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Sclerosing acral skin perineurioma: clinicopathologic study of ten cases (eight classical and two with xanthomatous changes)

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Abstract

Introduction: *Perineurioma is an infrequent and benign cutaneous neoplasm characterized by proliferation of perineurial cells. It is classified into two main types: intraneural and the extraneural or soft tissue perineurioma, in which the sclerosing variant is included. Sclerosing perineurioma is more frequently found on acral skin. Clinically, they are well-circumscribed, skin colored, nodular tumors.* **Objective:** *Describe and communicate clinicopathologic findings from a case series of sclerosing acral perineurioma.* **Material and Methods:** *This is a clinical, morphological and immunohistologic case study of eight patients with the diagnosis of sclerosing perineurioma.* **Results:** *It included five men and five women, with ages ranging between nine and 66 years. All of them had lesion on acral skin. At microscopy study, the lesions showed a proliferation of epithelioid and spindle-shaped perineurial cells, arranged in small aggregates and short fascicles between thickened collagen bundles. Immunohistochemistry studies revealed that the proliferating cells expressed EMA, Claudin-1 and Glut-1, and were negative for S-100 protein.* **Conclusions:** *It is important to report these infrequent skin tumors, so they can be taken into account in the differential diagnoses of acral lesions.*(Gac Med Mex. 2015;151:280-5)

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KEY WORDS: *Perineurioma. Perineurium. EMA. Glut-1. Claudin-1.*

Introduction

Perineurioma is a benign and infrequent neoplasm characterized by clonal proliferation of peripheral nerve perineurial cells. This neoplasm was first described in 1978 by Lazarus and Trombetta[1]. Currently, it is classified in two main clinicopathological types: intraneural perineurioma and soft-tissue perineurioma[2], which includes the sclerosing, plexiform and reticular variants[3,4], each one with morphological features of their own[5].

Microscopically, proliferating cells in perineurioma show membranous immunoreactivity for EMA, GLUT-1, vimentin, claudin-1, laminin and type IV collagen, and are at the same time negative to immunolabeling for S-100 protein[6-9]. Variable expression of the CD-34 marker has also been described in some cases[10].

The sclerosing variant of perineurioma, described in 1997 by Fetsch, occurs more frequently on acral skin of young adults[11,12], although cases in other anatomical sites, such as the upper and lower limbs, the lips and oral mucosa, have also been described[10,13]. Clinically, they are semi-spherical neoformations with papular or

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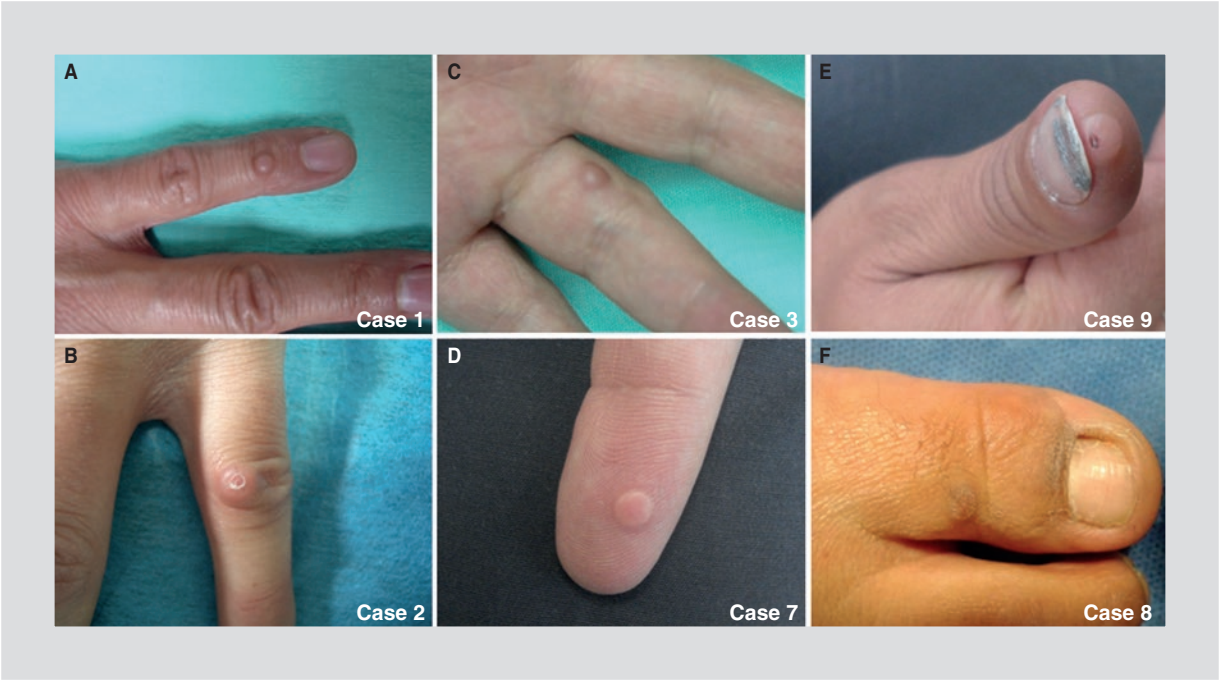

Figure 1. *Clinical appearance of six cases:* **A:** *case 1: distal interphalangeal joint lesion.* **B:** *case 2: proximal interphalangeal joint lesion.* **C:** *case 3: proximal phalanx lateral internal side lesion.* **D:** *case 7: distal phalanx palmar aspect lesion.* **E:** *case 9: right thumb pad lesion.* **F:** *case 8: right foot, first toe dorsal aspect lesion.*

nodular appearance, skin-colored and well circumscribed. As these are uncommon lesions and they have no distinctive clinical features, they are rarely considered within probable differential diagnoses[14].

Objectives

To make a description of clinical findings in a case series of patients with sclerosing acral skin perineurioma with the purpose of diffusing these results, which, at the moment of this communication, have only been published as isolated reports in indexed medical literature.

Materials and methods

The cases of nine patients with acral skin neoformations and one with a lesion in the knee were reviewed. Seven patients attended the Dermatology Department outpatient clinic of the Dr. Manuel Gea González Hospital, and three, the private practices of specialist doctors (Figs. 1 A, B, C and D and Fig. 2); the main referral diagnoses included myxoid cyst, epidermoid cyst and digital fibroma.

Demographic and clinical data of all patients were recorded. All biopsies were fixed in 10% formalin, to be processed with standard histological technique, and stained with hematoxylin and eosin for observation with optical microscopy. On 5-µm paraffin sections, with the avidin-streptavidin-peroxidase technique, a panel of antibodies was applied, including: EMA, GLUT-1, claudin-1, S-100 protein, CD-68 and CD-34 with appropriate positive and negative controls.

Results

Clinical characteristics and evolution times of the patients are summarized in table 1.

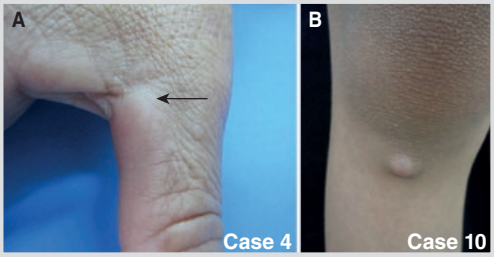

Figure 2. A: *sclerosing perineurioma with deeper location in the dermis, with slightly elevated subcutaneous nodular appearance.* **B:** *knee lesion (case 10).*

Table 1. Clinical manifestations of patients with sclerosing perineuriomas

Case	Sex	Age	Topography	Size	Morphology	Pain	Time	Referral diagnosis
1	Male	46 years	Left hand, 5th finger, dorsal aspect, distal interphalangeal joint	3 mm	Semi-spherical	Tenderness	1 year	Epidermoid cyst, ganglion, papular granuloma annulare
2	Male	31 years	Left hand, 5th finger, proximal interphalangeal joint	5 mm	Semi-spherical	No	2 years	Myxoid cyst, digital fibroma
3	Female	54 years	Right hand, ring finger, lateral internal side, proximal phalanx	4 mm	Semi-spherical	Yes	6 months	Myxoid cyst, myxoma, spiradenoma
4	Female	60 years	Right hand, palmar aspect, base of thumb	1 cm	Subcutaneous, exoendophytic	No	2 years	Inclusion cyst, giant-cell tumor
5	Male	57 years	Right hand, palm	8 mm	Prominent	Sometimes	Long	Solitary neurofibroma
6	Female	40 years	Right hand, 1st interdigital fold	1 cm	Subcutaneous, exo-endophytic	No	1 year	Epidermoid cyst
7	Male	45 years	Left hand, index finger palmar aspect	5 mm	Semi-spherical	No	1 month	Inclusion cyst, fibroma
8	Female	28 years	Right foot, dorsal aspect of great toe	6 mm	Semi-spherical	No	1 year	Dermatofibroma
9	Female	28 years	Right hand, thumb pad, close to hyponychium	8 mm	Semi-spherical	Yes	8 years	Digital fibroma, skin adnexal neoplasm
10	Male	9 years	Right knee, anterior side	8 mm	Semi-spherical	No	3 years	Neurofibroma

Histopathological results

The lesions were histologically very similar in all cases. They were well circumscribed, non-encapsulated neoformations with a thick and dense collagen stroma (Fig. 3 A). Proliferating cells showed an oval or spindle-like and elongated shape, with granular chromatin nuclei and small nucleolus (Fig. 3 B). They were grouped in small clusters or arranged in short bundles showing a swirly or trabecular appearance. Some perineurial cells were surrounding pre-existing nerve bundles, giving an appearance of "onion skin layers" (Fig. 4). No areas of necrosis, mitosis, pleomorphism or nuclear hyperchromasia were found. In two cases, foamy histiocytes were also found interspersed with fusiform cells, as well as cholesterol clefts formation (Fig. 5).

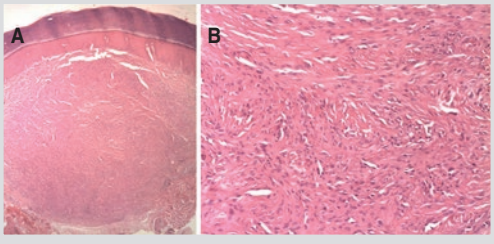

Figure 3. *Sclerosing acral skin perineurioma.* **A:** *well circumscribed, non-encapsulated neoformation (H&E 2X).* **B:** *oval and spindle-shaped perineurial cells, grouped in small clusters (H&E 10X).*

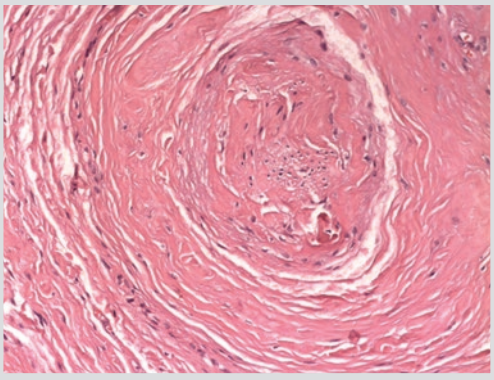

Figure 4. *Perineurial cells surround pre-existing nerve bundles giving an appearance of "onion skin layers" (H&E 10X).*

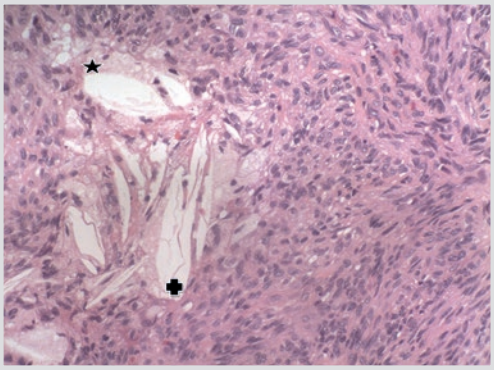

Figure 5. *Foamy histiocytes (*) interspersed with fusiform cells and cholesterol clefts formation (+).*

With immunolabeling, proliferating cells were diffusely positive for EMA and claudin-1. In four cases, they were positive for GLUT-1, and all were S-100 protein-negative (Fig. 6). In a single case, neoplastic cells were reactive to CD-34 immunolabeling and the foamy histiocytes found in two cases were enhanced with CD-68. The immunolabeling findings are reported in table 2.

Discussion

Tumors of the nervous tissue are formed by one or several normal cellular components of the peripheral nerve, with schwannomas and neurofibromas being the most common examples. Perineuriomas are rare tumors originating in the perineurium, a layer of flattened cells that lines the nerve fascicles[15].

The perineurium, also known as sheath of Henle or laminar sheath of Ranvier, is the structure that individually surrounds each nerve bundle and is composed by 8-15 continuous perineurial-cell layers, which are concentrical to each fascicle and are bound to each other by tight junctions and hemidesmosomes[15,17,18]. This epithelium has direct continuity with the pia-aracnoid membrane, to which it has large morphological, ultrastructural and immunohistochemical resemblance, and has even been regarded by some authors as the peripheral counterpart of meningiomas[2,15].

Perineuriomas are classified in two main varieties: intraneural and extraneural[2]. The intraneural form, formerly known as localized hypertrophic neuropathy, is histologically characterized by a proliferation of perineurial cells that generate “bulb-like” or “onion skin” formations, whereas the extraneural or soft-tissue form

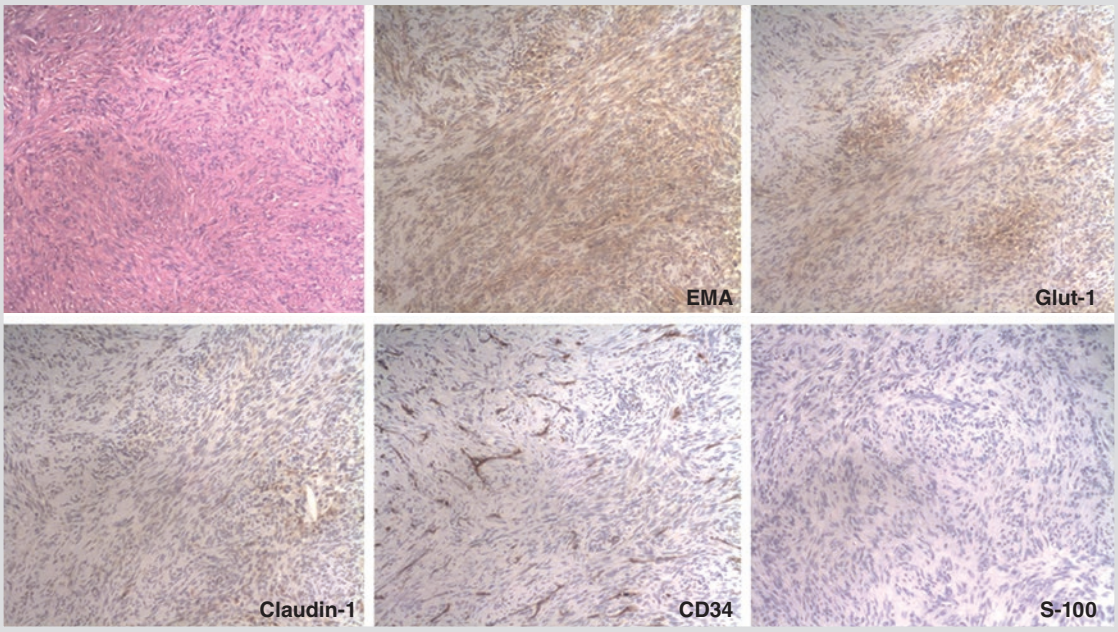

Figure 6. *Positive immunolabeling for EMA, GLUT-1 and claudin-1. S-100 protein and CD-34 are negative; the latter labels only blood vessels.*

Table 2. Immunohistochemical findings in patients with sclerosing perineurioma

Case	EMA	Claudin-1	GLUT-1	S-100	CD-68	CD-34
1	+	+	+	–	–	–
2	+	+	+	–	–	+
3	+	+	+	–	–	–
4	+	+	–	–	–	–
5	+	+	–	–	–	–
6	+	+	+	–	–	–
7	+	+	+	–	–	–
8	Weak	–	+	–	–	+
9	+	+	+	–	–	–
10	+	+	+	–	–	Perivascular

shows a swirling pattern that has certain variants depending on its histopathological features[2,3,13,16].

The extraneural or soft-tissue variety is the most commonly form found in the skin and it is also known as storiform perineurial fibroma. It is predominant in adult women and it is characterized by skin-colored, well circumscribed neoformations affecting the trunk and limbs.

In the light microscopy examination, a fusiform-cell mass with ovoid or elongated nuclei and eosinophilic cytoplasm, showing a swirly pattern, is observed[12]. By electron microscopy, the cells appear flattened, with thin (average thickness from 1 to 1.5 µm) bipolar cytoplasmic processes and show scarce organelles and close intercellular gaps including tight junctions and hemidesmosomes; additionally, they possess multiple pinocytic vesicles, predominantly distributed underneath the cell membrane[21,22].

This type of perineurioma can show certain variants, depending on the histological findings: cellular, atypical, sclerosing, reticular, plexiform, lipomatous, myxoid, hyaline, granular-cell conformation, with calcification or bone metaplasia[5,19,20].

In two cases of this study, vacuolated or foamy histiocytes and cholesterol clefts were found to be present. Vacuolated histiocytes were intensely positive with the CD-68 immunolabel and negative for the EMA, claudin-1 and GLUT-1 perineurial labels. These xanthomatous changes have only been briefly mentioned by Mentzel et al.[13], who describe the existence of small aggregates of xanthomatous cells with pale or granular eosinophylic cytoplasm in the stroma of one case of perineurioma. Both stromal sclerosis and the presence of macrophages and other inflammatory cells can be external trauma-related[24].

Perineurioma proliferating cells show membranous immunoreactivity for EMA, GLUT-1, vimentin, claudin-1, laminine and type IV collagen, and are negative for S-100 protein[6-9]. Variable expression of the CD-34 marker has also been described in some cases[10].

EMA, also known as episialine, belongs to a heterogeneous family of highly glycosilated transmembrane proteins, known as human milk fat globules, which are present in different cell lines. In the peripheral nerve, EMA differentiates the perineurium from Schwann cells[25].

Most mammal cells transport glucose via a family of transmembrane proteins known as glucose transporters (GLUT). Molecular clonation of these transporters has enabled identification of a family of related genes that codify for at least 13 proteins with a molecular weight of approximately 40-60 kDa, known as GLUT-1 to GLUT-13. By immunohistochemistry, GLUT-1 has been identified in different normal and neoplastic cells, as well as in the red blood cell membrane. In peripheral nerves, GLUT-1 is selectively expressed in perineurial cells of benign and malignant tumors[26].

Recently, claudin-1 has been identified as a perineurial-cell marker[27]. Claudins (from Latin *claudere,* "to close") are a group of approximately 20 integral membrane proteins, described in 1998 by Furose et al., which participate in cell binding[26]. In the peripheral nervous system, the expression of claudin-1 is restricted to the perineurial sheath[27,28].

In our cases, positive immunoreactivity was demonstrated for EMA, claudin-1 and GLUT-1, with most being negative for CD-34, S-100 and CD-68, thus confirming perineurial differentiation of these neoplasms. With histopathological findings of a tumor of fusiform cells in a swirling pattern, with areas of fibrosis and positive immunochemistry testing for perineurial tissue, it was possible to arrive to the final diagnosis of soft-tissue perineurioma with areas of fibrosis.

Conclusions

The importance of presenting this work consists in showing the macro- and microscopic characteristics of this type of tumours, which have a wide range of clinical and histological differential diagnoses. The first group of differential diagnoses includes intradermal nevus, dermatofibroma, angiofibroma, tendinous sheath fibroma, cysts, giant-cell tumor, epithelioid sarcoma, lipomas and neuromas, whereas the second group encompasses neurofibroma, dermatofibrosarcoma protuberans, myoepithelioma and, finally, sclerosing fibroma[10,12,14] and, therefore, these possibilities should be taken into consideration with patients presenting with similar lesions in acral zones, as well as making use of complementary techniques to corroborate the final diagnosis.

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