CASE REPORT

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Multiple asymptomatic cutaneous pilar leiomyoma *versus* spontaneous eruptive keloids – a case report

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Abstract

Cutaneous piloleiomyoma, angioleiomyoma and genital leiomyoma are variants of superficial cutaneous leiomyoma. The main purpose of this paper was to present clinical, histopathological and immunohistochemical diagnosis criteria for an unusual case of pilar leiomyoma in an 18-year-old male patient. The initial clinical aspect was very similar to spontaneous eruptive keloids: red-violet color, painless, aspect of "crab pincers" of some of the lesions, epidermis atrophy, telangiectasia, located on acneiform zones and compliance with cephalic extremity. The patient had no history of trauma, surgery or acne. Local treatment of one lesion was performed with cryotherapy using liquid nitrogen (-172^{0}C) together with intra-lesion steroid injections, occlusive dressings and silicone gel. Local therapy did not showed notable results, moreover the lesion become painful. Skin biopsy with histological and immunohistochemical analysis revealed the diagnosis of multiple cutaneous pilar leiomyoma without atypia. The particularity of the case stands in the atypical onset followed by explosive increasing of lesions number and the appearance of pathognomonic pain after local therapy.

Keywords: pilar leiomyoma, eruptive keloids, immunohistochemistry, hereditary leiomyomatosis and renal cell cancer (HLRCC).

Introduction

Muscle origin tumors are relatively rare in the skin. Striated muscle fibers are unusual tumors in the skin and the *World Health Organization* (WHO) classification from 2002 and 2006 contains only striated muscle hamartomas [1, 2].

In the skin smooth muscle, tissue is present in the hair erector muscles, hence pilar leiomyoma or piloleiomyoma and in the walls of blood vessels, where derived from vascular leiomyoma or angioleiomyoma. In anogenital skin areas may occur in the smooth muscle tissue, dartos muscle of the scrotum or in labia minora and majora. Another location of smooth muscle tissue is in nipple skin – areolar smooth muscle. From these locations may develop benign muscle tumors – leiomyomas or malignant – leiomyosarcoamas.

Cutaneous piloleiomyoma or pilar leiomyomas may present as a solitary lesion (especially in women) or multiple injuries (especially for men) [3]. Lesions can develop in the second or third decade, and rarely can be congenital [4].

To our knowledge, in literature there are only few cases presented, and none related to multiple lesions in a young male patient [5–8]. Usually, it involves the extremities, scalp or trunk. Multiple lesions of pilar leiomyomas are clinically characterized by a large number of nodular or papules lesions with diameters ranging from a few millimeters to 20 mm, reddish-brown in color, often are painful spontaneous and at palpation [9]. General microscopy architecture of the lesions shows a nodular tumor located in dermis, with irregular edges. Tumor proliferation consist of smooth muscle fibers arranged in fascicles, sometimes associated with nuclear pleomorphism or a small number of mitoses, without losing the benign character. Typical, the nuclei have cigar shape with blunted ends. Based on these criteria, the diagnosis usually is easy to determine in histology, but with high importance in clinical decision-making [10, 11].

The aim of this paper was to present clinical, histopathological and immunohistochemical diagnosis criteria for an unusual case of pilar leiomyoma in an 18-year-old male patient. The particularity of the case stands in the atypical onset followed by explosive increasing of lesions number and the appearance of pathognomonic pain after local therapy.

Case presentation

We present the case of an 18-year-old male patient, which was admitted in the Clinic of Dermatology, with asymptomatic papular-nodular rash, on acneiform areas: anterior and posterior chest, shoulders and the proximal 1/3 of arms consisting in over 200 injuries with onset during the last two years (Figure 1).

Local examination distinguished three types of lesions: (1) papules, slightly raised, colored similar with normal skin; (2) nodular red-purple lesions with diameter between 5 to 30 mm, well defined, firm to the touch, without inflammatory phenomena; and (3) nodular lesions with lateral extensions of "crab pincers" with epidermis atrophy,

discrete telangiectasia and appearance of reminiscent keloids (Figure 2).

No pathological findings were evidenced at the oral and maxillofacial and ENT (ear, nose and throat) examination. According to anamnesis, these three types of lesions evolved from papules, slightly raised colored similar to surrounding skin. Lesions were painless even at palpation. Personal medical history of trauma, surgery or acne was negative. History and clinical examination of family members revealed no similar lesions to those found on the patient. Full blood count tests revealed no pathological findings.

Initial clinical diagnosis was spontaneous eruptive keloids. Local treatment of one lesion was performed with cryotherapy using liquid nitrogen (-172^{0}C) together with intra-lesion steroid injections, occlusive dressings and silicone gel. Following these treatments, the lesion did not show any significant change and become painful spontaneously and at palpation. The number of injuries had increased and later included other areas: chest and upper limbs. Although the patient was young, we thought even that skin lesions represent metastases due to the eruptive and asymptomatic features.

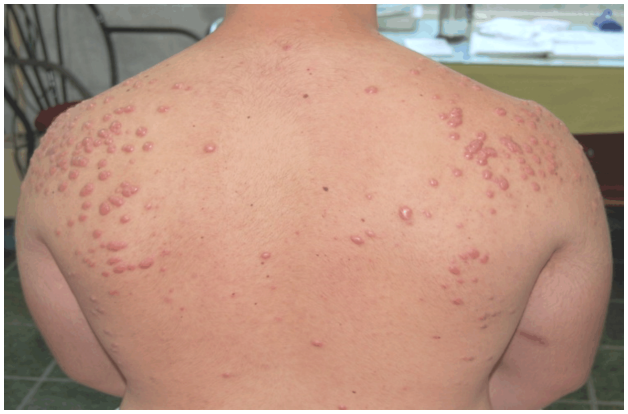

Figure 1 – ***Clinical aspects – pilar leiomyoma: multiple erythematous nodules and papules.***

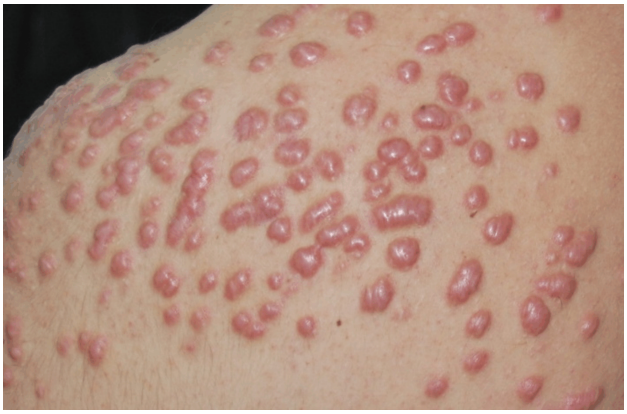

Figure 2 – ***Clinical aspects – pilar leiomyoma: erythematous nodules, close-up view.***

After patient and family informed consent for surgical excision, biopsy was performed from a series of five skin lesions in different clinical stages. Tissue was send for histological examination. The excised tissue fragments were fixed in 10% buffered formalin and they were processed using the histological classical method for paraffin-embedding blocks [12]. Briefly, the paraffin blocks were sectioned at 3–4 μm thick segments. For each block have been used Hematoxylin–Eosin (HE) staining and special stainings for collagen fibers: Van Gieson and Masson's trichrome. Subsequently, serial sections were performed and displayed on glass slides coated with poly-L-Lysine for the immunohistochemical examination. The immunohistochemical method used was the two-step technique with Streptavidin–Biotin–Peroxidase as secondary antibody, and the substrate chromogen used for visualizing the immunoreactions was DAB (3,3'-diaminobenzidine). The primary antibodies used were: S-100 protein (polyclonal, DakoCytomation, 1:500 dilution), α-SMA (alpha-smooth muscle actin) (clone 1A4, Dako, 1:50 dilution), desmin (clone D33, Dako, 1:100 dilution) [13].

There were examined five fragments of skin covered by a keratinized stratified squamous epithelium, showing normal appearance of epithelium or a slight hyperplasia of the epidermal rete ridges. In dermis, there was found a relatively well-defined tumor proliferation without capsule, composed of smooth muscle fibers arranged in bundles parallel or concentric. Cells were with eosinophilic cytoplasm, cigar shaped nuclei with blunt ends (Figure 3).

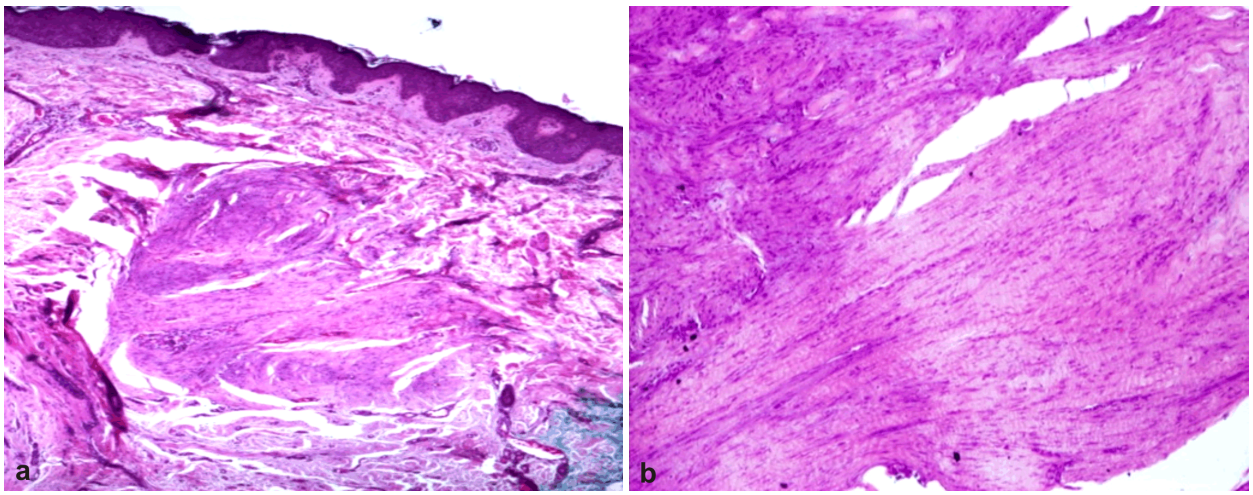

Figure 3 – ***Pilar leiomyoma: (a) Ill-defined tumor in the reticular dermis (HE staining, ×20); (b) The tumor cell nuclei with characteristically cigar shape (HE staining, ×40).***

No nuclear pleomorphism, mitoses or necrosis, typical for leiomyomas were found. Between tumor proliferation and epidermis remained an unaffected space. For positive and differential diagnosis, special stainings and immunohistochemistry were performed. Van Gieson and Masson's trichrome showed rare collagen fibers between smooth muscle fibers. Immunohistochemical tumor cells were strongly positive for α-SMA, focal positive for desmin and were negative for S-100 protein (Figure 4).

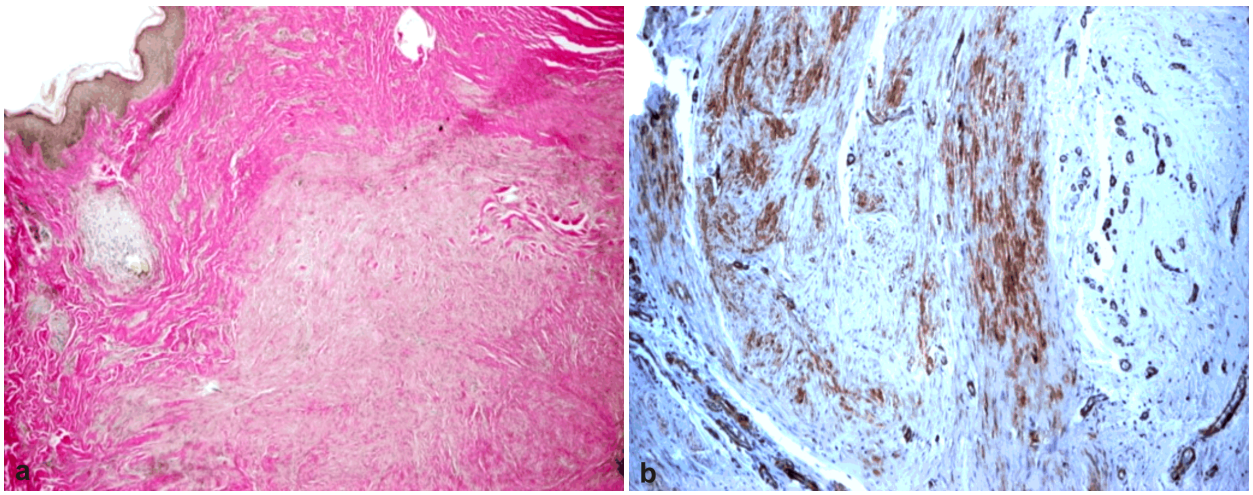

Figure 4 – ***Pilar leiomyoma: (a) The collagen fibers surrounding the tumor are colored in red (Van Gieson staining, ×20); (b) The tumor cells express α-SMA (Immunohistochemistry, ×40).***

Final histopathological diagnosis was multiple cutaneous pilar leiomyomas without atypia.

Based on final diagnosis, further clinical examinations were performed. Ultrasound examination and uro-CT (computed tomography) scan with contrast was without pathological findings. Human immunodeficiency virus (HIV) test was negative. Patient was referred to a genetic test to identify fumarate hydratase (FH) gene mutation, which can lead to association of pilar leiomyoma with renal tumors; unfortunately, long-term follow-up was not possible due to patient's migration in another country.

Discussion

The presented case is relevant for clinical decision-making, in the context of integrating all tools available: clinical, histological and immunohistochemical examinations, for a better case management. Due to the poorly related literature data on the subject and relatively rare appearance of this disease, is important to report all available cases in order to headlight a unitary management of disease. We presented an unusual case of pilar leiomyoma in an 18-years-old male patient, which is even rarely. The particularity of the case stands in the atypical clinical onset followed by explosive increasing of lesions number and the appearance of pathognomonic pain after local cryotherapy.

In terms of clinical appearance, we first considered differential diagnosis with spontaneous keloids eruption. Post-acne keloid scars were excluded from anamnesis, due to no previous presence of acne lesions. From anamnesis, physical and imaging examination, we could exclude neurofibromatosis type II that begins around the age of 20 years, also the patient undergone oral and maxillofacial and ENT examination, which revealed no hearing disorders with normal audiometric examination. Neurofibromatosis type I was excluded by the absence of other specific skin lesions such as stains "café au lait", axillaries freckles, and no history of von Recklinghausen's neurofibromatosis [9]. Mastocytosis papulo-nodes were excluded due to absence of Darier's sign and skin itching. Although these lesions are mostly single ones, multiple lesions could not be excluded from clinical point of view. Initial painless lesions represented an obstacle in directing the clinical diagnosis to eruptive pilar leiomyomas.

The clinical aspect, especially for large lesions with a diameter of more than 20 mm, red-violet, presence of telangiectasia, associated with asymptomatic nature pleaded for initial clinical diagnosis of spontaneous eruptive keloids, reason why liquid nitrogen cryotherapy was tempted, radiofrequency monopolar therapy in combination with ultrasound and controlled cooling and also intralesional steroid injections, with occlusive dressings and silicone gel. Although keloids occur more frequently after local trauma, are described cases with multiple lesions arising spontaneously [14].

Unsatisfactory results, subsequent appearance of tender lesions and literature reports of skin metastases in young patients [15] imposed skin biopsy and histopathological diagnosis. HIV test was performed due to association of multiple pilar leiomyoma with HIV infection, especially in cases with a large number of injuries [16].

The differential diagnosis from histopathological point of view is with connective tissue, muscle or nerve tumors, with benign or malignant character. For a unique lesion, differential diagnosis includes: solitary dermatofibroma, cutaneous schwannoma or neurofibroma. For multiple lesions, as in our case, should be excluded other skin leiomyomas, angioleyomioma and genital leiomyoma. Vascular leiomyoma includes vascular spaces filled with red blood cells with thin walls constituted from a benign smooth muscle proliferation. Genital leiomyoma was excluded based on anatomical location and clinical examination of external genital organs. In women, usually occurs in the labia majora (vulvar leiomyoma) or the nipple (nipple leiomyoma) as single lesions, varying in

size from a few mm to several cm. In man, appears more often in the scrotum (scrotal leiomyoma) [17]. Lesions at this level may often present hyaline zone, myxoid changes or chronic inflammation with formation of lymphoid follicles. Special stainings useful in these lesions are Masson's trichrome and Van Gieson for the differentiation of smooth muscle cells from collagen fibers and nerve fibers.

Leiomyoma should be differentiated from leiomyosarcoma. Leiomyosarcoma has an infiltrative nature, cyto-nuclear atypia, vesicular nuclei with "cigarette" aspect and numerous mitoses. Necrosis can be present in large lesions, a characteristic of malignancy. In case of leiomyoma, the epithelium is unaffected or reactive hyperplasia is observed in about 30–50% of the cases. Between epithelium and injury remains an unaffected dermis area, "green zone". Very rarely was described bone metaplasia [18]. Overexpression of p53 in immunohistochemistry was associated as a marker of malignancy in leiomyosarcomas [19, 20].

Immunohistochemically, tumor cells are expressing specific constant and intense muscle markers α-SMA, desmin, caldesmon, calponin and are negative for S-100. In genital localization, also expresses the estrogen receptor and progesterone (the nipple and vulvar leiomyomas) and androgen receptor (in the scrotal leiomyomas) [17].

The first therapeutic possibility in keloids is cryotherapy, but in our case did not achieved significant results after 3–4 sets of applications, moreover the action of liquid nitrogen transformed the initially asymptomatic lesion in spontaneously tender to touch. Severe pains in lesions after minor trauma or after lowering the temperature can be considered a diagnostic sign in pilar leiomyomas and for asymptomatic lesions CO_2 laser ablation is recommended [21].

In multiple leiomyomas with familial aggregation, is required exclusion of Reed's syndrome – multiple cutaneous and uterine leiomyomatosis (MCUL) [22] or hereditary leiomyomatosis and renal cell cancer (HLRCC) syndrome [23]. This syndrome is caused by an autosomal dominant character of FH gene mutation localized on chromosome 1q42.1-q43 [24]. FH acts as classic tumor suppressor gene in HLRCC/MCUL. Genetic or epigenetic alterations in FH gene can lead to subsequent oxidative stress and tumorigenesis [23]. Multiple cutaneous leiomyomas often appear before those of the uterus in women, which are very painful. For both sexes, cutaneous leiomyomas are associated with development of invasive renal cell carcinoma: papillary type or Bellini collecting ducts type. Follow-up of patients with pilar leiomyomas is mandatory for detecting symptoms of possible kidney tumors (HLRCC syndrome) [23] or a possible polycythemia [9].

Conclusions

Pilar leiomyoma is rarely in man. Young age, atypical clinical onset followed by explosive increasing of lesions number and the appearance of pathognomonic pain after local cryotherapy are relevant pathological signs for pilar leiomyoma. A good clinical decision-making it requires integration of all available tools: clinical, histological and immunohistochemical examinations. Fumarate hydratase gene mutation detection is mandatory for excluding autosomal dominant familial aggregation syndromes, both in women and men. Otherwise, long-term follow-up could early detect a hereditary leiomyomatosis and renal cell cancer syndrome.

Conflict of interests

The authors declare that they have no conflict of interests.

Acknowledgments

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