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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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 Trombetta¹. Currently, it is classified in two main clinicopathological types: intraneural perineurioma and soft-tissue perineurioma², which includes the sclerosing, plexiform and reticular variants³⁴, each one with morphological features of their own⁵.

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 protein⁶⁹. Variable expression of the CD-34 marker has also been described in some cases¹⁰.

The sclerosing variant of perineurioma, described in 1997 by Fetsch, occurs more frequently on acral skin of young adults¹¹,¹², although cases in other anatomical sites, such as the upper and lower limbs, the lips and oral mucosa, have also been described¹⁰,¹³. Clinically, they are semi-spherical neoformations with papular or
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\textsuperscript{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-\mu m 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).
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).

Table 1. Clinical manifestations of patients with sclerosing perineuriomas

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

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).
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...
shows a swirling pattern that has certain variants depending on its histopathological features\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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, laminine and type IV collagen, and are negative for S-100 protein\textsuperscript{6-9}. Variable expression of the CD-34 marker has also been described in some cases\textsuperscript{15}.

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\textsuperscript{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 perineural cells of benign and malignant tumors\textsuperscript{26}.

Recently, claudin-1 has been identified as a perineurial-cell marker\textsuperscript{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\textsuperscript{26}. In the peripheral nervous system, the expression of claudin-1 is restricted to the perineurial sheath\textsuperscript{27,28}.

Table 2. Immunohistochemical findings in patients with sclerosing perineurioma

<table>
<thead>
<tr>
<th>Case</th>
<th>EMA</th>
<th>Claudin-1</th>
<th>GLUT-1</th>
<th>S-100</th>
<th>CD-68</th>
<th>CD-34</th>
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<tbody>
<tr>
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<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>Perivascular</td>
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</table>
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 perineural 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 perineural 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. 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.

References