Case Report: Squamous Cell Carcinoma Referred for Mohs Surgery Found to be Cutaneous Leishmaniasis

Miguel Darío Prieto,^{1*} Andrés Felipe Uribe-Restrepo,^{1,2} Daniela Arcos,¹ and Diego Alejandro Vargas³

¹*Leishmaniasis Clinical Research Unit, Centro Internacional de Entrenamiento e Investigaciones Médicas (CIDEIM), Cali, Colombia;* ²*Public and Comunitary Health Department, Facultad de Ciencias de la Salud, Universidad Icesi, Cali, Colombia;* ³*Pathology Department, Universidad del Valle, Cali, Colombia*

Abstract. Chronic skin lesions constitute a clinical diagnostic challenge. We report the case of a patient whose facial lesion was histopathologically compatible with squamous cell carcinoma and hence programmed for Mohs surgery. However, review of the clinical and epidemiological history led to laboratory diagnosis of cutaneous leishmaniasis, treatment with miltefosine, and complete resolution of the lesion.

INTRODUCTION

Squamous cell carcinoma (SCC) is the second most common nonmelanoma skin cancer worldwide after basal cell carcinoma.¹ Because this cancer has a high risk of recurrence and metastasis at 5 years, early diagnosis is vital to favorable prognosis and minimization of sequelae.² Diagnosis of SCC is based on skin biopsy and histopathology, which typically show nests of squamous epithelial cells arising from the epidermis that extend into the dermis. However, numerous other inflammatory pathologies can present histological findings mimicking SCC, particularly pseudoepitheliomatous hyperplasia (PEH)³: a response to long-term skin irritation including cancer, trauma, inflammation, and infectious diseases such as leishmaniasis and deep mycosis. Pseudoepitheliomatous hyperplasia typically displays proliferation of epithelial skin cells toward the dermis and can be easily mistaken for a well-differentiated SCC.⁴

Alternative diagnoses of SCC, particularly in an endemic context, include cutaneous leishmaniasis (CL). This vector-borne, parasitic disease is prevalent in many tropical and subtropical areas including Colombia.^{5,6} Cutaneous leishmaniasis is pleomorphic and lesion appearance is related to time since onset. In the Colombian context, it typically shows chronic lesions that begin as papules that advance to plaques and localized ulcers with swollen borders in the first 6 months of disease, but it can also present atypical lesions that include other forms of papules, plaques, nodules, and ulcers.^{6,7} Thus, diagnosis of CL must be confirmed by parasitological diagnosis, which also prevents misadministration of highly toxic treatments; this is usually accomplished by smear or culture (smear may be positive ~90% of cases). Skin biopsy can also be used for diagnosis, but has a lower sensitivity, and definitive diagnosis requires visualization of *Leishmania*-compatible amastigotes. However, biopsy can be useful in evaluating other potential etiologies of chronic skin lesions, although it must be recognized that there can be overlap in some findings.⁸

Overall, the medical evaluation of a chronic lesion in the skin requires a highly experienced physician who integrates information from the clinical history, laboratory evaluations, and epidemiologic context to make a diagnostic impression.^{9,10}

We present a case where histopathological findings led to the referral for surgical treatment of a skin lesion as SCC. The medical history and epidemiologic background suggested CL, which was ultimately diagnosed and successfully treated. Written informed consent was obtained from the patient for use of clinical and laboratory information.

CASE SYNOPSIS

A 61-year-old female Afro-Colombian patient was referred to a tertiary care institution in Cali with a diagnosis of SCC and recommendations for Mohs surgery; the diagnosis was based on compatible histopathological findings. She presented a lesion of 3 years of duration on the left zygomatic arc, a zone having high sun exposure, which consisted of a rounded ulcer with crust and patches of necrosis. She also had a keloid scar on the right neck and no other skin lesions were present. Also, no enlarged lymph nodes were present at examination and the patient denied having them previously. The dermatologist evaluated the complete medical history, finding that the patient had worked in the eastern plains of Colombia around the time of onset of the disease. The clinical history also revealed that initially she presented four papules at different body sites, which at the time of the first medical visit had progressed to a papule (face) and two ulcers (neck and lower limb), with the remaining lesion healing spontaneously. Considering the epidemiological context, direct smear of the lesion was conducted and she was diagnosed with CL. She was prescribed standard-of-care treatment with meglumine antimoniate (Glucantime[®], Sanofi-Aventis Brazil, São Paulo, Brazil) for 20 days at an unknown dose, but received only 18 days of treatment because of limited access to health care. After treatment, the papule located on the face persisted and subsequently increased in size and ulcerated, becoming the lesion later diagnosed as SCC. A year after treatment of CL, she consulted a rural basic hospital (municipality of Puerto Tejada), where two Giemsa-stained smears were evaluated and determined to be negative for *Leishmania*. The following year, a biopsy was taken in Puerto Tejada (report and specimen not available) with results suggestive of SCC. Consequently, she was referred for treatment with Mohs surgery to the tertiary care hospital. Based on the history, the dermatologists challenged the diagnosis, obtained a new skin biopsy to evaluate alternative disorders, and referred the patient to Centro Internacional de Entrenamiento e Investigaciones Médicas, a regional reference center for leishmaniasis, to

* Address correspondence to Miguel Darío Prieto, Leishmaniasis Clinical Research Unit, Centro Internacional de Entrenamiento e Investigaciones Médicas, Carrera 125 #19-225, Cali 760031, Colombia. E-mail: mdprietoc@cideim.org.co

rule out CL. The skin lesion was evaluated by direct smear (Giemsa stained) and culture of aspirate samples from the border of the lesion. Microscopic evaluation of the Giemsa-stained smear showed *Leishmania* amastigotes, and *Leishmania* promastigotes were cultured and isolated from 1/4 lesion aspirates, confirming the diagnosis of CL. The strain was identified as *Leishmania* (*Viannia*) *panamensis* using a panel of monoclonal antibodies and immunofluorescent antibody test (IFAT), as described previously.^{11,12}

The biopsy taken on referral for Mohs surgery showed the findings in Figure 1, including *Leishmania* amastigotes. The evidence of epithelial mitosis, keratin pearls, and pseudo-infiltration in the dermis could be interpreted as SCC; however, the abundant inflammatory infiltrate suggested a reactive epithelial change more likely associated with infection. Considering the previous response to Glucantime®, the patient was treated with second-line miltefosine (Impavido®, Paesel & Lorei GmbH & Co., Duisburg, Germany) at 2.5 mg/kg/day (150 mg/day) for 28 days in January 2017. During treatment, she reported only mild abdominal pain and diarrhea that resolved after finishing treatment. Follow-up at 26 weeks after initiation of treatment confirmed healing of the lesion and clinical cure (complete epithelialization and resolution of inflammatory signs); only a hyperpigmented scar remained as sequelae of the disease, Figure 2.

DISCUSSION

Neglected tropical diseases, among them leishmaniasis, are closely associated with poverty and have a particular

sociocultural context that creates barriers to health care. Most of these diseases occur in rural areas where patients have limited access to advanced health-care institutions and must rely on local centers.¹³ Clinicians in these local centers should be trained as first responders to the most important diseases in the regional context, facilitating diagnosis and management of cases at the local level. However, barriers to access to health-care services may prolong the time to diagnosis and treatment, thereby contributing to complications associated with the progression of the disease. Delayed diagnosis can also obscure clinical appraisal as chronic lesions tend to be less typical in appearance.

Because of the persistence of *Leishmania* infection following treatment and difficulties to isolate the parasite after treatment, the definition of therapeutic outcome is based solely on clinical findings, as explained by Olliaro et al.^{14,15} In case of a nonhealing lesion at the end of follow-up (persistent inflammatory signs or incomplete epithelialization), efforts should be made to isolate the parasite strain; however, the clinical outcome is independent of the persistence of infection.^{14,16} If, at the end of follow-up, the lesion remains unhealed and no alternative diagnosis is considered, the recommendation is to give a new course of therapy.¹⁷ Therefore, clinical expertise is crucial to define the outcome of treatment and to consider possible alternative diagnosis.

Skin biopsy can be useful to diagnose chronic skin lesions and differentiate alternative diagnoses, yet has to be interpreted together with appropriate clinical and epidemiological information. As the only confirmatory finding of CL is visualization of *Leishmania* amastigotes (sensitivity 15–30% in skin

FIGURE 1. Photomicrographs of the ulcer skin biopsy. (A) Acanthotic epidermis with corneal pearls formation and exuberant chronic inflammatory infiltrate (hematoxylin and eosin [H&E] staining, 10x magnification). (B and C) Squamous cells with dyskeratosis and mitotic figures, arrowheads in B and C respectively (H&E staining, 40x magnification). (D) Significant lymphohistiocytic inflammatory infiltrate (H&E staining, 40x magnification). (E) Arrowheads show *Leishmania* amastigotes in the periphery of parasitized histiocytic cells (Giemsa staining with immersion oil, 100x magnification). This figure appears in color at www.ajtmh.org.

FIGURE 2. Progression of the lesion in the right cheek of the patient, during treatment and follow-up. (A) Initial visit: before diagnosis. Marker shows suture of biopsy. (B) Epithelialized lesion with a crusty plaque at the end of treatment. (C) Completely epithelialized lesion without inflammatory signs, 3 months after start of treatment. (D) Definitive cure: residual scar at 5 months after the end of treatment. This figure appears in color at www.ajtmh.org.

biopsies),¹⁷ skin biopsies should be carefully used and interpreted if CL is suspected. Immunohistochemistry could improve sensitivity, but is not widely available in endemic areas,^{7,18} and findings in skin biopsies of CL can suggest other diseases, including skin cancer. A case series of 57 polymerase chain reaction-confirmed Old-World CL cases showed histopathological results clearly suggestive of an etiology other than leishmaniasis, among them, squamous cell carcinoma, deep fungal infections, tuberculosis, and syphilis.⁹ These atypical

presentations of CL may be common and have a wide range of histopathological findings.^{19,20} Particularly, PEH, an unorganized proliferation of keratinocytes toward deeper tissue in response to chronic inflammation, can easily be mistaken as squamous cell carcinoma (Table 1).^{8,9} However, SCC is but one cause of this condition and findings such as abundant inflammatory infiltrate, dermal compromise, and absence or limited mitotic activity in the epidermis should prompt investigation of alternative diagnosis.^{21,22} This evidence about

TABLE 1
Comparison of histological characteristics between pseudoepitheliomatous hyperplasia and squamous cell carcinoma

	Pseudoepitheliomatous hyperplasia	Well-differentiated squamous cell carcinoma
Marked acanthosis	Constant	May be present
Infiltrative rods and nests	Usually absent	Constant
Cellular atypia	May be present	Commonly present
Mitotic activity	May be present	Commonly present
Keratin pearls formation	Variably present	Constant
Keratinocytes maturity	Conserved	Altered
Chronic inflammatory infiltration	Present (exuberant)	Present (variable)
Association with precursor lesion	Absent	Present

histopathological characteristics of SCC underscores features of this pathology in the differential diagnosis when faced with lesions compatible with CL.

To summarize, the context in which CL appears requires that clinicians in or serving rural areas be well versed in the disease profile of the region. In addition, CL and other chronic skin lesions share nonspecific findings on histopathological examinations that can mislead the clinician if no confirmatory finding is detected. Therefore, it is paramount to address each case individually as characteristics such as lesion time since onset, speed of progression, occupational risk, region of residence or origin, previous exposures, skin tone, and other risk factors allow the clinician to establish diagnostic priorities. In this particular case, despite the remarkably lower incidence of SCC in African descendants and women,²³ a diagnosis of malignant disease was made based on histopathological findings, but a careful and in-depth review of patient information by clinicians ultimately led to the diagnosis and successful treatment of CL.

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Authors' addresses: Miguel Dario Prieto and Daniela Arcos, Centro Internacional de Entrenamiento e Investigaciones Médicas (CIDEIM), Cali, Colombia, E-mails: mdprieto@cideim.org.co and dalearco181@hotmail.co. Andrés Uribe-Restrepo, Department of Public Health, Universidad Icesi, Cali, Colombia, and Centro Internacional de Entrenamiento e Investigaciones Médicas (CIDEIM), Cali, Colombia, E-mail: afur34@live.com. Diego Alejandro Vargas, Pathology Department, Universidad del Valle, Cali, Colombia, E-mail: dialejo_0519@hotmail.com.

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