Capcetabine-Induced Discoid Cutaneous Lupus☆

Lupus cutáneo discoide inducido por capecitabina

To the Editor:

Capecitabine, a prodrug of 5-fluorouracil (5-FU), is a chemotherapeutic agent that is administered orally. It is absorbed in the intestine and subsequently undergoes a series of enzymatic transformations via the thymidine phosphorylase pathway to produce the biologically active metabolite 5-FU.[1]

Recent years have seen an increase in capecitabine use, mainly for the treatment of cancer of the gastrointestinal tract and breast, owing to its oral route of administration and its better toxicity profile compared with 5-FU, which is associated with a higher incidence of serious adverse effects. The most frequent cutaneous adverse effect of capecitabine is palmoplantar erythrodysesthesia.[2] Cases of cutaneous lupus (mainly the subacute form) have also been associated with capecitabine treatment.

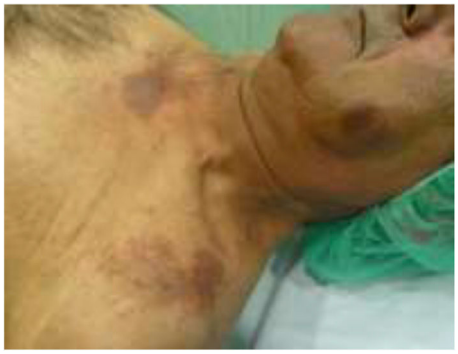

Figure 1 Erythematous–violaceous plaques on the face and upper chest.

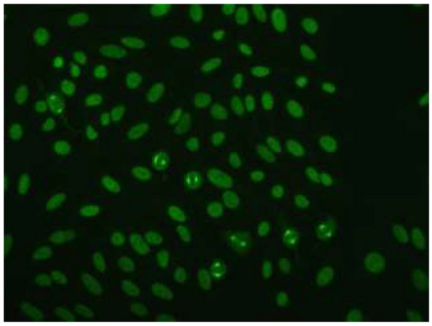

Figure 2 Indirect immunofluorescence for anti-NuMA 1: staining of nuclear granules and mitotic spindle fibers. Image courtesy of Dr. Eiras (Department of Immunology of the University Hospital Complex of Santiago de Compostela).

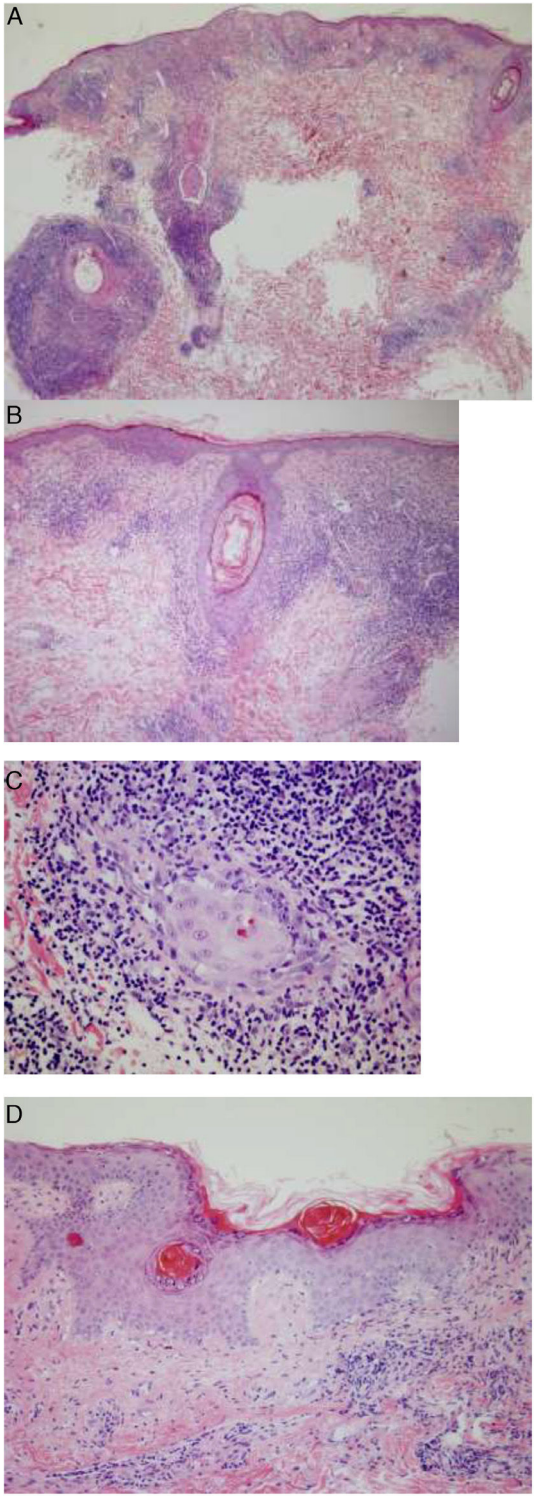

Figure 3 Histopathology of one of the lesions. A and B, Dense inflammatory infiltrate in the epidermis and pilosebaceous follicles. C, Infiltrate composed mainly of lymphocytes and histiocytes, with few plasma cells. D, Areas of epidermal atrophy, parakeratosis, and thickening of the basement membrane, alternating with other areas in which the architecture is better preserved.

☆ Please cite this article as: Moreiras Arias N, Rosón López ME, Suárez Peñaranda JM, Vázquez Veiga HA. Lupus cutáneo discoide inducido por capecitabina. Actas Dermosifiliogr. 2021;112:859–862.

Table 1 Cutaneous Lupus Associated With Capecitabine Treatment: Cases Published to Date

Authors	Histological Findings	Immunological Findings	Diagnosis	Latency Period	Lesion Progression After Discontinuing Treatment
Weger et al[5] 2007	Epidermal atrophy, interface dermatitis with cytolytic changes in basal layer keratinocytes, and marked mucinosis	Anti-Ro+	Subacute cutaneous lupus	7 d	Resolution in 6 wk
Merlin et al[6] 2008	Epidermal atrophy, liquefaction of the basal layer, perivascular and perifollicular lymphoid infiltrate	ANA+ Anti-DNA− Anti-ENA− Anti-Ro− Anti-La−	Discoid cutaneous lupus	3 mo	Resolution in 4 wk
Fernandes et al.[7] 2009	Interface reaction, vacuolar degeneration of the basement membrane, dyskeratosis, perivascular lymphocytic infiltrate, and interstitial mucin deposition	ANA+ Anti-histones + Anti-Ro+	Subacute cutaneous lupus	2 wk	Resolution in 4–6 wk
Floristan et al[8] 2009	Interface dermatitis with vacuolar degeneration of the basal keratinocyte layer	ANA+ Anti-Ro+ Anti-histones−	Subacute cutaneous lupus	3 wk	Resolution in 2 wk
Kindem et al[9] 2013	Epidermal atrophy with necrotic keratinocytes, vacuolar degeneration, perifollicular and perivascular lymphohistiocytic infiltrate in the dermis, and marked mucinosis	ANA+ Anti-Ro+ Anti-La− Anti-DNA− Anti-histones −	Subacute cutaneous lupus	10 d	Resolution in 3 wk
Ko et al[10] 2013	Interface dermatitis with basal hydropic changes, perivascular lymphocytic infiltrate, and interstitial mucin deposits	ANA+ Anti-Ro+ Anti-La+	Subacute cutaneous lupus	1 mo	Resolution
Fongue et al.[11] 2014	Epidermal atrophy with focal necrosis of keratinocytes, thinning of the basement membrane, perivascular lymphocytic infiltrate, and mucin deposits in the reticular dermis	ANA+ Anti-Ro+	Subacute cutaneous lupus	4 mo	Resolution in 3 wk
Li et al[12] 2014	Basal layer hydropic degeneration, perivascular lymphohistiocytic infiltrate, and abundant dermal mucin deposits	ANA+ Anti-Ro+ Anti-La+	Subacute cutaneous lupus	2 wk	Resolution in 12 wk
Kim et al[13] 2016	Vacuolar degeneration of the basal epidermal layer, periappendicular lymphocytic infiltrate, and mucin deposition in the dermis	ANA+ Anti-Ro+	Subacute cutaneous lupus	6 wk	Resolution
Present case, 2018	Epidermal and perianexial lymphohistiocytic infiltrate, dyskeratotic keratinocytes, and mucin deposition in the reticular dermis	ANA+ Anti-DNA− Anti-ENA− Anti-histone−	Discoid cutaneous lupus	5 mo	Resolution in 12 wk

Abbreviations: ANA, antinuclear antibody; ENA, extractable nuclear antigen.

We present the case of a 62-year-old man who was referred from the oncology to the dermatology department for assessment of pruritic skin lesions on the face and chest that had appeared 2 months earlier. His personal history included high blood pressure, dyslipidemia, and hyperuricemia, for which he had been receiving the same treatment for several years. The patient also had esophageal squamous cell carcinoma with bone metastasis, for which he had started capecitabine treatment 7 months earlier.

The physical examination revealed round erythematous plaques (approximately

3 cm) with focal desquamation located on the cheeks. Two larger erythematous–violaceous plaques were located on the upper chest (Fig. 1). No other lesions of interest were detected on the rest of the examined skin surface.

Based on the characteristics of the lesions, the following possible diagnoses were considered: cutaneous lupus, Sweet syndrome, fixed drug eruption, and cutaneous lymphoma. Blood tests and an immunological study revealed positive antinuclear antibodies (titer, 1:1280), with a NuMA-1-type fluorescence pattern (Fig. 2). The patient was negative for anti-DNA, anti-ENA (extractable nuclear antigen), and anti-histone antibodies.

One of the lesions was biopsied for histology, which showed a dense inflammatory infiltrate in both the epidermis and the pilosebaceous follicles composed mainly of lymphocytes and histiocytes, with few plasma cells. Focal dyskeratotic keratinocytes were also identified. Areas with epidermal atrophy, parakeratosis, and thickening of the basement membrane were also evident, alternating with other areas with better preserved architecture. Moderate mucin deposits were observed in the reticular dermis (Fig. 3).

Based on these findings a diagnosis of capecitabine-induced discoid cutaneous lupus was established. Capecitabine treatment was discontinued and replaced with the combination of carboplatin and placitaxel, which resulted in gradual improvement of the lesions and resolution 3 months later, leaving residual hyperpigmentation.

Drug-induced lupus erythematosus consists of the appearance of cutaneous signs compatible with lupus (both systemic and limited cutaneous forms), coinciding with the introduction of a new drug. This condition can be triggered by many drugs. Latency can range from a few weeks in some cases of subacute cutaneous lupus erythematosus to more than 6 months in chronic cases. Clinical signs usually resolve after discontinuation of the causative drug. The etiology remains unknown, although it is thought to be influenced by both individual susceptibility and metabolism of the drug in question.[3]

Drug-induced chronic cutaneous lupus erythematosus is an uncommon disease. It is characterized by erythematous squamous lesions that are located predominantly in photoexposed areas and tend to resolve leaving an atrophic scar. This condition has been associated with capecitabine, 5-FU, and anti–tumor necrosis factor agents (adalimumab, infliximab).[3]

The immunological profile usually reveals positivity for antinuclear antibody (ANA) only. In our case, immunohistochemistry revealed a characteristic ANA fluorescence pattern known as NuMA-1. This is a rare ANA subtype (<1%) that targets a mitotic spindle protein, and is mainly associated with autoimmune diseases (e.g. Sjögren syndrome, systemic lupus erythematosus) and, to a lesser extent, infections and neoplastic processes.[4]

At least 9 cases of cutaneous lupus erythematosus associated with capecitabine treatment have been described to date,[5–13] only one of which corresponds to discoid lupus (Table 1).

Therefore, although rare, capecitabine can induce discoid cutaneous lupus and this diagnosis should be suspected in patients who are treated with this drug and present a compatible clinical picture and concordant immunology and histology findings.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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https://doi.org/10.1016/j.adengl.2021.07.022

Secondary Amyloid Deposition in Pigmented Poroma☆

Depósito de amiloides secundario en poroma pigmentado

Dear Editor,

Secondary amyloid deposition is occasionally observed in both benign and malignant skin tumors; however, amyloid deposition in association with sweat gland neoplasms is rare.[1,2] We herein describe a case of secondary amyloid deposition in pigmented poroma.

A 78-year-old Japanese female visited our department, complaining of a nodule on the foot which appeared one year previously. A physical examination revealed a 13-mm diameter, well-circumscribed brownish nodule on the inner side of the right foot (Fig. 1a). Dermoscopic examination showed dark-brown, globe-like structures with polymorphous and hairpin vessels (Fig. 1b). After making a diagnosis by punch biopsy, the nodule was surgically removed under local anesthesia. Histological features showed cords of tumor cells extending from the epidermis to the mid-dermis (Fig. 2a). The tumor cells had basophilic cells with small round nuclei and cuticular cells with ductal differentiation showing positive CEA staining (Fig. 2b). Increased number of melanocytes was observed within the nests, which were confirmed by Fontana-Masson and MART-1 (Fig. 2c). The tumor nests contained abundant melanin deposition, and melanophages were also observed in the stroma (Fig. 2d). Of note, a number of circumscribed massive eosinophilic materials were detected within the stroma (Fig. 2d), which were positive for Congo-red and Dylon stain (Fig. 2e), as well as anti-cytokeratin CK5 antibody (Fig. 2f). Systemic amyloidosis was denied.

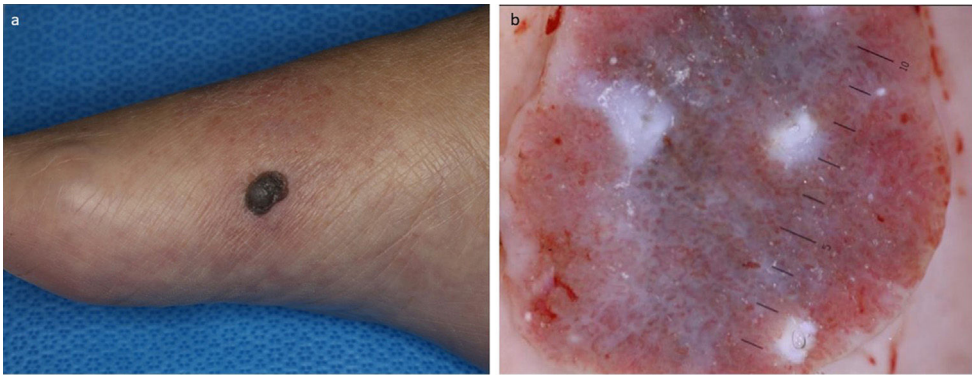

Figure 1 A well-circumscribed brownish nodule on the inner side of the right foot (a). Dermoscopy revealed globe-like structures with polymorphous vessels (b).

☆ Please cite this article as: Igari S, Ito T, Ishikawa M, Hiraiwa T, Yamamoto T. Depósito de amiloides secundario en poroma pigmentado. Actas Dermosifiliogr. 2021;112:862–864.