International Journal of Research in Dermatology
Joshi V et al. Int J Res Dermatol. 2025 Nov;11(6):541-545
http://www.ijord.com

DOI: https://dx.doi.org/10.18203/issn.2455-4529.IntJResDermatol20253401

Case Report

The skin's secret script: fingerprints of CD34 and the dolphin dance of Schwann cells

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Received: 25 July 2025
Revised: 18 August 2025
Accepted: 03 September 2025

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ABSTRACT

Segmental neurofibromatosis (SNF), or Riccardi type V, is an uncommon mosaic variant of neurofibromatosis type 1, arising from postzygotic mutations in the NF1 gene. It reveals itself through dermatomally confined clusters of neurofibromas, usually in the absence of systemic features or family history. A 55-year-old woman presented with multiple, progressively enlarging papulonodular lesions localized to the left upper arm. Histopathological analysis demonstrated a non-encapsulated dermal spindle cell tumor with elongated, wavy, buckled nuclei-reminiscent of "diving dolphins"-set within a fibro-myxoid, mast cell-rich stroma. Immunohistochemistry further refined the picture: Schwann cells showed diffuse S100 positivity, while CD34 staining unveiled the delicate "fingerprint" pattern of dendritic fibroblasts. Taken together, these findings confirmed the diagnosis of neurofibroma. The segmental distribution and absence of systemic features established the diagnosis of SNF. The lesions were excised sequentially using elliptical incisions, leading to uneventful recovery and satisfactory cosmetic results. This case underscores the diagnostic value of correlating clinical distribution with distinctive microscopic clues. The dermatomal clustering of lesions, the evocative "diving dolphin" nuclei, and the CD34 fingerprint pattern together form a compelling diagnostic triad of SNF. Awareness of these features helps avoid misclassification among spindle cell tumours and ensures that management remains both accurate and tailored to patient needs.

Keywords: Segmental neurofibromatosis, Spindle cell tumour, S100, CD34, Immunohistochemistry

INTRODUCTION

Neurofibromas are benign tumours of peripheral nerve sheath origin and represent the most common neoplasms within this group. They are frequently associated with neurofibromatosis type 1 (NF1), a well-recognized genetic condition characterized by multiple cutaneous, neurological, and skeletal manifestations.[1] Histologically, neurofibromas represent a heterogeneous admixture of non-myelinating Schwann cells, perineurial cells, fibroblasts, and mast cells, which together create their unique morphological and immunohistochemical identity.[2]

A less frequent but clinically significant variant is segmental neurofibromatosis (SNF), also referred to as Riccardi type V. This mosaic disorder arises from postzygotic mutations in the NF1 gene, producing a distinct phenotype in which neurofibromas are restricted to one or more dermatomes. Unlike classical NF1, systemic involvement and familial transmission are uncommon in this variant.[1] The clinical diagnosis of SNF can be elusive, as it lacks many of the pathognomonic hallmarks of NF1 such as café-au-lait macules, axillary freckling, and Lisch nodules.

From a histopathological standpoint, neurofibromas are spindle cell neoplasms that may easily be mistaken for a variety of cutaneous and subcutaneous tumours.

Immunohistochemistry (IHC) is indispensable in these scenarios, as it highlights the neural and fibroblastic components of the lesion and solidifies the diagnosis.

In this report, we describe a case of segmental neurofibromatosis in a middle-aged woman, emphasizing both its clinical subtleties and the microscopic hallmarks-particularly the "diving dolphin" nuclei and the CD34 "fingerprint" pattern. We further outline its management, which in this patient involved sequential elliptical excision with favorable cosmetic outcomes.

CASE REPORT

A 55-year-old woman presented with a six-month history of multiple, gradually enlarging, occasionally painful, elevated lesions confined to the left upper arm. There was no history of trauma, prior infection, or surgical intervention at the site. Although the lesions were largely asymptomatic, the patient expressed significant cosmetic concern, prompting clinical evaluation. She denied systemic symptoms, and there was no family history of similar findings. Importantly, she categorically denied pain exacerbation on exposure to cold, emotional stress or friction.

On physical examination, multiple soft, non-tender, skin-coloured to hyperpigmented papules and nodules were observed, distributed in a dermatomal fashion over the left upper arm (Figure 1). When subjected to vertical pressure with the index finger, a positive buttonhole sign was noted, while pinching the lesion between the thumb and index finger failed to produce dimpling, indicating a negative dimple sign. No café-au-lait macules, axillary or inguinal freckling were present. An ophthalmological and skeletal survey ruled out Lisch nodules and bony abnormalities.

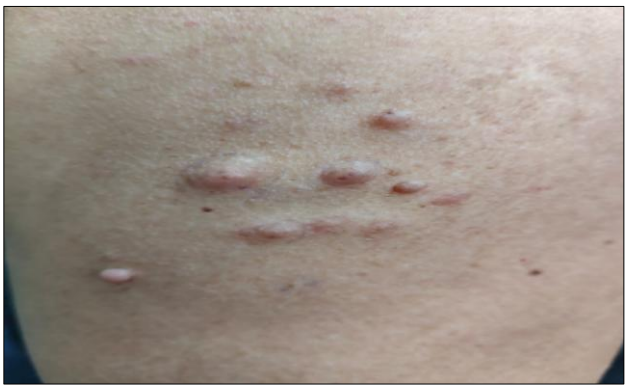

Figure 1: Multiple, soft, non-tender, skin-colored to hyperpigmented papulonodules over left arm in segmental distribution.

Based on the localized distribution, the differential diagnosis included segmental neurofibromatosis, segmental leiomyomas, and segmental spiradenomas. A 4-mm punch biopsy obtained from a representative lesion revealed a non-encapsulated dermal tumour with a grenz zone (Figure 2a). The tumour comprised spindle-shaped cells in a fibro-myxoid stroma (Figure 2b). The nuclei were elongated, wavy, and buckled, arranged in a seemingly disorderly manner but evocative of "diving dolphins" (Figure 2c). Numerous mast cells were interspersed within the stroma.

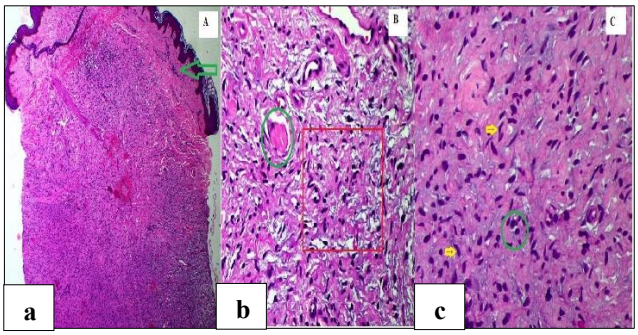

Figure 2: (a) Photomicrograph (H & E, 4x) – mamillated epidermis with grenz zone (green arrow), dermal non-capsulated spindle cell tumor with myxoid stroma and deep dermal involvement (blue star); (b) higher magnification (H & E, 20x) – shows spindle cell proliferation, loose fibromyxoid stroma (red square) and collagen trapping (green circle); and (c) higher magnification (H & E, 20x) – cells with buckled ('diving dolphins') nuclei (yellow arrow) and mast cells in the stroma (green circle).

IHC confirmed the lineage: spindle cells demonstrated strong, diffuse S100 positivity (Figure 3a), consistent with Schwann cell origin. CD34 immunostaining highlighted dendritic fibroblasts, arranged in delicate, parallel lines, yielding a classic fingerprint pattern (Figures 3b and c). The combination of clinical and histopathological features established the diagnosis of segmental neurofibromatosis.

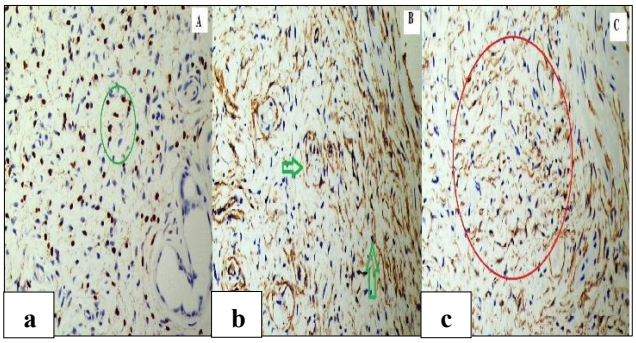

Figure 3: (a) Photomicrograph (20x) – immunohistochemistry stain showing S-100 positivity (green circle) in spindle cells; (b) IHC CD34 staining showing positive staining for fibroblastic dendritic processes forming whorls and ridges (green arrows) with unstained intervening stroma and Schwann cells, a pattern akin to human fingerprints; and (c) another area (red circle) within the tumor showing IHC CD34 'fingerprint positivity'.

Given the cosmetic distress of the patient, sequential elliptical excision of lesions was performed. Healing was uneventful, and the patient was highly satisfied with the aesthetic outcome.

DISCUSSION

Segmental neurofibromatosis, first described by Crowe et al, represents a fascinating mosaic form of NF1.[1] Unlike classical NF1, which demonstrates widespread systemic manifestations, SNF results from postzygotic somatic mutations in the neurofibromin gene, leading to localized cutaneous lesions. In most instances, the condition is sporadic; however, gonadal mosaicism may, on rare occasions, allow vertical transmission to offspring.

Riccardi's classification remains the most widely cited framework, dividing NF into eight subtypes: NF-1 (von Recklinghausen's disease), NF-2 (acoustic type), NF-3 (mixed type), NF-4 (diffuse café-au-lait macules and neurofibromas with/without central nervous system tumors), NF-5 (segmental form with café-au-lait macules or neurofibromas restricted to one side of the body), NF-6 (café-au-lait macules without neurofibromas), NF-7 (late-onset type), and NF-8 (unclassified).[2,3]

For SNF, diagnostic criteria include unilateral distribution of lesions without crossing the midline, absence of systemic features, and lack of family history.[1,2] Gayathri et al expanded on this, documenting its prevalence at a mere 0.0014–0.002% and describing several phenotypic variants: pigmentary changes only, neurofibromas only, combined pigmentary and tumoral lesions, or isolated plexiform neurofibromas.[2] Roth et al further proposed subclassifications into true segmental, hereditary, deep tissue, and bilateral types.[2]

The clinical differential diagnosis of clustered, segmental lesions is broad. Segmental leiomyomas, arising from arrector pili muscles or vascular smooth muscle, are typically painful tumours exacerbated by cold, friction, or emotional stress.[4] Spiradenomas, thought to originate from eccrine or occasionally apocrine glands, present as blue cell–rich nodules in the dermis, often tender to touch.[5] Segmental dermatofibromas are rare but recognizable by their storiform fibro-histiocytic proliferation, vascular hyperplasia, and collagen trapping.[6] Histopathology, coupled with IHC, allows confident distinction between these entities.

Neurofibromas are non-encapsulated spindle cell neoplasms infiltrating the dermis and sometimes subcutis, often entrapping adnexal structures. They characteristically lack cytological atypia, necrosis, or destructive invasion.[3] Their most striking feature is the undulating, elongated nuclei that resemble "diving dolphins".[3] The background stroma is variably myxoid or collagenous and is rich in mast cells. The above features were seen in our case.

The role of mast cells extends beyond histological curiosity. Originally termed Mastzellen by Paul Ehrlich, these cells are now understood as active participants in neurofibroma pathogenesis. Through paracrine signalling, they stimulate Schwann cell proliferation.[3,7] Hong et al demonstrated their abundance in both familial and sporadic neurofibromas.[8] Riccardi's neurofibroma-cellular interaction hypothesis further implicated mast cells as drivers of tumor development.[8] Yang et al elucidated the mechanism: NF1-deficient Schwann cells overproduce Kit ligand, attracting c-Kit+ mast cells via the Ras/PI3K/Rac2 pathway. These mast cells secrete angiogenic and growth factors, fostering proliferation and neovascularization.[8] Multiple histological variants of neurofibroma have been recognized (Table 1).[9] Immunohistochemically, neurofibromas demonstrate diffuse S100 positivity, confirming Schwannian lineage, and a distinctive CD34 fingerprint pattern (as seen in our case), due to parallel arrays of dendritic fibroblasts.[10] Table 2 delineates the IHC profiles across benign and malignant spindle cell tumours of neural, fibro-histiocytic, smooth muscle, and melanocytic origin.[10,11]

Table 1: Histopathological variants of neurofibroma.[9]

S. no.	Histopathological variants of neurofibroma
1	Cellular
2	Myxoid
3	Hyalinized
4	Epithelioid
5	Plexiform
6	Diffuse
7	Pigmented
8	Granular cell
9	Pacinian
10	Atypical
11	Glandular
12	Epithelial
13	Muscular differentiation
14	Lipomatous
15	Fatty changes

Radiological imaging, particularly magnetic resonance imaging (MRI), is helpful in deeper or plexiform lesions. The characteristic "target sign" on T2-weighted imaging- a central hypointense fibrous core encircled by a hyperintense myxoid rim- is regarded as highly suggestive of neurofibroma.[12] Management of SNF is usually conservative, with intervention reserved for symptomatic or cosmetically distressing lesions. In our patient, sequential elliptical excision provided excellent aesthetic results. In unresectable or plexiform variants, particularly within NF1, targeted therapies such as MEK inhibitors (selumetinib, mirdamitinib, trametinib) have emerged as promising agents by suppressing the upregulated MAPK/ERK pathway resulting from NF1 loss.[13]

Table 2: Immunohistochemistry profile of spindle cell tumours- fibro-histiocytic, smooth muscle, neural and melanocytic tumours.[10,11]

Tumor/ differen-tial	S100	SOX10^	CD34	EMA †	Factor XIIIa	SMA §	Desmin	Mel-an A	Calre-tinin	CD56	Other features
Neurofib-roma	+	+	Diffuse/high sensitivity (80.2%)	–	–	–	–	–	–	9.8 %	Fingerprint pattern
Desmopl-astic melanoma	+	+	–/Patchy	–	–	–	–	–	–	–	Melanocy-te tumor
Schwann-oma	+	–	Patchy (42.6%)	–	–	–	–	–	+ (Spec-ific)	77.2 %	Capsule+, Verocay bodies
DFSP*	–	–	Diffuse	–	–	–	–	–	–	–	COL1A1-PDGFB ‡ fusion
Perineur-ioma	–	–	+	+	–	–	–	–	–	–	Perineurial cell marker
Dermato-fibroma	–	–	–	–	+	–	–	–	–	–	Benign fibrohistio-cytic
Leiomyo-ma	–	–	–	–	–	+	+	–	–	–	Smooth muscle tumor
Neurotized nevus	+	–	–	–	–	–	–	+	–	–	Melanoc-yte lesion

*DFSP-Dermatofibrosarcoma protuberans, ^SOX-SRY related HMG box, †EMA-epithelial membrane antigen, §SMA-smooth muscle actin, ‡COL1A1-PDGFB-collagen, type I, alpha 1 chain-platelet-derived growth factor, beta polypeptide fusion gene

CONCLUSION

Recognition of segmental neurofibromatosis requires a keen eye for its subtle, yet distinctive clinical and microscopic signatures: dermatomal clustering of lesions, spindle cells with "diving dolphin" nuclei in a fibro-myxoid mast cell- rich stroma, and the S100/CD34 fingerprint immunoprofile. Accurate clinicopathological correlation is indispensable to avoid misclassification among dermal spindle cell neoplasms. Surgical excision remains the treatment of choice for symptomatic or cosmetically significant lesions, offering excellent patient satisfaction. Beyond management, the case underscores the importance of awareness: dermatologists and pathologists must keep this mosaic variant in mind whenever evaluating unilateral dermatomal lesions, ensuring it is consistently included in the differential diagnosis.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Joshi V, Bhoite K, Kharkar V, Joshi R, Das S. The skin's secret script: fingerprints of CD34 and the dolphin dance of Schwann cells. Int J Res Dermatol 2025;11:541-5.