Multiple Cutaneous and Uterine Leiomyomatosis with Associated Simple Renal Cysts

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Cutaneous leiomyoma (CL) is an uncommon benign smooth muscle neoplasm, derived from arrector pili muscle. In Reed's syndrome, a small proportion of patients affected by multiple cutaneous and uterine leiomyomatosis have increased risk of hereditary leiomyomatosis and renal cell carcinoma (HLRCC).

A thirty-three-year-old female presented with multiple papules and nodular swelling on the back, chest and right arm, confirmed as cutaneous leiomyomas on skin biopsy. She had undergone uterine myomectomy with characteristic microscopic appearance, unusual from that of classical leiomyoma, which is highly suggestive of Reed's syndrome. Asymptomatic simple unilateral renal cysts were found on regular follow-up of the kidneys.

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Reed's syndrome is a rare autosomal dominant disorder characterized by multiple cutaneous and uterine leiomyomatosis. The condition is known as hereditary leiomyomatosis with renal cell cancer (HLRCC) if there is an increased risk of renal cell carcinoma[1-2]. About 10-16% of the patients will develop papillary renal cell carcinoma[3]. The syndrome is caused by mutation of the fumarate hydratase (FH) gene on chromosome 1q42.3-43[4]. Smooth muscle fibers in the skin are found in certain areas such as the tunica dartos of the scrotum, the areola of the nipple, vulva and around pilosebaceous apparatus[5].

Cutaneous leiomyoma (CL) is uncommon benign smooth muscle neoplasm, derived from arrector pili muscle, which is responsible for piloerection of hair follicles. It may occur in multiple numbers or sporadically as part of autosomal dominant disease. Meanwhile, uterine leiomyomas (fibroids) are common as it can be found in one of five women during their reproductive years and they are rare under the age of 20. However, females with Reed's syndrome usually have uterine leiomyomas with a characteristic pathology and can be seen earlier than those of the general population[6].

The aim of this presentation is to report an adult female with multiple cutaneous and uterine leiomyomatosis, associated with incidental finding of unilateral benign renal cysts.

THE CASE

A thirty-three-year-old female presented with a 12-year history of multiple nodular swellings over the trunk, arms, back and pressure pain. The patient was worried about the increasing number of lesions. There was no family history of a similar condition. During her illness, she was diagnosed to have uterine fibroid, where she had myomectomy.

Skin examination revealed multiple firm pinkish-brown papules/nodules; some were coalesced to form plaques over the chest, upper back and right arm. They vary in size from <1 cm to approximately 5x5 cm on the back, see figures 1 and 2. The lesions on the back were tender on deep pressure. A biopsy of the skin lesion was sent for pathology diagnosis.

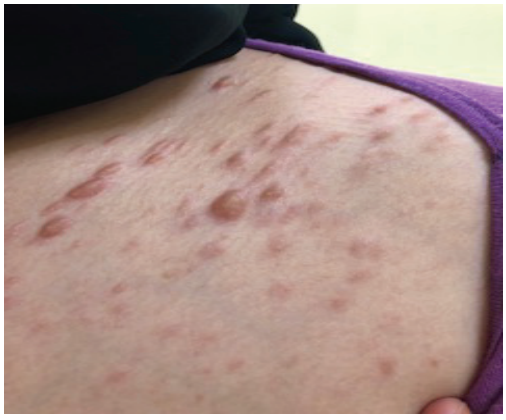

Figure 1: Multiple Firm Pinkish Brown Papules/Nodules of Cutaneous Leiomyomas in the Upper Chest

The histopathology of the skin biopsy revealed non-capsulated spindle cell tumors, consistent with cutaneous leiomyoma. The tumor cells showed a positive reaction for immunohistochemistry muscle markers actin and desmin, see figures 3 and 4.

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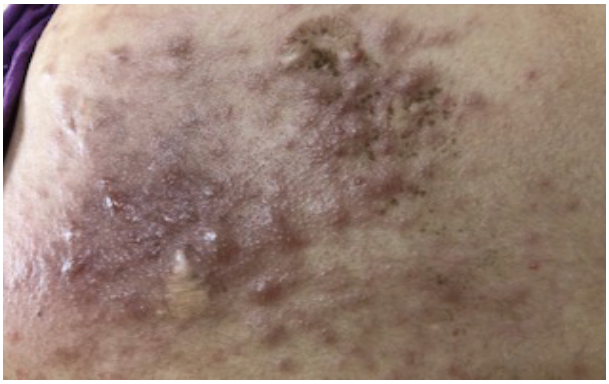

Figure 2: Upper Back Shows Tender Plaques of Cutaneous Leiomyomas

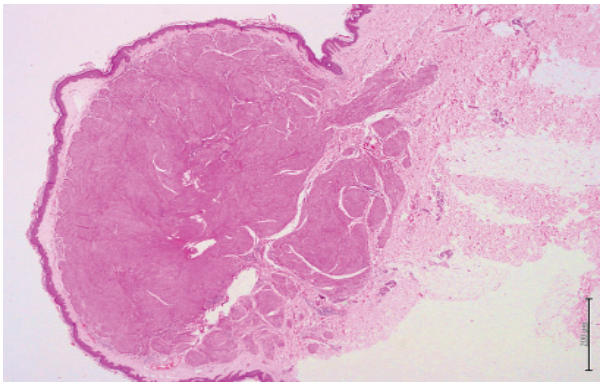

Figure 3: Low Power Microscopic View Showing a Non-Capsulated, Well Defined Cutaneous Leiomyoma of the Shoulder (H&E)

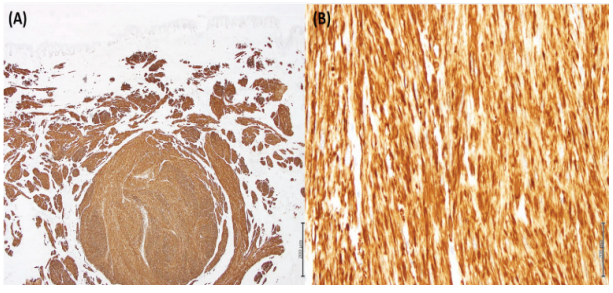

Figure 4 (A) **Figure 4 (B)**

Figure 4: (A) Low Power and (B) High Power Microscopic View of the Cutaneous Leiomyoma Showing Strong Positive Brown Reaction of the Tumor Cells for Desmin Immunohistochemistry Marker

Review of the previous histology of the uterine leiomyoma showed proliferating spindle myocytes (tumor cells) with a storiform pattern with mild nuclear atypia. The tumor cells showed staghorn vasculature appearance. In addition, the tumor cells showed perinuclear halos and intracytoplasmic inclusions, characteristic and unusual microscopic appearance of uterine leiomyoma which is described in Reed's syndrome.

Ultrasound of the abdomen and pelvis revealed simple cortical cysts in the upper pole of the right kidney, the largest was 1.8x1.6 cm. No renal tumor was found.

DISCUSSION

CLs called piloleiomyomas are uncommon benign smooth muscle tumors derived from arrector pili muscle, which is responsible for piloerection of hair follicles[7]. Meanwhile, uterine leiomyomas (known as fibroids) are benign monoclonal tumors, derived from the smooth muscle cells of the myometrium. Steroid hormones play roles in fibroid pathogenesis by up-regulation of aromatase, estrogen and progesterone receptors[8].

The association of multiple cutaneous and uterine leiomyomas (MCUL) formerly known as Reed's syndrome occurs in multiple numbers or sporadically as part of an autosomal dominant disease.

Launonen et al described the association between MCUL and an aggressive form of renal cancer, HLRCC caused by mutation of the fumarate hydratase (FH) on chromosome 1q42.2[9]. It is known that fumarate hydratase is a fundamental enzyme of cellular energy production in Kreb's cycle[10-11]. Other studies reported the association between MCUL and benign renal cysts, as seen in our patient[12,13].

CL is an uncommon neoplasm. A study by El Savador et al found 34 (0.04%) cases of CL out of 85,349 surgical pathology specimens[14].

CL is classified into piloleiomyoma, solitary genital leiomyoma (dartoic leiomyoma) and angioleiomyoma. The uterus is the most common site for leiomyoma followed by the skin, accounting for 5% of the cases. Toro et al found that between 70%-98% of women with CL had uterine fibroids[15].

CL typically presents during adolescence or early adulthood with equal sex distribution. It presents as solitary or multiple red-brown, pink skin-colored papules or nodules. The most common sites are the extremities and trunk, with solitary lesion favoring the limbs and multiple lesions on the trunk[16]. CL can be associated with pain which is either spontaneous due to release of neuropeptides or induced due to contraction of smooth muscle, compression of nearby nerves or increase number of nerve fiber[17].

Microscopically, leiomyomata are spindle cell tumors composed of proliferating myocytes. Smooth muscle differentiation is obvious in hematoxylin and eosin stain and can be confirmed by red staining with Mason's trichrome special stain or by application of immunohistochemistry study for smooth muscle markers such as actin and desmin which are positive in our case. The morphology of uterine leiomyoma in MCUL has very characteristic appearances. The tumor cells show a staghorn vasculature pattern, and they have perinuclear halos with intracytoplasmic inclusions.

Differential diagnoses include other spindle cell skin tumors such as dermatofibroma, schwannoma, neurofibroma, and adnexal tumor. In addition, painful skin tumors such as blue rubber bleb nevus, angiolipoma, glomus tumor, eccrine spiradenoma, and others should be excluded.

Treatment of localized CL is by simple surgical excision.

However, in extensive lesions, pain can be controlled by the application of intralesional steroids, nifedipine or CO2 laser ablation[18-19].

Screening is recommended for the patient with multiple leiomyomata. This includes clinical history and physical examination, skin biopsy, periodic renal and pelvic ultrasound, full blood count and urine examination. FH gene analysis and referring the patient to a gynecologist and nephrologist/ urologist is also recommended.

CONCLUSION

CLs are rare smooth muscle tumors; they are important clinical differential diagnosis of painful papule/nodules and must be biopsied in order to differentiate them from other spindle cell lesions. Multiple CLs should be considered as a sign of internal involvement such as uterine leiomyoma or renal cell carcinoma. Genetic counselling of (FH) mutation is important in patient management.

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