Acquired perforating dermatosis in the setting of hepatocellular carcinoma

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INTRODUCTION
Acquired perforating dermatosis was first described by Rapini et al1 in 1989 as a secondary type of perforating dermatosis in adults with systemic disorders, and its histopathologic findings included transepithelial elimination of elastic and collagen fibers.

Currently, the estimated incidence is 2.53 per 100,000 inhabitants per year, but it is believed that many cases remain undiagnosed. Both sexes may be affected, and it usually appears during the fifth decade of life.2

Although the etiology is not fully understood, acquired perforating dermatosis is associated with systemic diseases, mainly diabetes mellitus and chronic renal disease.3

The association with liver and oncological diseases has become increasingly frequent, suggesting that it can manifest as a paraneoplastic syndrome.3

The largest retrospective study of acquired perforating dermatosis reported that 9.1% of the reviewed patients presented with a solid or lymphoproliferative malignancy.2

Herein, we report the case of a patient with acquired perforating dermatosis that revealed a diagnosis of multinodular hepatocarcinoma, which led to early treatment. To our knowledge, this is the fourth case to be published in the international literature.

CASE REPORT
A 67-year-old man presented with a 7-month history of body-disseminated papules and nodules associated with intermittent pruritus. The patient’s medical history included systemic arterial hypertension, type 2 insulin-dependent diabetes mellitus, hyperuricemia, smoking, and alcohol abuse; his medications included olmesartan 20 mg daily, atenolol 100 mg daily, linagliptin 2.5 mg twice daily, metformin 850 mg twice daily, and insulin glargine injection 40 IU daily.

Dermatologic examination revealed erythematous-violaceous papules and nodules, with elevated borders, central umbilation, and hyperkeratotic crusts, disseminated over the occipital, interscapular, lumbar, and lower limb regions (Fig 1). He presented with linear injuries on the lower limbs and reported a trauma by a pet scratch, compatible with the Köebner phenomenon.

Histopathologic findings included areas of epidermal hyperplasia with invagination, showing neutrophil exocytosis and parakeratosis. Around this area, verticalized dermal fibers were present with transepithelial migration and collection in the dilated lumen, and elastic fibers stained by the Verhoeff van-Gieson. The superficial dermis showed slight fibroplasia with focal giant cell reaction and slight perivascular lymphocytic inflammatory infiltrate (Fig 2). Tests for fungal elements using Grocott and periodic acid–Schiff staining and alcohol-acid-fast analysis using Ziehl-Neelsen staining were negative. Masson’s trichrome staining was negative for intraepithelial verticalized fibers. The diagnosis was compatible with elastic fiber-perforating dermatosis.
The laboratory tests revealed anemia as an underlying condition. The patient's laboratory results were as follows: Blood urea nitrogen, 43 mg/dL (normal range, 10-50 mg/dL); creatinine, 1.04 mg/dL (normal range, 0.6-1.10 mg/dL); aspartate aminotransferase, 66 U/L (normal range, < 40 U/L), alanine aminotransferase, 62 U/L (normal range, < 41 U/L), gamma glutamyl transferase, 728 mg/dL (normal range, 12-73 U/L), alkaline phosphatase, 322 mg/dL (normal range, 40-129 U/L), and albumin, 2.4 g/dL (normal range, 3.5-5.2 g/dL). The international normalized ratio was 1.2, and total and indirect bilirubin was 0.88 mg/dL and 0.15 mg/dL, respectively. The alpha fetoprotein concentration was 322 μg/L, and lipase and amylase levels were normal. Serology was negative for hepatitis B, hepatitis C, HIV, and syphilis; HbA1C was 6%, and carbohydrate antigen 19-9 was increased.

Abdominal computed tomography showed 3 focal lesions, compatible with multinodular hepatocellular carcinoma and alcoholic liver cirrhosis (Child-Pugh A; Fig 3).

The patient was treated with hydroxyzine 25 mg daily, prednisone 20 mg daily, methylprednisolone aceponate cream twice daily, and was subject to superselective transarterial chemoembolization using DC-Beads 100-300 μm and doxorubicin. Follow-up arteriography showed devascularization of the nodules and preservation of the remaining nontarget arterial vessels.

The patient's skin manifestations showed improvements, presenting a good response to transarterial chemoembolization, with no relapse within 1 month of treatment. He is currently being monitored by the oncology team due to the risk of recurrence.
DISCUSSION

Cases of acquired perforating dermatosis associated with liver and oncological diseases are increasing in frequency. A retrospective study reported that liver diseases are the third most frequently associated disorder with perforating dermatosis, following non-insulin-dependent diabetes mellitus and chronic dialytic renal disease. Despite this, there are only 2 studies and one case report of acquired perforating dermatosis in the setting of hepatocarcinoma in the literature (Table I). In a previous case report, the onset of skin lesions and hepatocellular carcinoma were concomitant, and a subsequent remission and recurrence of both diseases occurred simultaneously as well. The same temporal relationship with perforating dermatosis lesions has been reported during recurrence of other malignancies, favoring the hypothesis that it could play the role of a paraneoplastic dermatosis. Moreover, in all these cases, skin lesions were treated along with the underlying disease.

Most patients have more than one systemic disorder associated with perforating dermatosis. Diabetes mellitus and chronic renal disease can contribute to the etiopathogenesis and could play a role as confounders in our case report. Revisiting the literature, we found that renal diseases are predominantly associated with perforating dermatoses in patients who are undergoing the early stages of hemodialysis. In the setting of type 2 diabetes, retrospective studies showed that 72% to 88.2% of the patients were not undergoing insulin treatment, and 90.9% had a microvascular comorbidity. Our patient had never required hemodialysis and had been undergoing insulin treatment for his diabetes for 7 years.

Despite this, all patients with diabetes and chronic renal disease showed elimination of collagen fibers, which was a situation that was different from the one observed with the present patient, who presented elimination of elastic fibers, confirmed by Verhoeff van-Gieson staining.
The clinical variant compatible with the elimination of elastic fibers is serpiginous perforating elastosis. However, in our case, we noticed the absence of this serpiginous conformation, which has been reported by other authors as well. Perforating dermatosis may be underdiagnosed, since its appearance may be that of excoriation. Identifying the diagnosis is important, however, as 9.1% of patients may have an underlying malignancy. In this case report, the correct dermatological diagnosis resulting in the early investigation of malignancies provided for timely diagnosis and management of the hepatocarcinoma, before the stigma of liver disease or metastasis had occurred. More studies are needed to determine whether

**Fig 3.** Abdominal computed tomography scan. A, Abdominal computed tomography revealed features compatible with chronic liver disease with 3 focal lesions: A hypervascularized nodule with washout in segment VIII measuring 5.6 cm (LIRADS 5), a hypervascularized nodule with washout in segment VIII measuring 3.6 cm (LIRADS 5), a hypervascularized nodule with washout in segment VII measuring 2.0 cm (LIRADS 5), and a hypervascularized nodule without washout in segment V measuring 0.7 cm (LIRADS 3). Periaortic and interaortocaval lymph nodes were slightly increased in number, measuring 1.5 x 0.9 cm. The diagnoses were multinodular hepatocellular carcinoma and alcoholic liver cirrhosis (Child-Pugh A). B, Abdominal computed tomography compatible with hepatocarcinoma LIRADS 5.

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**Table 1.** Malignancies reported with concomitant perforating dermatosis

| Associated tumor | Perforating material | Concurrent manifestations | Follow up | Reference |
|------------------|----------------------|--------------------------|----------|----------|
| Hepatocarcinoma  | Collagen and elastic fibers | Papulonodular lesion associated with pruritus and excoriation | Remission of lesions after chemoembolization | Lee et al (1996) |
| Periampullary carcinoma | Collagen fibers | Umbilicated hyperkeratotic papules on the trunk and extremities | Relieved lesions after treatment with NB-UVB and topical steroids | Kawahara et al (2018) |
| Hepatocarcinoma  | Collagen fibers | Papular lesions associated with jaundice | Remission after surgery | Chae et al (1998) |
| Metastatic liver cancer | Collagen fibers | Multiple crusted dome-shaped papules on the back | Patient died soon after diagnosis | Kilic et al (2006) |
| Metastatic renal cell carcinoma | Collagen fibers | Generalized erythematous papules with crusting | Patient died 3 months after diagnosis | Bong et al (2009) |

NB-UVB, Narrowband ultraviolet B irradiation.
perforating dermatosis is a paraneoplastic disorder. We believe that our case report can contribute to increasing the arsenal of data on systemic diseases in the context of perforating dermatoses.

Conflicts of interest
None disclosed.

REFERENCES
1. Rapini RP, Herbert AA, Drucker CR. Acquired perforating dermatosis. Evidence for combined transepidermal elimination of both collagen and elastic fibers. Arch Dermatol. 1989; 125(8):1074-1078.
2. García-Malinis AJ, Del Valle Sánchez E, Sánchez-Salas MP, Del Prado E, Coscojuela C, Gilaberte Y. Acquired perforating dermatosis: clinicopathological study of 31 cases, emphasizing pathogenesis and treatment. J Eur Acad Dermatol Venereol. 2017;31(10):1757-1763.
3. Kılıç A, Gönül M, Cakmak SK, Gül U, Demiriz M. Acquired reactive perforating collagenosis as a presenting sign of hepatocellular carcinoma. Eur J Dermatol. 2006;16(4):447.
4. Saray Y, Seçkin D, Bilezikçi B. Acquired perforating dermatosis: clinicopathological features in twenty-two cases. J Eur Acad Dermatol Venereol. 2006;20(6):679-688.
5. Kawahara S, Mitoma C, Murai M, Furue M. Acquired perforating collagenosis in a non-diabetic patient with advanced prostate carcinoma: a review of perforating dermatosis associated with malignancy. J Dermatol. 2018;45(8):e219-e220. https://doi.org/10.1111/1346-8138.14272
6. Kurban M, Uthman I, Kibbi AG, Ghosn S. Acquired perforating dermatosis heralding metastatic renal cell carcinoma to the liver. Int J Dermatol. 2008;47(10):1038-1040. https://doi.org/10.1111/j.1365-4632.2008.03734.x
7. Kim SW, Kim MS, Lee JH, et al. A clinicopathologic study of thirty cases of acquired perforating dermatosis in Korea. Ann Dermatol. 2014;26(2):162-171. https://doi.org/10.5021/ad.2014.26.2.162
8. Lee YS, Vijayasingam S, Tan YO, Wong ST. Acquired perforating dermatosis associated with recurrent hepatocellular carcinoma. Int J Dermatol. 1996;35(10):743-745.
9. Chae KS, Park YM, Cho SH, Cho BK. Reactive perforating collagenosis associated with periampullary carcinoma. Br J Dermatol. 1998;139(3):548-550. https://doi.org/10.1046/j.1365-2133.1998.02435.x
10. Bong JL, Fleming CJ, Kemmett D. Reactive perforating collagenosis associated with underlying malignancy. Br J Dermatol. 2000;142(2):390-391. https://doi.org/10.1046/j.1365-2133.2000.03326.x