P53 and Granzyme B may have a role in progression to malignancy in hypertrophic discoid lupus erythematosus

To the Editor: Hypertrophic discoid cutaneous lupus erythematosus (HDLE) is a rare form of chronic discoid cutaneous lupus erythematosus (DLE) characterized by epidermal hyperplasia rather than atrophy (Fig 1, *A* and *B*). Squamous cell carcinoma (SCC) can arise in scarring DLE lesions, but it occurs 10 times more often in HCLE.[1] When it arises as a complication of DLE, SCC shows a higher rate of recurrence (40% vs 20%), metastatic spread (26.9% vs 6%), and progression to death (26.1% vs 1%) when compared with SCC in skin without DLE.[2] To study the role of *p53* and COX-2 protein expression as well as inflammatory and anti-inflammatory markers in dermal inflammatory cells and keratinocytes in the process of carcinogenesis in HDLE, we reviewed retrospectively the clinical, epidemiological, and histological characteristics of skin biopsies of 15 patients with HDLE, hospitalized from 1993 to 2012 at the UNICAMP Outpatient Clinic, and matched their data with those of 17 patients with DLE, controlled for sex, age, and body site.

All samples were sectioned again for immunohistochemical techniques (Fig 1, *C* to *E*). At least 1000 cells were recorded, and the ratio of the number of immune-stained cells/total was obtained using ImageJ software. Clinical data were captured from the patients' charts, and the results were analyzed using SAS System for Windows.

No patient in either group had concomitant systemic disease. The lesions in 3 patients out of 15 in the HDLE group progressed to well-differentiated SCC, but no recurrence or metastatic spread occurred. Comparing patients with HDLE and DLE, no significant differences were found in the duration of the disease and the immune expression of *CD8*, *perforin*, *granzyme A*, *granulysin*, *CD4*, *Fox-P3*, and *COX-2*. However, in HDLE, the immunoexpression of granzyme B and *p53* was significantly higher (Table I).

P53 protein suppresses genomic instability triggering apoptosis. In the skin, *p53* expression increases after DNA damage occurs from exposure to ultraviolet light. Chronic or repeated exposure to UV-B, in turn, leads to mutations in *p53*. Studies show that p53 detected by immunohistochemistry is the product of a mutant gene, which gives it a longer half-life allowing its visualization in the nucleus.[3] The altered protein is not able to correct the mutagenic errors that occur during the processes of apoptosis and cellular hyperproliferation that characterize HDLE. Granzymes are proteases present in the granules of cytotoxic T lymphocytes, involved in immune-mediated cell death. Both T-CD4 and T-CD8 lymphocytes express granzyme B. It is possible that granzyme B acts on the epithelial hyperproliferation of HDLE, as described in other inflammatory skin diseases such as lichen planus, psoriasis, and allergic contact dermatitis,[4] and could possibly play a role in epithelial hyperplasia and the development of carcinoma in HDLE.[5] The number of HDLE patients studied is small, which is a limitation of this study

Apoptotic mechanisms and cytotoxic cell damage are involved in the genesis of cutaneous lupus and may be associated with the type of lesion and progression to malignancy. Immunohistochemistry may potentially identify high-risk lesions. Larger studies to validate these findings, however, are needed.

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Conflicts of interest

None disclosed.

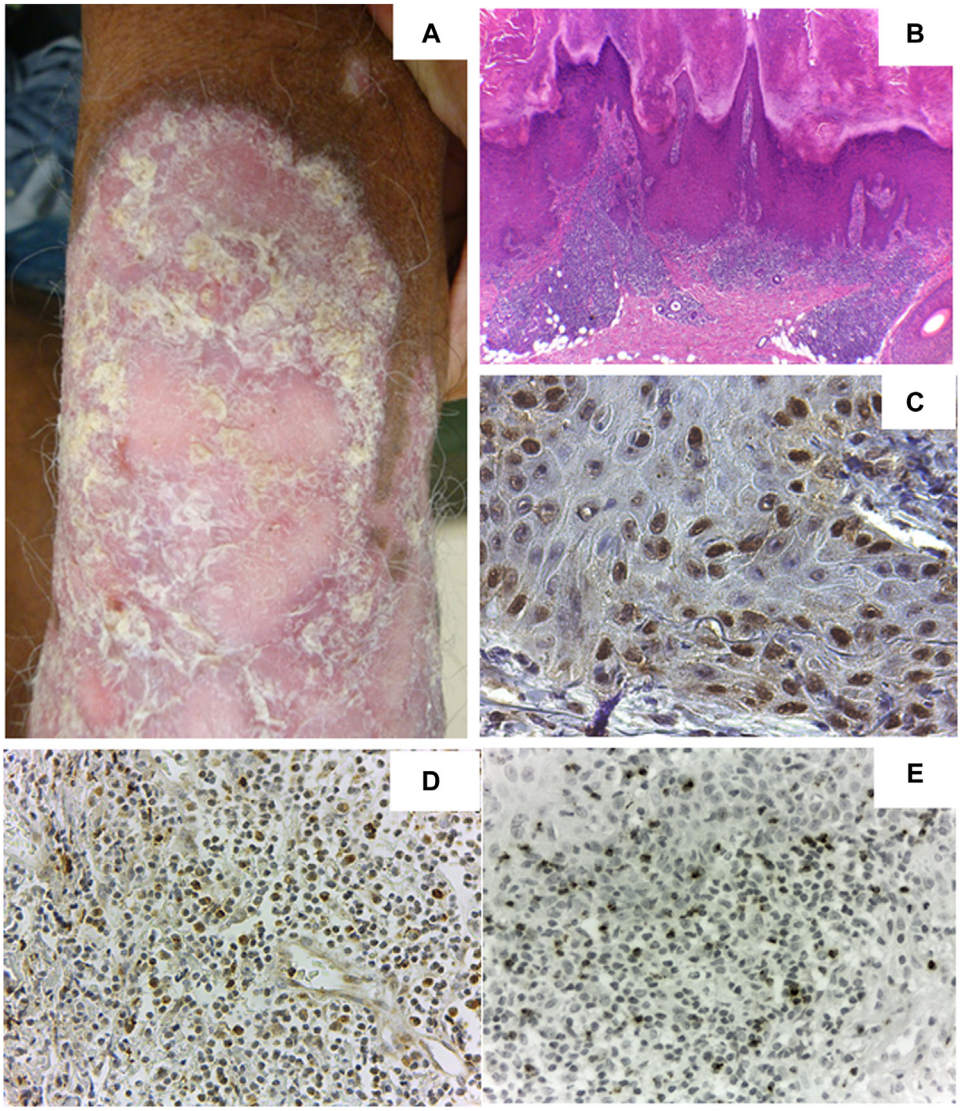

Fig 1. A, Hypertrophic cutaneous discoid lupus erythematosus (HDLE)- a forearm lesion showing intense hyperkeratosis, especially at the border and central skin atrophy. **B,** HDLE-histopathology shows hyperkeratosis, papillomatosis, epidermal hyperplasia, and inflammatory infiltrate, located in the perivascular and periadnexal location as well as the superficial and reticular dermis and epidermal-dermal junction. **C,** p53-immunostained keratinocytes in an HDLE biopsy. **D,** Granzyme B-immunostained inflammatory cells in an HDLE biopsy. **E,** Granzyme B-immunostained inflammatory cells in a DLE skin biopsy. (Original magnifications: **B**, ×40; **C**, ×400; **D** and **E**, ×200.)

Table I. Immunohistochemical results in DLE and HDLE patients

Immunomarker	DLE (n = 17)*	HDLE (n = 15)*	P value
Granzyme B mean	16.95 ± 20.85	45.14 ± 38.27	.0453
Granzyme B median	7.47 (2.0-85.80)	33.63 (1.5-96.89)	
P53 area mean	102.26 ± 30.01	147.69 ± 57.54	.0174
P53 area median	98.25 (53.09-161.25)	117.41 (77.9-254.55)	

Mann-Whitney test for continuous variables.
HDLE, Hypertrophic discoid cutaneous lupus erythematosus; *DLE*, discoid cutaneous lupus erythematosus.
*Ratio of the number of immune-stained cells/total.

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