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Familial multiple cutaneous leiomyomatosis in siblings: A rare case report

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Abstract
Piloleiomyoma, also known as Leiomyoma cutis, is a rare and benign smooth muscle tumour developing from the arrector pili muscle. It typically manifests as reddish-brown papules or nodules that are commonly present over the trunk and extremities, and are frequently associated with episodic pain. Familial multiple cutaneous leiomyomatosis have been reported in twins, siblings and multiple generations in a family which have a genetic predisposition and are found to be closely associated with uterine leiomyomas and renal cell carcinomas. In this article, we report a rare case of multiple cutaneous leiomyomatosis in siblings aged 54 years and 58 years respectively, diagnosed clinically and further confirmed with histopathological examination revealing typical features of cutaneous leiomyoma and positive immuno-histochemical testing for smooth muscle actin (SMA).

Keywords: Piloleiomyoma, cutaneous leiomyoma, benign, arrector pili muscle

Introduction
Benign smooth muscle tumours are called Leiomyomas. Depending on their origin, they are known as piloleiomyomas if derived from arrector pili muscle, angioleiomyoma if derived from dermal blood vessel media and genital leiomyoma if derived from the smooth muscle cells of labia majora, tunica dartos of scrotum and nipples. Cutaneous leiomyomas comprise 3/4th of extrauterine leiomyomas [2].
Incidence of piloleiomyoma is more common in early adult life, although it can occur from birth onwards and it can affect both males and females equally. The characteristic features of this condition include skin-coloured to reddish-brown papules and nodules which can either be solitary or multiple. It is commonly associated with pain that can either be spontaneous or can be triggered by external stimuli.
Virchow in 1854 and Koepfler *et al*. in 1858 construed the Autosomal dominant inheritance with variable penetrance in familial form of multiple leiomyomatosis. In addition, uterine myomas and Type 2 papillary renal cell carcinomas are strongly associated with familial forms, thus further investigations are always warranted [3].

Case report
Sibling 1:
A 54 year old male (brother) presented to the dermatology OPD with complaints of multiple painful raised skin lesions all over the body for the past 40 years, which gradually increase in number & size, and few lesions were associated with severe pain and pruritis for the past 5 years, usually triggered on exposure to cold. Patient denied any history of discharge from these lesions or ulceration. Patient denied history of fever or any other systemic complaints. Birth and developmental history was normal. Patient is a known case of type 2 diabetes mellitus and systemic hypertension for 7 years and is on treatment for the same. On local examination, discrete and grouped skin-coloured to pigmented nodules with excoriation marks were seen over the face (Fig 4), back (Fig 1&2), chest (Fig 3), bilateral upper limbs (Fig 3). Tenderness was present, diascopy was negative, Button hole sign not elicited, Darier's sign negative and no lymphadenopathy was noted. Palms and soles were normal. Oral and genital mucosa were normal. On histopathological examination, Epidermis was normal and dermis revealed interlacing bundles of smooth muscle fibres in close relationship to hair follicle (Fig 5&6).

The induvidual cells were spindle shaped with moderate cytoplasm and eel-like blunt edged nuclei (Fig 7). Perivascular chronic inflammatory infiltrate with focal dilated blood vessels were also seen in the dermis. There was no evidence of nuclear atypia/ necrosis or atypical mitosis. Immunohistochemical testing for SMA (smooth muscle actin) was positive in the lesion demonstrating the predominance of myofibroblastic spindle cells.
The patient was given Gabapentin and Nifedipine for pain relief and was not advised excision due to high rates of recurrence.

Sibling 2
A 58 year old female (sister) presented to the dermatology OPD with complaints of multiple painful skin lesions predominantly over her back and chest for the past 20 years, which were associated with itching. Patient denied any history of discharge from these lesions or ulceration. Patient denied history of fever, abdominal pain or any other systemic complaints. Patient attained menopause 10 years back. Birth and developmental history was normal. Patient is a known case of hypothyroidism for the past 10 years and is on treatment for the same. On local examination, multiple discrete and grouped pigmented nodules ranging from 2-5mm in diameter were present over the back, bilateral arms and trunk region (Fig 8-10). Tenderness was present, diascopy, button hole sign and Darier's sign were negative. No lymphadenopathy was noted. Palms and soles were normal. Oral and genital mucosa were normal.

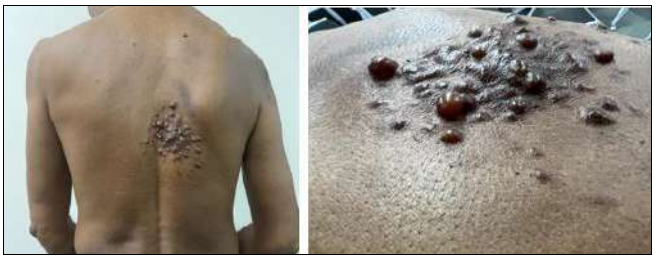

Fig 1&2: Grouped tender pigmented nodules ranging from 2-7mm in diameter present over the back.

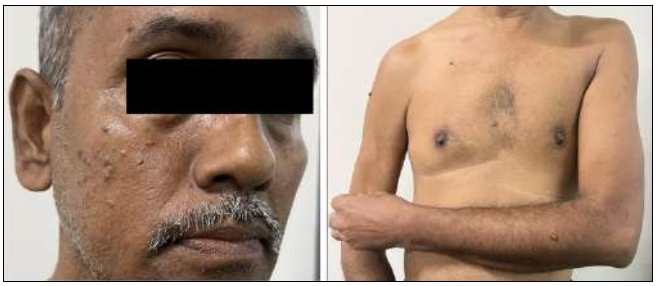

Fig 3: Discrete skin-coloured to pigmented nodules present over chest and bilateral upper limbs.

On histopathological examination, superficial and deep dermis revealed spindle cells arranged in nodules and fascicles. (Fig 11 & 12). Spindle cells revealed eosinophilic cytoplasm and cigar-shaped nuclei (Fig 13).Periadnexal and Perivascular chronic inflammatory infiltrate were seen (Fig 11). There was no evidence of nuclear atypia/ necrosis or atypical mitosis. Immunohistochemical testing was positive for smooth muscle actin (SMA) confirming the predominance of myofibroblastic spindle cells.
The patient was prescribed Gabapentin for pain relief. Due to cosmetic reasons, 2 large nodules on the back were excised.
The patients and their attenders were explained in detail regarding the nature of the disease, the need for avoidance of triggering factors and its close association with internal malignancies that include utreine leiomyoma and renal cell carcinoma. Patient was advised to follow up with the respective departments for early detection of internal malignancies.

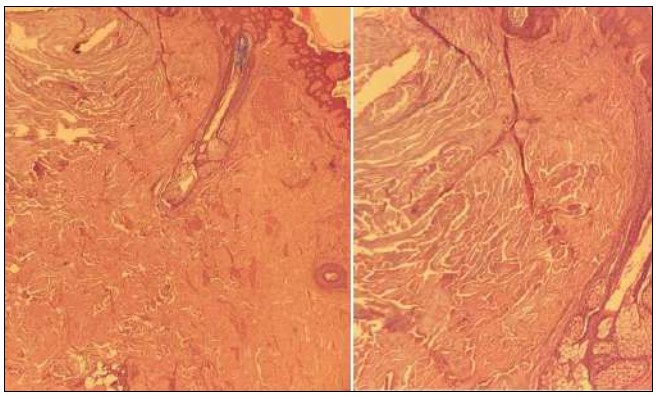

Fig 5 (10X) & 6(40X): Normal Epidermis with Dermis showing interlacing bundles of of smooth muscle fibres in close relation with hair follicles with perivascular chronic inflammatory infiltrate

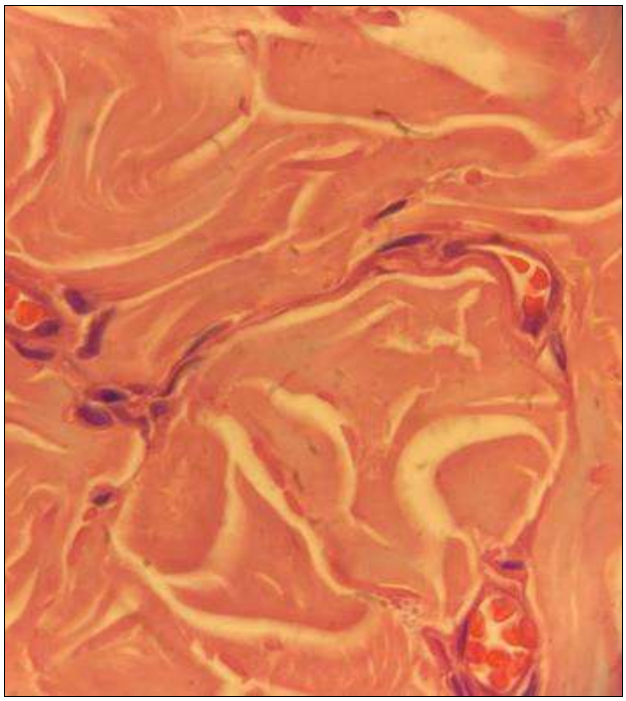

Fig 7: Spindle shaped cells with moderate cytoplasm and eel-like blunt edged nuclei observed in oil immersion.

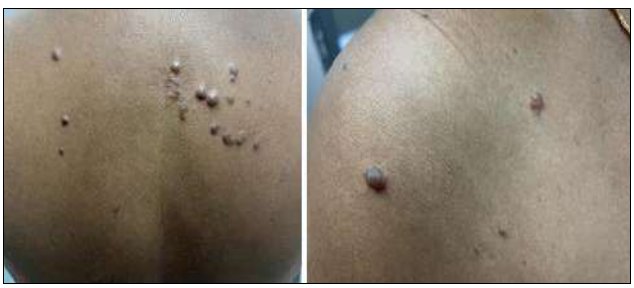

Fig 8 & 9: Discrete pigmented nodules over the upper back and right arm region

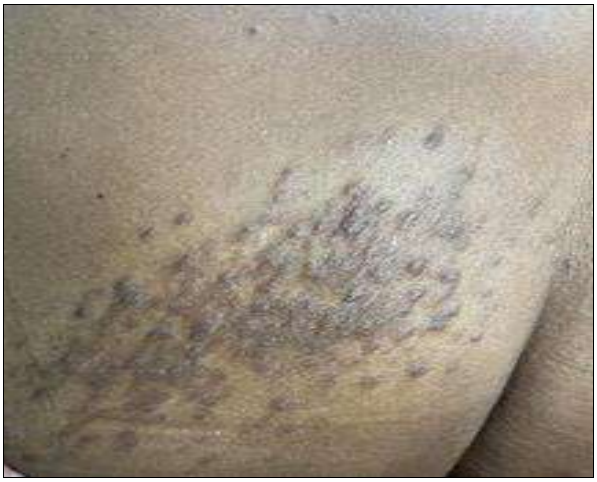

Fig 10: Grouped tender pigmented nodular lesions over the lower back region

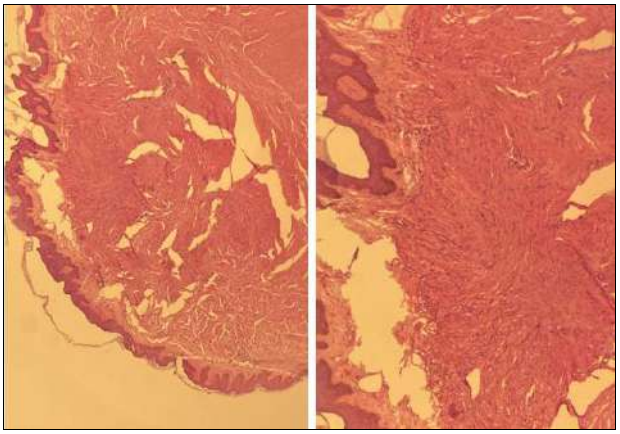

Fig 11(10x) & 12(40x): Spindle cells arranged in nodules and fascicles in superficial and deep dermis with periadnexal and perivascular inflammatory infiltrate.

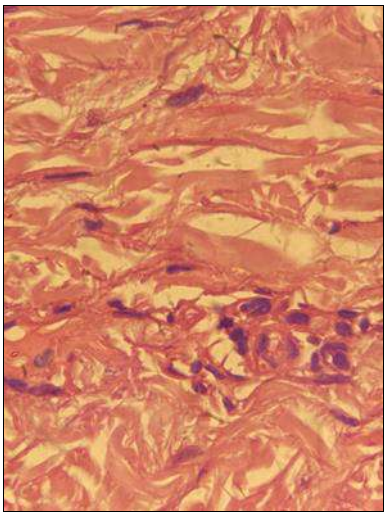

Fig 13: Eel-shaped blunt edged nuclei present within the spindle cells observed in oil immersion.

Discussion

5% of all benign smooth muscle tumours are cutaneous leiomyomas, which are distinctly classified as piloleiomyoma, angioleiomyoma and genital leiomyoma depending on their origin from arrector pili muscle, dermal blood vessel and genital regions respectively. They frequently affect the 20-40 years age group and commonly occur over extensor aspects of extremities, trunk, face and neck. Classic clinical manifestations include skin- to tan-coloured papulonodules over the above said areas. They can present as Disseminated, zosteriform or segmental distribution over the trunk. Proximally, the arrector pili muscle attaches to the hair follicle and distally to multiple points in the papillary & reticular dermis and basement membrane zone and hence, piloleiomyoma can arise from any of these points [8-12].

Typically, most of the piloleiomyomas are associated with pain, which can either be spontaneous or can be due to an external trigger. The common triggering factors include cold, touch or emotional stimuli. Multiple theories have been proposed to explain the occurrence of pain in piloleiomyoma. These include:

1. Due to Infiltration of mast cells
2. Local pressure exerted on the dermal nerves by the tumour mass
3. Muscle contraction: Sympathetic nervous system causes excitation of the arrector pili muscle which in turn causes influx of calcium ions at the motor end plate leading to muscle contraction, which can cause pain. Hence, calcium channel blockers are prescribed sometimes to relieve the pain.

Piloleiomyomas can have either genetic or sporadic inheritance. Commonly they are fixed due to their development from papillary dermis, although, are mobile over deep subcutaneous tissue. In Familial cases, Autosomal dominant inheritance with variable penetrance is observed and most of the familial cases present with multiple pilar leiomyomas that occur between 10-30 years of age anywhere in the body with a variety of distribution patterns and are associated with increased rates of recurrence unlike in case of solitary cutaneous leiomyomas that are significantly larger in comparison (upto 2 cms), commonly occur in adulthood and usually present over the lower limb [1, 2].

The gene responsible for multiple cutaneous leiomyomas is located on chromosome 1q42.3-q43. This can also predispose to other internal malignancies including uterine leiomyomas (Multiple cutaneous and uterine leiomyomatosis, also known as REED syndrome (MCUL) and to renal cell carcinoma (especially type 2 papillary renal cell carcinoma). This occurs due to a heterogenous germline mutation in the gene that codes for the enzyme Fumarate hydratase, a vital enzyme involved in Krebs cycle [3, 14, 15].

The Typical histopathological features of this condition include epidermal hyperplasia and Grenz zone (clear zone between epidermis and muscle fibres) and dermis reveals interlacing bundles of smooth muscle cells (which can be differentiated from collagen using Trichome stain and aniline blue stains) and these muscle fibres are straight and have eel-like thin, long blunt edged nuclei with perinuclear clear zone leading to slight vacuolisation.

A number of immunohistochemical studies for spindle cells that include smooth muscle actin- more sensitive (SMA), smooth muscle myosin (SMMS), desmin- more specific, h-caldesmon (high molecular weight caldesmon), calponis and HHF35 (for muscle actin) can be done to confirm the

diagnosis [16].

Piloleiomyomas can be associated with a number of other conditions like Reeds syndrome, visceral organ involvement (Gastro-intestinal tract and retroperitoneum) and haematological abnormalities like erythrocytosis, polycythemia. Differential diagnosis of this condition include angiolipoma, dermatofibroma, neurofibroma, eccrine spiradenoma, naevus, schwannoma and angioleiomyoma. Cutaneous leiomyoma can be differentiated from these conditions based clinical presentation and histopathological features [4]. Common differential diagnosis for Cutaneous Leiomyomas and their differentiating features [17, 18].

Table 1: Show the clinical presentation disease

Disease	Clinical presentation	HPE
Dermatofibroma	-Firm, tender, dome-shaped nodules with central pigmentation -Dimple sign +	-Proliferation of spindle shaped cells in the dermis arranged in the form of short intersecting fascicles
Smooth muscle hamartoma	-Pigmented to skin coloured plaques with prominent vellus hairs	-Discrete bundles of spindle cells set in dermal collagen
Neurofibromatosis type 1, 3, 4	-Numerous well circumscribed tan coloured papules and nodules -Cafe au lait macules -Freckles in intertrigous areas -Button holes sign +	-well circumscribed lesions comprising Schwann cells, fibroblasts and mast cells
Histoid leprosy	- Cutaneous and subcutaneous nodules - Skin-coloured to reddish in colour, overlying skin stretched and shiny - Constriction around the base	-A well circumscribed lesion with spindle shaped cells and large quantity of bacilli -Grenz zone + -Interlacing bands and whorls of spindle shaped histiocytes

Treatment protocol for piloleiomyomas are primarily based on patient's symptoms. Often, reassurance and avoidance of trigger are sufficient. However, large and painful lesions can be excised though high rates of recurrence have been noted in cases of multiple piloleiomyomas. Medical treatment is essentially given to relieve patient's pain, and includes calcium channel blockers (eg. Nifedipine), alpha-adrenergic blockers (eg. Phenoxybenzamine), nitrates, anti-depressants, gabapentin and analgesics. Additionally, CO2 laser ablation, cryotherapy has also shown satisfactory results [5-7, 13].

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Not available

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