammatory cells targeted by the parasite migrated by proximity to the medial orbital wall and participated and probably contributed to the same granulomatous reaction seen in the oral and nasal mucosae. Since these lesions have a typically low parasite

load, it is not surprising that the amastigote forms of the parasite could not be visualized. Orbital involvement in leishmaniasis was documented only once in a patient with acquired immunodeficiency syndrome. This patient presented with sphenoiditis and apical orbital infiltration. A biopsy from the sphenoid sinus revealed intracellular organisms identified as *L. braziliensis*.⁹ Of note, 23 years have passed since the present patient was diagnosed and treated for MCL, and there is no clinical evidence of immunosuppression.

FIGURE 2. Immunohistochemistry and detection of *Leishmania* kinetoplast DNA by polymerase chain reaction (PCR) in biopsy samples from patient B11827/11. (A) Agarose gel-fractionation of the PCR products from DNA extracted from biopsy samples and *Leishmania* parasite culture. L: 50-bp DNA Ladder (Invitrogen, Carlsbad, CA). C⁻ (mock): PCR reactions without genomic DNA were used as negative controls. C⁻ (patient): DNA from biopsy samples of a different patient without clinical disease. C⁺ (H3327): DNA from *Leishmania braziliensis* promastigotes, H3327 strain. bp = base pairs. (B) Scheme representing the blastn result against nucleotide database (National Center for Biotechnology Information). Two sequences (red blocks) match with "*Leishmania panamensis* isolate loc41 kinetoplast minicircle DNA" (gb|AF118464.1|AF118464) (yellow block). The universal minicircle sequence (UMS) is represented as a green block. The sequence alignments are accessible at Supplemental File 1.

Our unique case nicely highlights the necessity of a comprehensive molecular analysis of atypical cases of “idiopathic” orbital inflammation. We believe that a substantial number of cases of granulomatous orbital inflammations might represent inflammatory reactions to unknown infective antigens.

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Authors' addresses: Antonio Augusto V. Cruz and Gherusa Milbratz-Moré, Department of Ophthalmology, School of Medicine of Ribeirão Preto, University of São Paulo, Ribeirão Preto, Brazil, E-mails: aavecruz.fmrp@gmail.com and gherusa1983@yahoo.com.br. Eliza V. C. Alves-Ferreira, Patricia C. Ruy, and Angela Kaysel Cruz, Department of Cell and Molecular Biology, School of Medicine of Ribeirão Preto, University of São Paulo, Ribeirão Preto, Brazil, E-mails: eliza_cameiro@yahoo.com.br, patriciaruy@usp.br, and akcruz@fmrp.usp.br. Fernando Chahud, Department of Pathology, School of Medicine of Ribeirão Preto, University of São Paulo, Ribeirão Preto, Brazil, E-mail: chahud@fmrp.usp.br. Maria Irma Seixas Duarte, School of Medicine of University of São Paulo, São Paulo, Brazil, E-mail: miduarte@usp.br.

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