Because of their superficial nature, trichoepithelioma is amendable to ablative methods such as carbon dioxide or erbium: yttrium-aluminum-garnet (Erb:YAG) Erb:YAG laser evaporation or electro surgery.[15] Positive and negative regulators of CYLD hold promise, but they have not been extensively investigated to date. For example, the use of antagonists of *CYLD* such as tumor necrosis factor alpha inhibitor coupled with salicylic acid (nuclear factor κB antagonist) resulted in a gradual improvement of multiple cylindromas.[16] In addition, topical application of salicylic acid to multiple cylindromas resulted in partial to complete tumor remission in a minority.[17] Contrarily, topical imiquimod, an agonist of CYLD function and stimulator of tumor necrosis factor alpha and interferon gamma combined with tretitoin cleared approximately 80% of trichoepitheliomas after 3 years of therapy.[18]

In conclusion, we report the third MFT family with the c.1112C> A/p.S371X nonsense *CYLD* mutation that was associated with a severe disfiguring phenotype. As 3 FC families have also been reported with this nonsense mutation,[3–5] a direct genotype–phenotype correlation is not apparent, and other genetic factors combine with loss of *CYLD* function to produce multiple facial cutaneous adnexal tumors of varied type and size. The fact that CYLD function affects both morphogenesis of the folliculosebaceous–apocrine unit and inflammation may underlie these complex phenotypes.

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REFERENCES

1. Kazakov DV, Vanecek T, Zelge B, et al. Multiple (familial) trichoepitheliomas: a clinicopathological and molecular biological study, including CYLD and PTCH genes analysis, of a series of 16 patients. *Am J Dermatopathol*. In press.
2. Blake PW, Toro JR. Update of cylindromatosis gene (CYLD) mutations in Brooke-Spiegler syndrome: novel insights into the role of deubiquitination in cell signaling. *Hum Mutat*. 2009;30:1025–1036.
3. Bowen S, Gill M, Lee DA, et al. Mutations in the CYLD gene in Brooke-Spiegler syndrome, familial cylindromatosis, and multiple familial trichoepithelioma: lack of genotype-phenotype correlation. *J Invest Dermatol*. 2005;124:919–920.
4. Bignell GR, Warren W, Seal S, et al. Identification of the familial cylindromatosis tumour-suppressor gene. *Nat Genet*. 2000;25: 160–165.
5. Saggar S, Chernoff KA, Lodha S, et al. CYLD mutations in familial skin appendage tumours. *J Med Genet*. 2008;45:298–302.
6. Van den Ouweland AM, Elfferich P, Lamping R, et al. Identification of a large rearrangement in CYLD as a cause of familial cylindromatosis. *Fam Cancer*. 2010. [Epub ahead of print].
7. Amaro C, Freitas I, Lamarao P, et al. Multiple trichoepitheliomas–a novel mutation in the CYLD gene. *J Eur Acad Dermatol Venereol*. 2010;24:844–846.
8. Kazakov DV, Schaller J, Vanecek T, et al. Brooke-Spiegler syndrome: report of a case with a novel mutation in the CYLD gene and different types of somatic mutations in benign and malignant tumors. *J Cutan Pathol*. 2010; 37:886–890.
9. Scholz IM, Numann A, Froster UG, et al. New mutation in the CYLD gene within a family with Brooke-Spiegler syndrome. *J Dtsch Dermatol Ges*. 2010;8:99–101.
10. Wang FX, Yang LJ, Li M, et al. A novel missense mutation of CYLD gene in a Chinese family with multiple familial trichoepithelioma. *Arch Dermatol Res*. 2010;302:67–70.
11. Rajan N, Trainer AH, Burn J, et al. Familial cylindromatosis and Brooke-Spiegler syndrome: a review of current therapeutic approaches and the surgical challenges posed by two affected families. *Dermatol Surg*. 2009;35: 845–852.
12. Kazakov DV, Thoma-Uszynski S, Vanecek T, et al. A case of Brooke-Spiegler syndrome with a novel germline deep intronic mutation in the CYLD gene leading to intronic exonization, diverse somatic mutations, and unusual histology. *Am J Dermatopathol*. 2009;31:664–673.
13. Sima R, Vanecek T, Kacerovska D, et al. Brooke-Spiegler syndrome: report of 10 patients from 8 families with novel germline mutations: evidence of diverse somatic mutations in the same patient regardless of tumor type. *Diagn Mol Pathol*. 2010;19: 83–91.
14. Kazakov DV, Zelger B, Rutten A, et al. Morphologic diversity of malignant neoplasms arising in preexisting spiradenoma, cylindroma, and spiradenocylindroma based on the study of 24 cases, sporadic or occurring in the setting of Brooke-Spiegler syndrome. *Am J Surg Pathol*. 2009;33:705–719.
15. Rallan D, Harland CC. Brooke-Spiegler syndrome: treatment with laser ablation. *Clin Exp Dermatol*. 2005;30:355–357.
16. Fisher GH, Geronemus RG. Treatment of multiple familial trichoepitheliomas with a combination of aspirin and a neutralizing antibody to tumor necrosis factor alpha: a case report and hypothesis of mechanism. *Arch Dermatol*. 2006;142:782–783.
17. Oosterkamp HM, Neering H, Nijman SM, et al. An evaluation of the efficacy of topical application of salicylic acid for the treatment of familial cylindromatosis. *Br J Dermatol*. 2006;155:182–185.
18. Urquhart JL, Weston WL. Treatment of multiple trichoepitheliomas with topical imiquimod and tretinoin. *Pediatr Dermatol*. 2005;22:67–70.

Cutaneous Leishmaniasis With Pseudoepitheliomatous Hyperplasia Simulating Squamous Cell Carcinoma

To the Editors:

In Rio de Janeiro state, Brazil, American tegumentary leishmaniasis is caused by *Leishmania (Viannia) braziliensis*. The main clinical presentation is a single skin ulcer located in areas exposed to vector bites. Diagnosis is established by isolation of *Leishmania* in culture or by amastigote detection in smears or histological sections, but parasitological demonstration is not always attained.[1] Histopathological findings include granulomatous dermatitis and occasionally pseudoepitheliomatous squamous hyperplasia (PESH).[2] PESH is considered a response to chronic epithelial irritation of various etiologies and can simulate squamous cell carcinoma (SCC).[3,4] Cutaneous neoplasms are also frequently located on exposed areas of the body and are important in leishmaniasis differential diagnosis.[5]

A 59-year-old man from an endemic leishmaniasis rural area in Rio de Janeiro presented with swelling and

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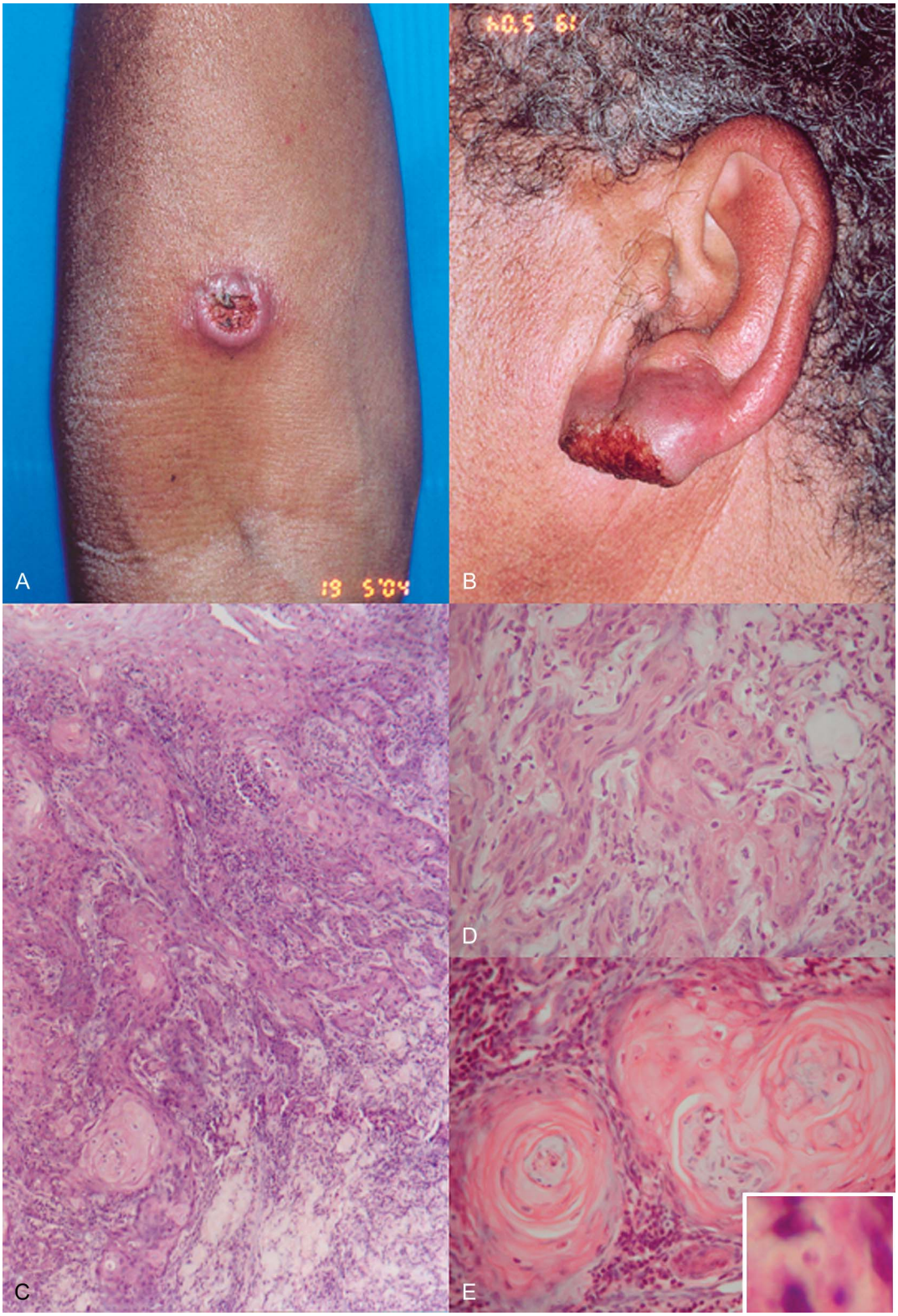

FIGURE 1. Ulcers with firm raised edges on the right forearm (A) and earlobe (B). Squamous epithelial cell proliferation with infiltrating aspect (C) with cords, small nests (D), horny pearls (E), and rare amastigote forms (inset).

redness of the left ear and a nodule on the right forearm, both evolving into ulceration in 3 months. Physical examination disclosed ulcers with raised firm edges on the right forearm (Fig. 1A) and lower pendular portion of the left ear lobe (Fig. 1B), a palpable lymph node beneath the angle of the jaw, and no lesions on mucosae of the upper aerodigestive tract.

Leishmanin skin test was positive, with 21 mm of induration. Indirect immunofluorescence and enzyme-linked immunosorbent assay for leishmaniasis were negative on admission. Biopsy tissue sample submitted to histological examination measured 9 × 4 mm and was 3 mm thick. On microscopy, there was a squamous epithelial downgrowing proliferation with irregular contours and infiltrating aspect (Fig. 1C), arranged in cords and small nests (Fig. 1D) or occasionally, in concentric disposition, forming horny pearls (Fig. 1E). Some cords and nests were situated deep in the dermis. Cytological atypia or atypical mitoses were absent. There was mild mixed inflammatory infiltrate (Fig. 1C) and no granulomas. Two pathologists examined the slides and reported "atypical squamous proliferation consistent with well-differentiated SCC," with observations that the lesion was partially resected, the sample was superficial, and a hyperplastic process could not be ruled out. Parasitological culture in Novy–Nicolle–McNeal medium and subsequent isoenzyme analysis identified *L. (V.) braziliensis*. Histological slide review revealed rare structures consistent with *Leishmania* sp. amastigotes (Fig 1E, insert).

Treatment was started with meglumine antimoniate for 30 days. Three months after the end of therapy, lesions were reepithelialized. Histopathology of a new biopsy sample of the arm lesion showed fibrosis and very focal small granulomas. No epithelial proliferation or amastigotes were seen, and the lesion was considered consistent with a healing process. Patient was lost to follow-up.

PESH is a microscopic pattern of tissue reaction characterized by uneven growth of squamous cells toward underlying connective tissue. It can be distinguished from SCC by the coexistence of an exuberant inflammatory infiltrate and the lack of histological and cytological signs of malignancy.[6] Grunwald et al[3] stated that horny pearls are more frequent in SCC but can be seen in PESH.

Close clinicopathological correlation beside good communication between attending physicians and pathologists can avoid mistaken diagnoses and unnecessary therapeutic procedures.[7,8] Our case also emphasizes the importance of generous sampling and multidisciplinary approach in the differential diagnosis of cutaneous ulcers. A diagnosis of SCC may also be missed if histopathological examination is not included in this investigation.[9]

Concomitance of American tegumentary leishmaniasis and cutaneous neoplasms is theoretically possible and was recently reported,[10] but the patient's evolution and findings on second biopsy make this possibility extremely unlikely.

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REFERENCES

1. de Oliveira-Neto MP, Mattos MS, Perez MA, et al. American tegumentary leishmaniasis (ATL) in Rio de Janeiro State, Brazil: main clinical and epidemiologic characteristics. *Int J Dermatol*. 2000;39:506–514.
2. Dimier-David L, Ravisse P, Bustillos R, et al. [Histopathology of mucocutaneous leishmaniasis caused by *Leishmania (Viannia) braziliensis*]. *Ann Dermatol Venereol*. 1994;121: 387–392.
3. Grunwald MH, Lee JY, Ackerman AB. Pseudocarcinomatous hyperplasia. *Am J Dermatopathol*. 1988;10:95–103.
4. Hurwitz RM. Pseudocarcinomatous or infundibular hyperplasia. *Am J Dermatopathol*. 1989;11:189–192.
5. Grevelink SA, Lerner EA. Leishmaniasis. *J Am Acad Dermatol*. 1996;34(2 pt 1):257–272.
6. Murphy GF, Elder DE. Non-melanocytic tumors of the skin. In: Rosai J and Sobin LH, ed. Atlas of tumor pathology. Washington, DC: Armed Forces Institute of Pathology; 1991. Available from the American Registry of Pathology.
7. Khorsandi-Ashtiani MT, Hasibi M, Yazdani N, et al. Auricular leishmaniasis mimicking squamous cell carcinoma. *J Laryngol Otol*. 2009;123:915–918.
8. Gacek MR, Gacek RR, Gantz B, et al. Pseudoepitheliomatous hyperplasia versus squamous cell carcinoma of the external auditory canal. *Laryngoscope*. 1998;108(4 pt 1): 620–623.
9. Fagundes A, Schubach A, de Paula CC, et al. Evaluation of polymerase chain reaction in the routine diagnosis for tegumentary leishmaniasis in a referral centre. *Mem Inst Oswaldo Cruz*. 2010;105:109–112.
10. Karabekmez FE, Duymaz A, Keskin M, et al. Squamous cell carcinoma on cutaneous leishmaniasis lesion. *Dermatol Surg*. 2008;34: 1742–1743.