Unusual presentation of hereditary leiomyomatosis mimicking neurofibromatosis

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INTRODUCTION

Hereditary leiomyomatosis and renal cell cancer (HLRCC) syndrome is a rare, autosomal dominant condition that predisposes individuals to cutaneous leiomyomas (CLMs), renal cell carcinomas (RCCs), and uterine leiomyomas. In HLRCC, CLMs develop during adolescence or late adulthood as smooth-surfaced, skin-colored or pink-to-brown papules or nodules usually ranging from 0.2 to 2.0 cm in diameter and 1 to 150 in number.[1,2] Typical involvement includes the trunk, neck, face, and extensor surfaces. Lesions are painful in up to 90% of patients.[1,2] Predisposition to papillary RCC in affected patients necessitates evaluation for malignancy. We present a case of HLRCC initially thought to represent neurofibromatosis type 1 (NF-1).

Abbreviations used:

CLM:	cutaneous leiomyoma
HLRCC:	hereditary leiomyomatosis and renal cell cancer
NF-1:	neurofibromatosis type 1
RCC:	renal cell carcinoma

CASE PRESENTATION

A 42-year-old man with a history of stable bilateral adrenal adenomas and uncontrolled type 2 diabetes mellitus presented for evaluation of increasingly painful skin growths. He was referred to the genetics clinic for evaluation of what the referring physician thought might be NF-1. It was apparent that the skin lesions did not correspond with neurofibromas, however, which prompted referral from the genetics to the dermatology department. The patient reported a 20-year history of the lesions. Emotional stress and light touch exacerbated the pain; heat and gabapentin provided only minimal alleviation. His biological brother had similar skin lesions. Physical examination found several firm, skin-colored, and pink tumors ranging in size from 0.5 to 4 cm, some coalescing in the left T5 dermatomal distribution (Fig 1); a collection of firm, pink papules and plaques on the left dorsal forearm; and a few scattered pink papules and plaques on the extremities. All lesions were exquisitely tender to light touch. Differential diagnoses of the lesions included plexiform neurofibromas, cylindromas, and leiomyomas. Biopsy of a left forearm lesion found leiomyoma (Fig 2). The patient's multiple leiomyomas prompted genetic testing. Fumarate hydratase gene testing was positive for a pathogenic missense variant, defined as p.Arg233His, diagnostic of HLRCC syndrome. Computed tomography scans indicated no abnormalities of the kidneys. The patient is currently considering surgical removal of the affected region of his right back and chest.

DISCUSSION

Leiomyomas can present similarly to other cutaneous entities.[3-5] In this case, the appearance and size of the growths led to an initial consideration for NF-1. Cutaneous leiomyomas are derived from smooth muscle and subdivided into piloleiomyomas, angioleiomyomas, and genital leiomyomas.

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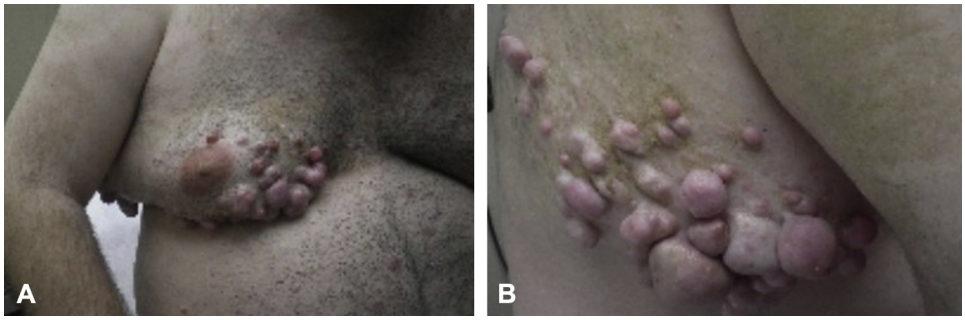

Fig 1. Multiple leiomyomas located on the patient's right chest (**A**) and back (**B**).

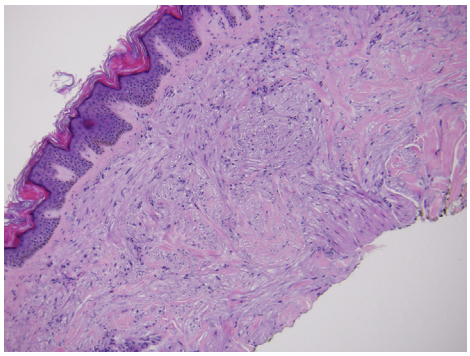

Fig 2. Histologic sections show proliferation of eosinophilic spindle cells with blunted end nuclei and perinuclear vacuoles. The spindle cells are arranged in a somewhat nodular and fascicular growth pattern.

Piloleiomyomas arise from the arrector pili muscle and are often painful, resulting in severe impairment in quality of life in 22% of those affected.[1] The presence of pain, often described as sharp, shooting, and in some cases induced by cold, stress, touch, or emotions, is a helpful diagnostic clue.[1] Biopsy and histopathology are necessary to confirm the presence of multiple cutaneous leiomyomas, followed by a positive germline fumarate hydratase mutation test to definitively diagnose HLRCC.

Papillary RCC as a consequence of this syndrome can lead to death within 5 years from metastatic disease in up to 70% of affected patients.[4] RCC tends to cluster within families, occurring in 20% to 34% of those affected.[1,6,7] Annual renal magnetic resonance imaging is recommended to screen for aggressive renal malignancy once the diagnosis of HLRCC is confirmed.

Although this patient presented to us with a diagnosis of NF-1, his unusual clinical presentation with severe pain on palpation prompted further testing and a skin biopsy leading to the diagnosis of leiomyomatosis. Key features help delineate leiomyomatosis from neurofibromatosis including age of onset, distribution, and pain. Multiple leiomyomas usually occur between the ages of 10 and 30 years, whereas clinical signs of NF-1, such as café-au-lait macules, axillary freckling, and neurofibromas, generally present in the first decade.[8,9] Leiomyomas are firm, whereas neurofibromas are soft.[8] Leiomyomas commonly occur in a grouped, linear, or dermatomal arrangement, whereas neurofibromas generally occur in a more diffuse presentation, although a segmental variant does exist, as was the source of confusion in the diagnosis of this patient.[10] Finally, pain is the most distinguishing feature and occurs in up to 90% of patients with piloleiomyomas, whereas neurofibromas are rarely painful.[1] Biopsy is necessary for accurate diagnosis of leiomyomas. Diagnosis of HLRCC is critical, as early initiation of RCC screening reduces mortality.

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