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Case Report

Dermatology Section

An Uncommon Presentation of Renal Angiomyolipoma in a Patient with Segmental Neurofibromatosis: A Case Report

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ABSTRACT

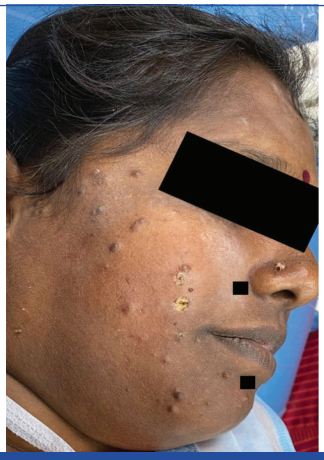
Segmental Neurofibromatosis (SNF) occurs sporadically and is characterised by neurofibromas with or without café-au-lait macules confined to an area or segment of the body. It is a rare type of NF and is not usually associated with systemic manifestations. This case report discusses a 39-year-old female with segmentally distributed neurofibromas of the right side of the face in association with Renal Angiomyolipoma (RAML). Knowing this association may help clinicians to suspect, diagnose and treat the RAML at the earliest. Although RAMLs are frequently associated with Tuberous Sclerosis (TS), their occurrence in the case of SNF may be attributed to the shared mTOR signalling pathway targeted in both neurocutaneous syndromes.

Keywords: mTOR inhibitors, Neurocutaneous syndromes, Tuberous sclerosis

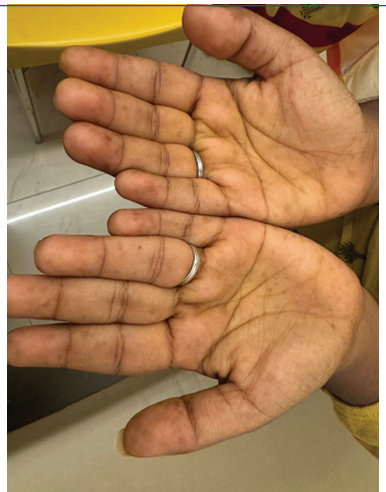
CASE REPORT

A 39-year-old female presented to the dermatology outpatient clinic with chief complaints of persisting multiple raised, asymptomatic lesions on the right side of the face for the past 10 years. The lesions initially started 10 years ago, as a solitary raised lesion over the right side of the chin, which then gradually increased in size and number to involve the right hemiface over the next three years to attain the present size. The patient did not notice any new lesions or growth of pre-existing lesions thereafter in the last seven years. She consulted a year back in a nearby private clinic for her skin condition and was prescribed some cream for the same, with which she did not find any resolution. The patient also expressed her desire to get the lesions removed completely. She had no history of seizures or other neurological complaints. She had no ocular complaints, no deafness and no skeletal abnormality. She was diagnosed with hypothyroidism and was on treatment for the same. However, other hormones were within normal limits. There was no history of similar complaints in her parents or siblings.

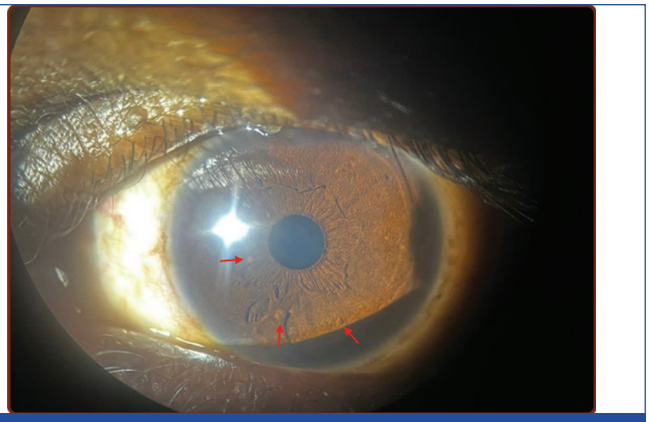
The patient's pulse rate, breathing and blood pressure were normal at the time of the visit. There was no pallor, icterus, cyanosis, clubbing or generalised lymphadenopathy. On cutaneous examination, the patient had multiple discrete, firm, non-tender, skin-coloured dome-shaped nodules, ranging in size from 1 to 2 cm along the mandibular division of the trigeminal nerve on the right side of the face [Table/Fig-1]. There was no bleeding, excoriations or oozing from the skin lesions. The surface of the lesions appeared smooth and unremarkable. A differential diagnosis of neurofibromatosis, TS, dermatofibroma or an adnexal tumour was considered at this point. On further examination, multiple discrete freckles, each ranging in size from 0.2 cm to 0.5 cm, were noticed over bilateral palmar skin, suggestive of Patrick's Yesudian sign [Table/Fig-2]. No café-au-lait macules were seen. On ophthalmological screening, 4-5 hamartomatous Lisch nodules were noted at 5 o'clock, 7 o'clock and 9 o'clock positions in the iris by slit lamp examination [Table/Fig-3]. The cutaneous nodules were excised and specimens were sent for histopathological examination. Haematoxylin and eosin-stained section of an excised nodule demonstrated well-circumscribed benign spindle cells, with typical wavy nuclei, in the mid and deep dermis [Table/Fig-4]. The presence of segmental distribution of cutaneous neurofibromas and more than two Lisch nodules on the iris fulfilled the revised diagnostic criteria of segmental or mosaic neurofibromatosis in this patient [1]. All the routine blood investigations were within normal limits. Ultrasound of the abdomen was done to screen for internal organ involvement associated with neurofibromatosis, which revealed a well-defined hyperechoic lesion



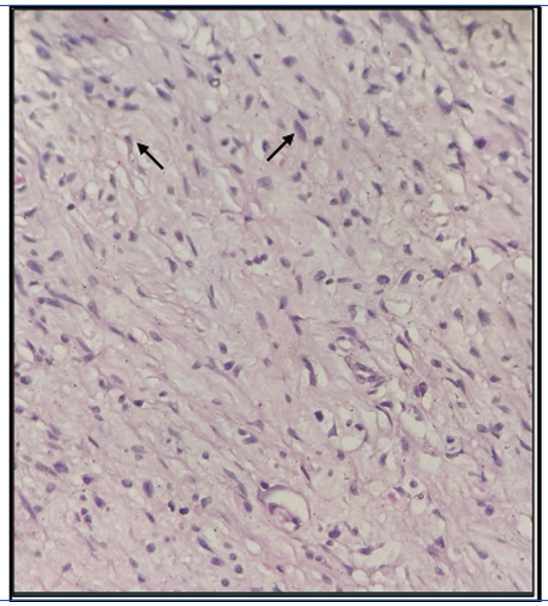
[Table/Fig-1]: A 39-year-old female with segmental neurofibromas on the right hemiface.



[Table/Fig-2]: Palmar freckles in our patient indicative of the Patrick-Yesudian Sign.

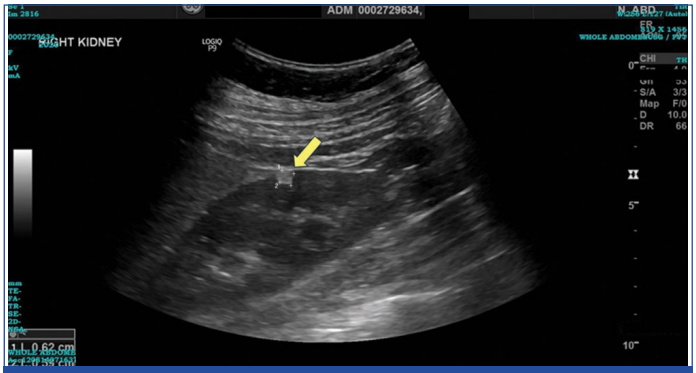


[Table/Fig-3]: Lisch nodules (hamartomas) on the iris (indicated by the red arrows) seen on slit lamp examination of the eye.

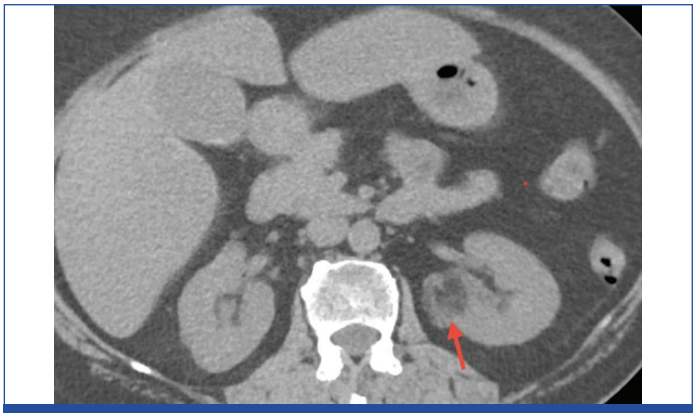


in the right kidney, which suggested a possibility of angiomyolipoma or a renal cell carcinoma [Table/Fig-5]. The patient was planned for Computed Tomography (CT) of the abdomen in the subsequent visit to confirm the same. Axial contrast-enhanced CT image of the abdomen demonstrated a right RAML (red arrow). The 3.5×3.75 cm lesion was located in the mid-pole of the right kidney and appeared as a well-defined, heterogeneous mass with areas of macroscopic fat attenuation, distinct from the normal renal parenchyma (–20 to –80 Hounsfield units), which is characteristic of angiomyolipomas. No signs of haemorrhage or invasion into surrounding structures were noted in the Computed Tomography (CT) imaging [Table/Fig-6]. Magnetic Resonance Imaging (MRI) of the brain was done to rule out any central nervous system involvement, which showed bilateral

[Table/Fig-4]: Haematoxylin and Eosin (H&E) stained section of an excised neurofibroma showing benign spindle cells (black arrows) in the mid and deep dermis. (40x magnification).

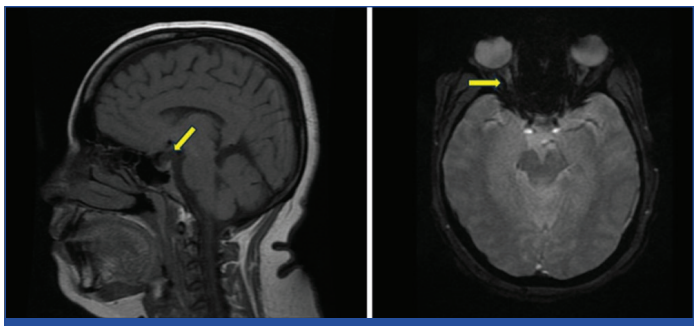


[Table/Fig-5]: Ultrasound abdomen showing a hyperechoic lesion in the lower pole of the right kidney.



[Table/Fig-6]: Axial contrast-enhanced CT image of the abdomen demonstrating a right Renal Angiomyolipoma (RAML) (red arrow), measuring approximately 3 × 3.75 cm.

optic nerve sheath thickening and partially empty sella, suggestive of benign intracranial hypertension [Table/Fig-7]. As the patient could not afford genetic testing, it was deferred. The nephrologist's opinion was sought for the renal condition, which was managed conservatively as the patient was asymptomatic. The patient was advised to undergo regular follow-up annually, henceforth, for her renal involvement and neuro-consultation. There was no recurrence of skin lesions in the subsequent three months of follow-up.



[Table/Fig-7]: Magnetic Resonance Imaging (MRI) of the brain (plain) showing partially empty sella and optic nerve sheath thickening.

DISCUSSION

The SNF is characterised by neurofibromas, with or without café-au-lait macules, confined to an area or segment of the body [2]. SNF has an estimated rare prevalence between 0.0014 and 0.002% [3]. The majority of the SNFs follow Blaschko lines on the right side of the body. Segmental cases occur due to postzygotic somatic mutations during late embryonic development. Nearly 93% of the SNF patients do not have a family history of NF; it is most often sporadic, as seen in this case [4].

According to Riccardi's classification, SNF is included in Type V neurofibromatosis, which constitutes unilateral SNF [5]. Roth RR et al., further subdivided SNF into four types: true segmental, localised cases with deep involvement, hereditary segmental and bilateral SN [6]. Clinically, patients may be divided into four groups: with only pigmentary changes, with only neurofibromas, with both pigmentary changes and neurofibromas, and with isolated plexiform neurofibromas [7]. The patient had pigmented freckles over the palms and facial neurofibromas. Commonly affected areas reported in SNF are the thorax and abdomen in 55% of cases, upper extremities and inguinal/axillary in 20% each, and lower limb and face in 10% each [8]. The incidence of neurofibromas on the face, particularly in the distribution of the trigeminal nerve, is uncommon, with only a limited number of cases reported in the literature. The majority of them occur sporadically and rarely with any systemic associations [9-11]. The patient had neurofibromas localised to the right side of the face. Though freckles were less frequently reported cutaneous manifestation in SNF, this patient had palmar freckling as could be seen in [Table/Fig-2]. The commonly reported extracutaneous manifestations in SNF, such as soft-tissue hypertrophy, skeletal

abnormalities, visceral neurofibromas, and unilateral renal agenesis, were not observed in this patient [4,9].

RAMLs are rare benign neoplasms that may occur sporadically in 80% of cases or may be associated with pulmonary lymphangioleiomyomatosis or TSC in the remaining 20%. Most angiomyolipomas are silent and asymptomatic and do not need any treatment. AMLs of size 4 cm or greater present symptomatically with acute flank pain and haematuria, whereas the subtle signs include anaemia and hypertension [12]. There is one prior report of SNF with renal AML in a 49-year-old woman who required nephrectomy for the acute presentation of haematuria [13]. The patient did not have any symptoms of renal involvement like haematuria, loin pain or anaemia and so she was managed without any medical or surgical interventions.

Research indicates that mammalian Target of Rapamycin (mTOR) plays a multifaceted role in the body's signalling pathways, including the phosphoinositide-3-kinase (PI3K)/AKT pathway, the TSC complex, the LKBL/AMPK pathway, and the VAM6/Rag GTPases pathway [14]. Under normal physiological conditions, mTOR serves as a pivotal regulator of cellular growth and division. However, in the context of tumour cells, abnormally activated mTOR transmits signals that promote tumour cell proliferation, metastasis, and invasion of healthy tissues [15]. There is limited evidence in the literature to suggest an association of SNF with RAML, with only one case reported previously [13]. The TS genes, TSC1 and TSC2, respectively, encode hamartin and tuberin, and function as tumour suppressors. They inhibit the mTOR, which is involved in tumour growth [13,16]. In TS, aberrant TSC1/TSC2 release inhibition for mTOR facilitates tumour growth. In NF, neurofibromin also acts as a tumour suppressor by inhibiting Ras signalling. Aberrant neurofibromin activates Ras signalling and increases phosphoinositide 3-kinase (PI3-kinase)/Akt signalling, leading to the phosphorylation of tuberin and, consequently, heightened mTOR signalling. Similarly, in TS, a loss of inhibition from TSC1/TSC2 results in increased mTOR signalling and tumour growth. The mechanisms underlying NF and TS are intricate, and the nature of their relationship remains uncertain and speculative at this juncture. However, it is plausible that they may be linked through the mTOR signalling pathway. The activation of the mTOR signalling pathway is responsible for tumour growth in TSC and may be so in SNF [17,18]. Unchecked activation of the mTOR signalling pathway can result in the formation of angiomyolipoma and its response to mTOR inhibitors like sirolimus and everolimus, resulting in size reduction, probably explains the possible mechanism. This female patient may have started to develop the angiomyolipoma in her kidney either before, along or after the commencement of neurofibromas on her face. However, active surveillance every 1-3 years and early diagnosis play a crucial role in preventing the dreaded complications of renal AMLs, like retroperitoneal haemorrhage. While it is mandatory to screen for AML in cases of TSC, it is not a routine practice in cases of neurofibromatoses.

The gold standard diagnostic method for renal AMLs is CT or MRI, whereas ultrasound of the abdomen can be used for follow-up surveillance [19,20]. Contrast CT of the abdomen showed conclusive evidence of RAML in the patient [Table/Fig-6]. Renal biopsy is rarely needed [21]. The main indications for active treatment of AML were increasing tumour size, symptomatic presentation like pain and bleeding and suspicion of cancer on radiographic imaging. The 4 cm cut-off to trigger active treatment has been followed for decades, mainly based on the assumption that larger tumours have an increased risk of bleeding [22]. However, there is very little evidence to support the 4 cm threshold, as elaborated in a systematic review by Fernández-Pello S et al., [21]. The patient had a 3.5 cm×3.75 cm-sized AML in her right kidney, which was smaller than the cut-off (>4 cm) for any active intervention. In addition, the patient was asymptomatic throughout the course of her disease. In a study by Seyam RM et al., it was observed that the growth rate of sporadic AML was 0.19 cm/year while that of TSC-associated AML was 1.25 cm/year at a mean follow-up of over three years [23]. Although various treatment options are available for RAML, such as mTOR inhibitors like temsirolimus and everolimus, radiofrequency or cryoablation, selective artery embolisation, and radical nephrectomy, the patient did not require any active intervention for her renal condition. She was reassured and advised to follow up annually with a nephrologist [24].

CONCLUSION(S)

The SNF is usually not associated with extracutaneous or systemic manifestations. Sporadic cases of RAML, excluding those associated with TSC, are uncommon but have been sparsely reported. This report of a rare association of RAML in a patient with facial SNF underscores the importance of comprehensive screening and mandatory imaging studies even in asymptomatic patients with NF to identify any underlying organ manifestation at the earliest, to prevent any unforeseen complications. CT and MRI prove to be the gold standard imaging techniques in diagnosing renal AMLs. However, not all patients with renal AML necessitate unnecessary therapeutic interventions unless otherwise justified and may be annually followed up. Further research on the role of mTOR signalling as the shared pathogenetic pathway for SNF and RAML is imperative to establish a definitive association between these conditions.

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