

## Case Report

# Multiple segmental neurofibromatosis: Report of two cases with different presentations

## 多發性節段性神經纖維瘤：二例以不同方式呈現之個案報告

CH Chu 朱建和, TC Chou 周采青, CI Liu 劉權毅, CS Hsu 許至昇, JY Chan 詹融怡,  
CL Ou 歐佳嵐

Segmental neurofibromatosis (SNF) is a rare variant of neurofibromatosis type 1 (NF-1) characterised by the occurrence of neurofibromas and/or café-au-lait macules (CALMs) limited to an area or a segment of the body. It is caused by a postzygotic mutation of the NF-1 gene, resulting in a phenotype of genetic mosaicism. Genetic mutations may occur in both somatic and gonadal cell lines. Early recognition of SNF and offering genetic counselling are important because the patients of SNF may have offspring with full-brown neurofibromatosis type 1. Herein, we report two cases of multiple SNF with different presentations: one presents with both neurofibromas and CALMs, the other presents with isolated neurofibromas.

節段性神經纖維瘤為第一型多發性神經纖維瘤(NF-1)的少見變異型，典型症狀為在身體局部或體表神經節出現多個神經纖維瘤以及/或者咖啡牛奶斑，目前認為是NF-1基因發生接合子後的體細胞突變所造成，由於基因突變不只影響體細胞，性腺細胞也可能受影響，意謂著患有節段性神經纖維瘤個案之後代可能罹患第一型多發性神經纖維瘤，早期辨認出節段性神經纖維瘤並提供遺傳諮詢是非常重要的，在此我們將報告二例以不同方式呈現的多發性節段性神經纖維瘤之個案。

**Keywords:** Café-au-lait macule, segmental neurofibromatosis, neurofibroma

**關鍵詞：**咖啡牛奶斑、節段性神經纖維瘤、神經纖維瘤

### Department of Dermatology, Cathay General Hospital, Taipei, Taiwan

CH Chu, MD  
TC Chou, MD  
CI Liu, MD  
JY Chan, MD  
CL Ou, MD

### Department of Family Medicine, Sijhih Cathay General Hospital, New Taipei City, Taiwan

CS Hsu, MD

Correspondence to: Dr. CL Ou

Department of Dermatology, Cathay General Hospital, 280 Renai Rd. Section 4, Taipei, Taiwan

## Introduction

Neurofibromatosis type 1 (NF-1) is an autosomal dominant, multisystem disorder, which primarily affects neural crest-derived cells, occurring at a rate of one case per 3,000 live births with nearly 100% penetrance of the disease. Segmental neurofibromatosis (SNF) is an uncommon variant of NF-1, caused by a postzygotic mutation in NF-1 gene. The classic features of SNF include café-au-lait spots (CALMs), freckles and/or neurofibromas in a dermatomal distribution or following lines of Blaschko, without family history

or systemic involvement. We describe two cases of SNF with different presentations.

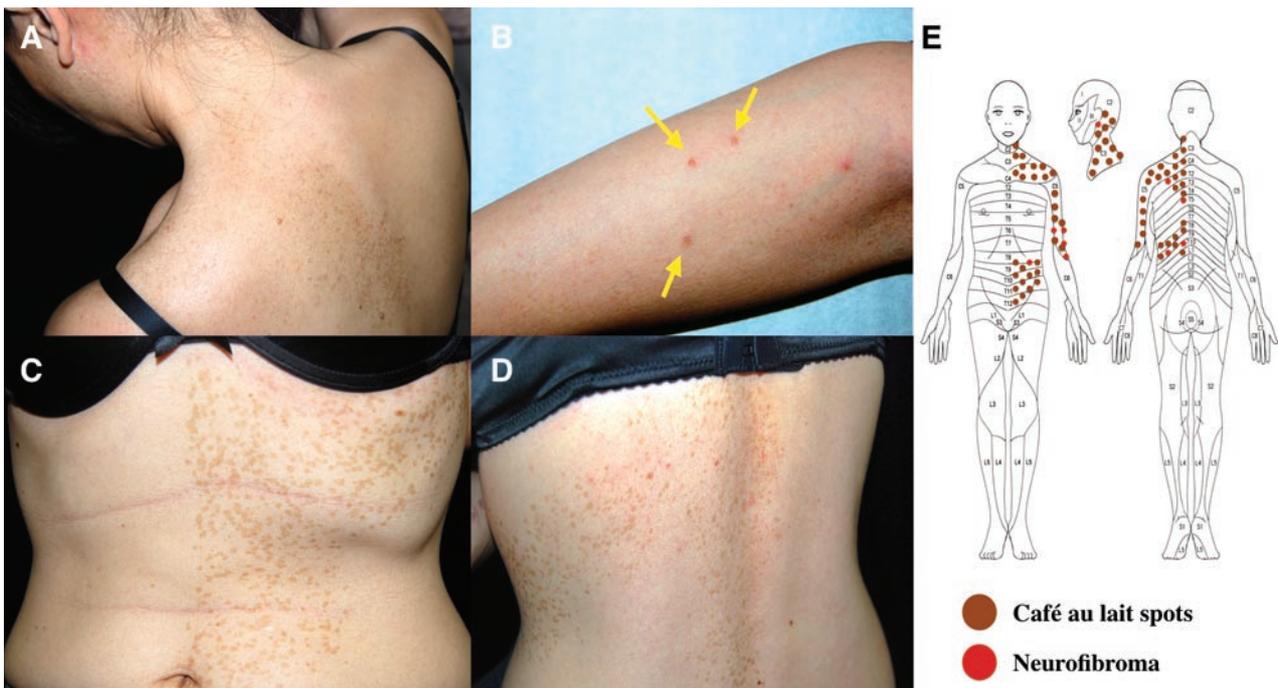
### Case 1

A 43-year-old woman presented to our hospital with progressive development of several skin-colored to erythematous soft papules on her left postauricular area, forearm, and back, admixed with reticular tan macules on her left postauricular area, neck, nape, shoulder, upper limb, abdomen, and back (Figures 1a-d). She reported that those tan macules had developed in her childhood but the skin-coloured papules appeared and increased in number in recent 10 years. All these lesions were asymptomatic. On physical examination, all lesions were confined to left C2-C5 and T7-T10 dermatomes (Figure 1e). Histopathological examination showed typical features of neurofibromas for soft papules on her left postauricular area (Figures 2a & 2b) and left forearm (Figures 2c-e) and the pathology of those tan macules was compatible with CALM (Figure 2f).

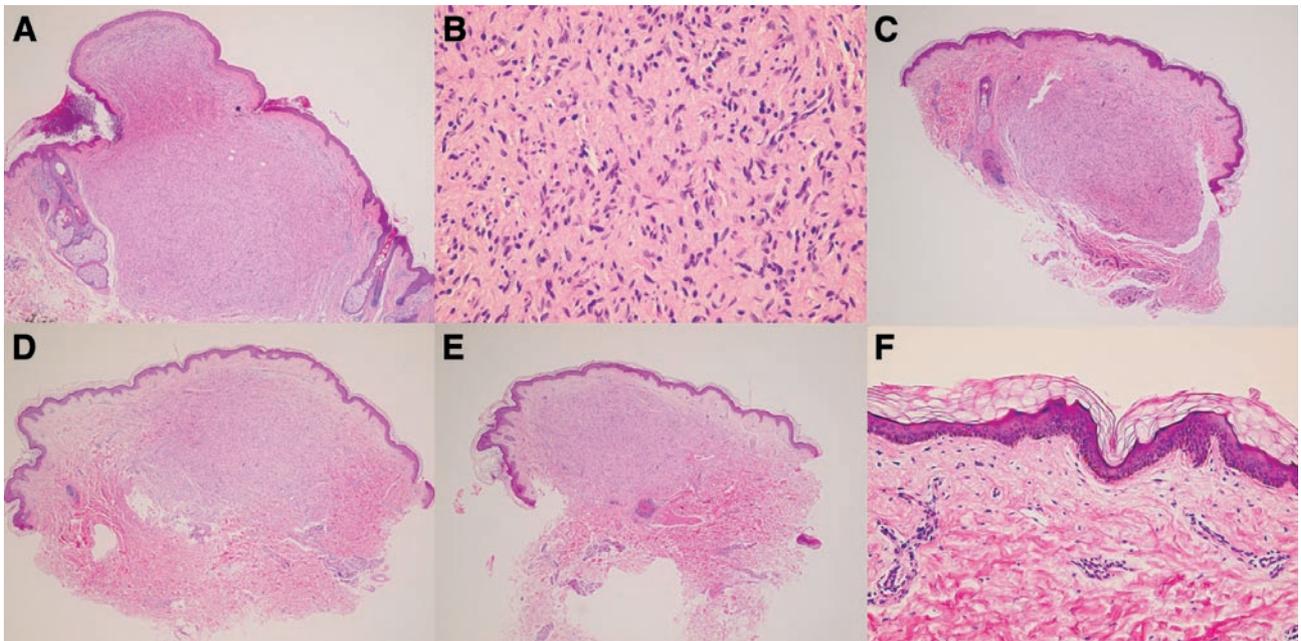
### Case 2

A 49-year-old woman presented with a history of multiple skin tumours, which first appeared as a single nodule on her right side of chest wall at age 40. She did not seek any medical opinion or treatment as the lesion was very small and painless. Since then, she noted gradually increasing numbers of these lesions which extended to the right shoulder and back (Figures 3a & 3b). Physical examination showed multiple scattered 3-5 mm erythematous papules as well as violaceous anetodermic patches, following the right C4-C5 and T7-T10 dermatomes (Figure 3c). No axillary freckles or CALMs were noted. Histopathological examination of the papule and the anetodermic patch both revealed the usual types of neurofibromas (Figures 4a & 4b).

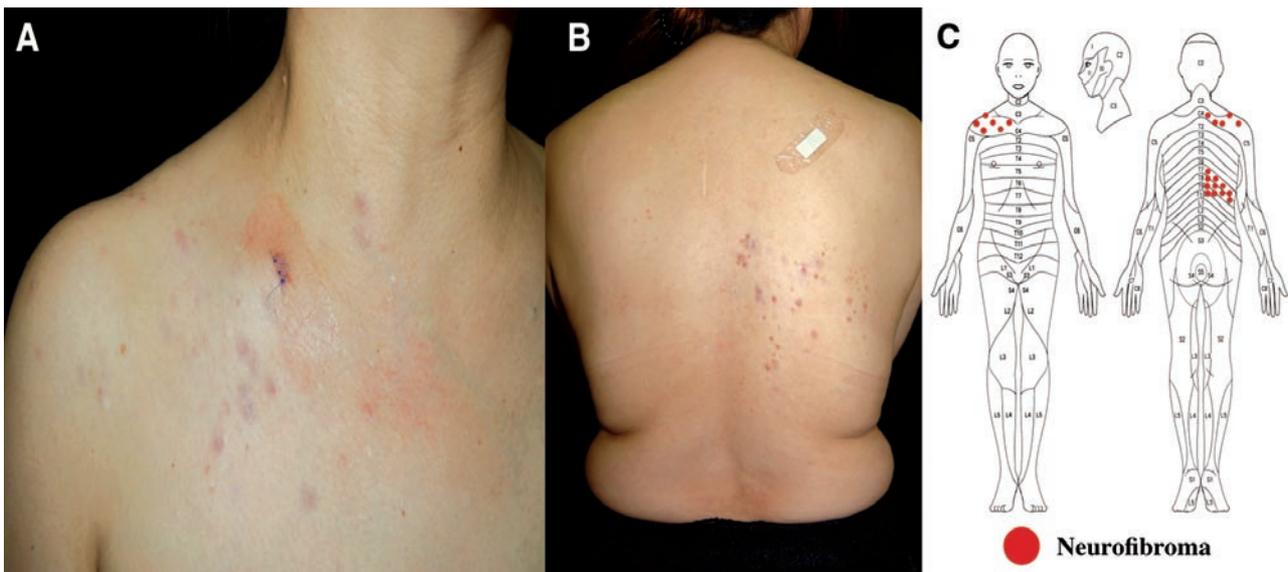
Both of cases had no family history of neurofibromatosis and denied similar lesions in their children (except case 1 who did not have any children). None of them showed other features of generalised (classic) neurofibromatosis type 1.



**Figure 1.** Few skin-coloured to erythematous papules admixed with multiple tan macules on (a) the left side of nape, shoulder, upper back, postauricular area, (b) upper limb (arrows indicate the biopsy sites), (c) abdomen, flank and (d) back. (e) Illustration of distribution of lesions in this patient.



**Figure 2.** Scanning views of the papules from (a) left postauricular area and (c)(d)(e) left upper limb: relatively well-circumscribed dermal tumours composed of small spindle cells (H&E, original magnification x 40). (b) Left postauricular area tumour consisting of loosely arranged spindled cells with scanty pale cytoplasm and elongated wavy nuclei set in a fibrillar stroma (H&E, original magnification x 400). (f) Section of left abdominal macule: increased melanin in basal layer without increased melanocytes or elongation of rete ridges: findings compatible with CALM (H&E, original magnification x 400).



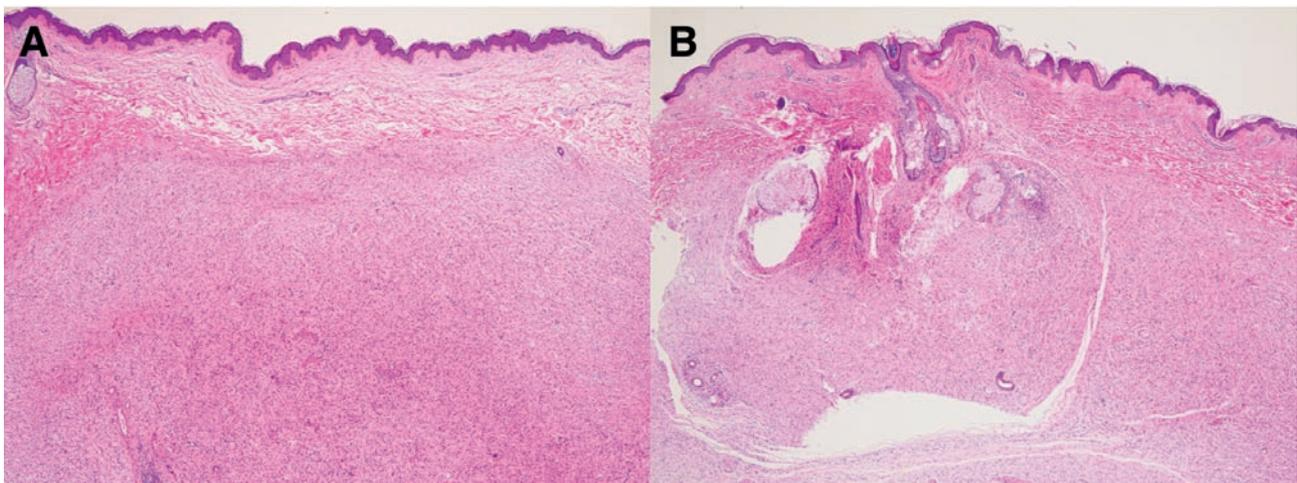
**Figure 3.** Multiple 3-5 mm erythematous papules and violaceous anetodermic patches on (a) right anterior chest, shoulder and (b) back. (c) Distribution of lesions in this patient.

## Discussion

Neurofibromatosis is a heterogeneous group of disorders, affecting multiple systems, mainly the nervous system and skin. The major features include CALMs (six or more), axillary or inguinal freckling, peripheral neurofibromas, and pigmented iris hamartomas (Lisch nodules). Von Recklinghausen first described neurofibromatosis type 1 in 1882, and Riccardi classified neurofibromatosis into eight subtypes, based on the great variability of its clinical presentation in 1982.<sup>1</sup> He defined SNF as neurofibromatosis type 5. This uncommon variant of neurofibromatosis is characterised by the presence of neurofibromas and/or CALMs

limited to circumscribed body segments. There is usually neither family history of NF nor systemic involvement.<sup>1</sup> The estimated prevalence of SNF in general population is 0.0006%.<sup>2</sup> However, it is proposed that this prevalence is underestimated because the manifestations of SNF are usually subtle.

Clinically, patients of SNF may be divided into four groups: those with both neurofibromas and pigmentary changes (as case 1), those with neurofibromas only (as case 2), those with pigmentary changes only and those with isolated plexiform neurofibromas (Table 1).<sup>3,4</sup> Females are affected twice as often as males. Lesions are usually unilateral in a dermatomal distribution



**Figure 4.** Histopathological examinations of (a) the anetodermic patch on the right upper back and (b) a papule on the right clavicular area. There is extensive infiltration of the reticular dermis by neurofibromatous tissue in both cases (H&E, original magnification x 40).

**Table 1.** The reported two largest case series

	<b>Case number</b>	<b>Mean age (years)</b>	<b>Pigmentary changes only</b>	<b>Neurofibromas only</b>	<b>Neurofibromas and pigmentary changes</b>	<b>Solitary plexiform neurofibroma</b>	<b>Complications</b>
Ruggieri M et al <sup>3</sup> (Neurology. 2001)	124	17.4 (range from 4 to 70)	86	20	10	8	7 (5.6%)
Tanito K et al <sup>4</sup> (J Dermatol. 2014)	58	23.4 (range from 1 to 69)	32	5	13	8	4 (6.9%)

although about 6% of cases manifest with bilateral involvement of the body segments and pigmentary changes along the lines of Blaschko.<sup>3</sup> Most commonly, patients present with neurofibromas only or pigmentary changes only, and lesions occupy cervical or thoracic dermatome.<sup>3,4</sup> The majority of patients are asymptomatic.<sup>4,5</sup> The onset of skin lesions in SNF is similar to generalised NF-1: pigmentary changes and plexiform neurofibromas in childhood and neurofibromas in adulthood.<sup>3</sup> However, not all patients with pigmentary changes develop neurofibromas in the affected area in adulthood. For patients with only pigmentary changes or neurofibromas only, the mutations seem to appear late in embryonic development involving only melanocytic or neurological cell lineages.

As for patients with pigmentary changes only, the differential diagnosis includes McCune-Albright syndrome and partial unilateral lentiginosis (PUL). Compared with SNF, the CALMs of McCune-Albright syndrome are typically larger and fewer in number with a midline demarcation; polyostotic fibrous dysplasia and/or endocrine hyperfunction may also be present. PUL is characterised by multiple lentigines grouped within an area of normal skin, often in a segmental pattern and appearing at birth or in childhood. It has been speculated that PUL might represent a forme fruste or even be part of the spectrum of SNF because SNF or Lisch nodules have been present in some cases of PUL.<sup>6</sup>

Segmental neurofibromatosis is explained by somatic mosaicism of the postzygotic NF-1 gene mutation. The sporadic patients of generalised NF-1 represent mutations occurring very early in embryonic development. At the other extreme, in individuals with isolated CALMs and/or neurofibromas without other disease features, the somatic mutations occur in terminally differentiated cells. Since SNF results from postconceptional mutations of NF-1 gene in a subset of cells, nearly all cases are sporadic. Recent research has confirmed that postzygotic

NF-1 gene mutation may occur in both somatic and gonadal cell lines. It means that the offspring of patients with SNF are at risk of developing full-brown (generalised) NF-1.<sup>7</sup> The exact risk of transmission of mutant NF-1 gene from patients with SNF to offspring is not yet known, but based on animal studies, it seems to be proportionate to the percentage of body surface area involved, rather than on the affected skin overlying the gonads.<sup>3</sup> The small risk of having a child with full-brown (generalised) NF-1 should be discussed with those planning to have children.

Complications associated with generalised NF-1 include learning difficulties; plexiform neurofibromas; neurological, orthopedic and ophthalmological complications; as well as an increased risk of specific malignancies.<sup>8</sup> In contrast to generalised NF-1, systemic involvement is uncommon in patients of SNF.<sup>3,4</sup> Ruggieri et al reported 124 patients with SNF and found that only 7 (5.6%) of patients had NF-1-associated complications, which included learning difficulties, plexiform neurofibromas, optic pathway gliomas, and pseudarthrosis.<sup>3</sup> In another series of 58 cases, only four (6.9%) patients had NF-1-associated complications, including language delay (n=1) and bone deformity (n=3).<sup>4</sup> Lisch nodules, are rarely encountered.<sup>5,6,9,10</sup> Some authors have propose that in the absence of Lisch nodules, the risk of genetic transmission is minimal.<sup>10</sup> In contrast to generalised NF-1, Lisch nodules are observed unilaterally in patients of SNF.

According to the American Society of Clinical Oncology, the overall lifetime risk of developing cancer in patients of generalised NF-1 is about 7%.<sup>11</sup> Segmental neurofibromatosis was previously considered to be less commonly associated with malignancy. However, one recent study suggests that the incidence of malignancy in patients with SNF may be comparable to generalised NF-1.<sup>12</sup> The most prevalent malignancies in SNF are similar to generalised NF-1, including malignant peripheral nerve sheath tumor, malignant melanoma, breast cancer, colon cancer,

gastric cancer and lung cancer. Therefore, age-appropriate malignancy screening is recommended.

Initial evaluation of patients with suspected SNF is directed at detection of generalised disease. Dermatologists should perform a thorough physical examination to investigate other related cutaneous findings, radiological examination for possible bone deformity and refer for screening for Lisch nodules by an ophthalmologist. A positive family history and the presence of bilateral Lisch nodules in patients raises the possibility of generalised NF-1 instead of SNF.<sup>10</sup> Genetic testing may help to confirm the diagnosis in uncertain cases.

To date, there are no specific management guidelines for SNF. Although patients with SNF are at a lower risk for developing generalised NF-1 associated complications, the estimated occurrence of related malignancies in these patients may be approaching the frequency observed in generalised NF-1. Long-term monitoring for complications and malignancies, as in patients with generalised NF-1, is still recommended. Genetic counselling and prenatal diagnostic testing should be provided to those considering having a baby.

In conclusion, we presented two cases with different patterns of SNF; both involve multiple segments. Dermatologists should be aware of this under-recognised entity to provide appropriate genetic counselling and periodic monitoring for associated complications and malignancies.

## References

1. Riccardi VM. Neurofibromatosis: clinical heterogeneity. *Curr Probl Cancer* 1982;7:1-34.
2. Wolkenstein P, Mahmoudi A, Zeller J, Revuz J. More on the frequency of segmental neurofibromatosis. *Arch Dermatol* 1995;131:1465.
3. Ruggieri M, Huson SM. The clinical and diagnostic implications of mosaicism in the neurofibromatoses. *Neurology* 2001;56:1433-43.
4. Tanito K, Ota A, Kamide R, Nakagawa H, Niimura M. Clinical features of 58 Japanese patients with mosaic neurofibromatosis 1. *J Dermatol* 2014;41:724-8.
5. Sloan JB, Fretzin DF, Bovenmyer DA. Genetic counseling in segmental neurofibromatosis. *J Am Acad Dermatol* 1990;22:461-7.
6. Wong SS. Bilateral segmental neurofibromatosis with partial unilateral lentiginosis. *Br J Dermatol* 1997;136:380-3.
7. Consoli C, Moss C, Green S, Balderson D, Cooper DN, Upadhyaya M. Gonosomal mosaicism for a nonsense mutation (R1947X) in the NF1 gene in segmental neurofibromatosis type 1. *J Invest Dermatol* 2005;125:463-6.
8. Boyd KP, Korf BR, Theos A.. Neurofibromatosis type 1. *J Am Acad Dermatol* 2009;61:1-16.
9. Ruggieri M, Pavone P, Polizzi A, Di Pietro M, Scuderi A, Gabriele A, et al. Ophthalmological manifestations in segmental neurofibromatosis type 1. *Br J Ophthalmol* 2004;88:1429-33.
10. Demierre MF, Gerstein W. Segmental neurofibromatosis with ipsilateral renal agenesis. *Int J Dermatol* 1996;35:445-7.
11. Cancer.net. Neurofibromatosis Type 1. Update: September 2014. Available at <http://www.cancer.net/cancer-types/neurofibromatosis-type-1>. [Date accessed: March 15, 2015].
12. Dang JD, Cohen PR. Segmental neurofibromatosis and malignancy. *Skinmed* 2010;8:156-9.