CASE REPORT

Neurofibromatosis with Unilateral Segmental Lentiginosis: A Case Report

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Abstract: Neurofibromatosis type 1 (NF1) is a genetic, neuroectodermal, and multisystemic disease caused by NF1 loss-of-function variants with an autosomal dominant inheritance pattern. It leads to developmental abnormalities in neural, osseous, and epidermal tissues, resulting in impaired regulation of cell growth and differentiation, and ultimately in tumorigenesis and non-neoplastic manifestations. We report the case of a 59-year-old Filipino female presenting with papules and nodules on the trunk and extremities, as well as macules and patches on the left side of the face, trunk, and extremities. The lesions had been evolving since birth, with no prior consultations or interventions. This report aims to describe a rare presentation of bilateral segmental NF1 with partial unilateral lentiginosis, contributing to the scarce literature on mosaic NF1 variants in the Philippines.

Keywords: Neurofibromatosis type 1, NF1, Neurofibroma, Von Recklinghausen disease, Lentiginosis, Case report

Introduction

Neurofibromatosis type 1 (NF1) is an inherited neurocutaneous and multisystemic disorder characterized by developmental complications in neural, osseous, and epidermal tissues [1]. Also known as Von Recklinghausen disease, NF1 is a tumor-predisposition syndrome caused by loss-of-function mutations in the neurofibromin 1 gene, arising either through inheritance or de novo events [2].

NF1 follows an autosomal dominant pattern of inheritance, involves multiple tissues, and is clinically characterized by features such as ≥6 café-au-lait macules (CALMs), neurofibromas of any type including plexiform, axillary or inguinal freckling, hamartomatous Lisch nodules of the iris, optic pathway gliomas, and disease-specific bony dysplasia. In addition to benign and malignant tumor development, affected individuals are also at increased risk of musculoskeletal, cardiovascular, and nervous system abnormalities [2].

Mosaicism occurs when a postzygotic gene mutation gives rise to two genetically distinct cell lines within the same individual [3]. Mosaic forms of NF1 may present as segmental, generalized, or gonadal variants [4]. In segmental NF1, clinical manifestations are confined to a specific body region, whereas in generalized NF1, they involve the entire body [1,5].

A systematic review and meta-analysis by Lee et al. estimated the prevalence of NF1 at approximately 1 in 3,164 individuals, with a pooled birth incidence of 1 in 2,662 [6], underscoring its rarity yet global clinical significance. However, in the Philippines, the true incidence and prevalence remain unknown due to challenges in obtaining accurate epidemiological data. Many cases may be underreported or diagnosed late, as early manifestations often appear benign and may delay medical consultation.

This case report presents a rare case of bilateral segmental NF1 with partial unilateral lentiginosis in a 59-year-old female. Documenting this unusual dual presentation adds to the scarce literature on mosaic NF1 variants, highlights atypical patterns that are prone to misdiagnosis, and expands the recognized phenotypic spectrum of NF1. Such reports may also provide insights into shared embryologic and genetic mechanisms underlying its diverse clinical manifestations.

Case Presentation

A 59-year-old female patient presented with papules and nodules on the trunk and extremities, as well as dark pigmentation affecting the left side of the face, trunk, and extremities. The lesions had been present since birth, gradually increasing throughout childhood and extending to involve the trunk and left extremities. Despite the progressive nature of these changes, the patient's family did not seek medical consultation, and no interventions were initiated.

Over time, the areas of hyperpigmentation persisted without significant changes in size or number and were not associated with other symptoms. The patient reported that the lesions remained stable until approximately three years prior to consultation, when she began to notice the gradual development of multiple nodularities over the anterior and posterior trunk and the left upper and lower extremities. The persistence and progression of these lesions prompted medical evaluation.

At presentation, the patient denied visual changes, eye pain, or proptosis, as well as hearing loss or otalgia. She also denied musculoskeletal or neurologic symptoms, including limitations in movement, spinal deformities, dizziness, seizures, or altered sensorium. Family history was notable for skin hyperpigmentation on the maternal grandmother's left thigh; no other relatives were reported to have similar manifestations.

Dermatologic examination revealed Fitzpatrick skin type III, with multiple, well-defined brown macules and patches, largest measuring approximately 2.5 × 4.5 cm, distributed on the left side of the face, trunk **(Figure 1A)**, and left upper and lower extremities. Multiple well-defined, soft, skin-colored, non-pruritic, non-tender papules and nodules were also observed **(Figure 1B)**, several demonstrating the buttonhole sign. These were scattered over the anterior and posterior trunk and the left upper and lower extremities. Additional solitary nodules were noted on both breasts, one of which showed a central black punctum **(Figure 1C).**

Neurologic evaluation revealed intact sensory function, including normal vision and hearing, with motor strength graded 5/5 in all extremities. The remainder of the physical examination was unremarkable. Based on the clinical findings, the initial impression was NF1.

To evaluate the cellular architecture and characteristics of the lesions, a cyto-histopathologic assessment was performed. Skin tissue samples were obtained from two separate lesions: a 4 mm punch biopsy of the hyperpigmented patch and a shave biopsy of the skin-colored papule on the abdomen. The patient was prescribed mupirocin ointment for application to eroded areas twice daily for seven days. Systemic examination findings were unremarkable.

Histopathological analysis revealed elongated rete ridges with basal layer hyperpigmentation, consistent with a melanotic macule. Additionally, both the hyperpigmented macule and the skin-colored papule on the abdomen demonstrated unencapsulated, symmetrical proliferation of spindle-shaped cells with wavy nuclei, consistent with neurofibroma **(Figures 2A to 2D).**

With clinicopathologic correlation, a final diagnosis of bilateral segmental neurofibromatosis with partial unilateral lentiginosis was established. Although genetic sequencing and mammography were advised, the patient declined further diagnostic evaluation, expressing that her primary concern was symptomatic treatment rather than additional investigations

Definitive management was recommended, consisting of ablative laser treatment for the removal of neurofibromas and Q-switched neodymium: yttrium-aluminum-garnet (QS Nd:YAG) laser therapy for the lightening of hyperpigmented macules and patches. However, the patient declined intervention, citing a profound acceptance of her condition and a lack of concern regarding the cosmetic manifestations. Regular screening and periodic follow-up assessments were also recommended.

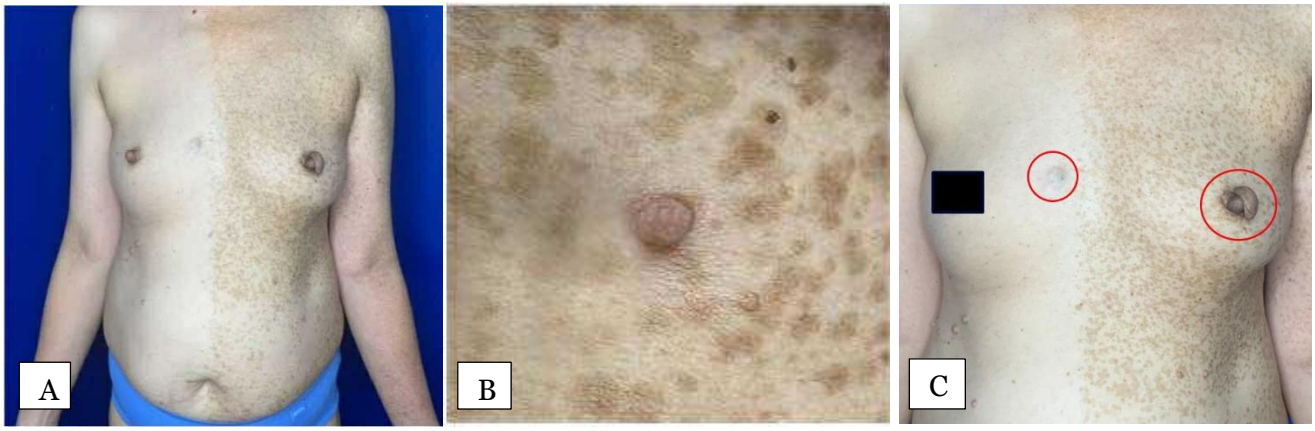

Figure 1. (A) Multiple brown macules and patches on the left side of the trunk, consistent with unilateral lentiginosis; **(B)** Multiple well-defined, soft, skin-colored, non-pruritic, non-tender papules and nodules, several demonstrating the buttonhole sign; **(C)** A well-defined, skin-colored nodule with a central black punctum at the 3 o'clock position of the right breast (~5 cm from the nipple), along with well-defined, soft nodules on the areola of the left breast, partially covering the nipple.

Discussion

NF1, is a tumor-predisposition condition caused by heterozygous germline pathogenic variants in the Neurofibromin 1 tumor suppressor gene (HGNC:7765), located on chromosome 17q11.2, which encodes the protein neurofibromin [2,7]. These variants lead to tumor development, predominantly in neural and epidermal tissues, though NF1 exhibits wide phenotypic variability. Early manifestations may appear as benign epidermal pigmentary changes, which often delay medical consultation.

Establishing the epidemiologic characteristics of NF1 remains challenging due to its phenotypic variability, age-dependent expression, and unpredictable disease course [8]. A diagnosis of NF1 is typically established based on the presence of two or more diagnostic criteria outlined by the National Institutes of Health (NIH) in 1988 [9]. These criteria were revised in 2020 to include additional clinical features and to incorporate genetic testing [10].

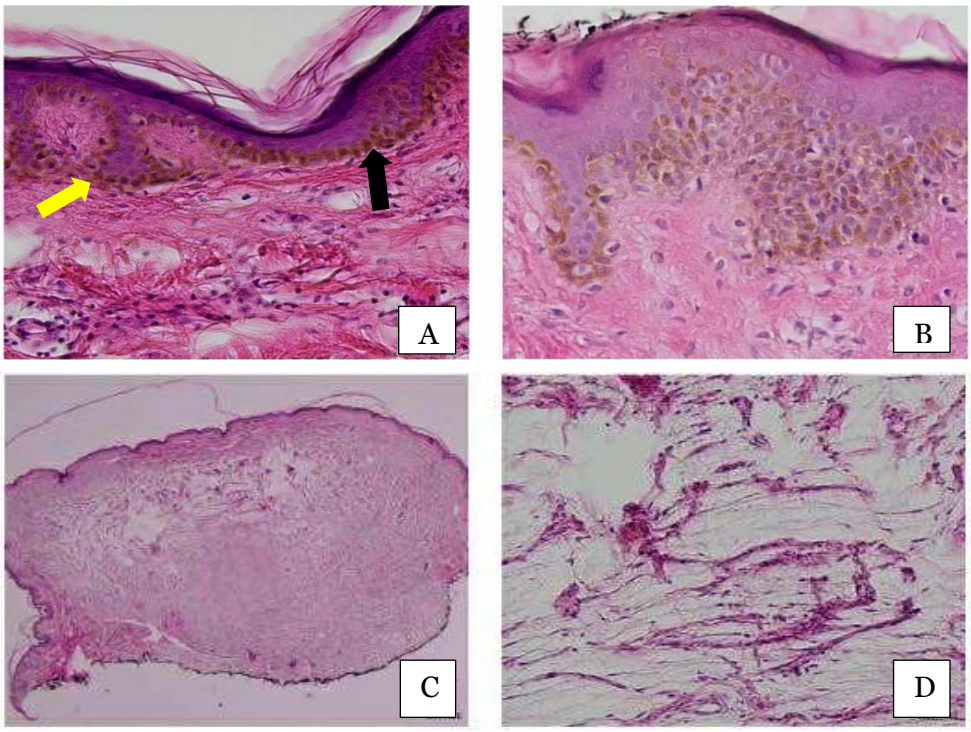

Figure 2. (A) Elongated rete ridges in the epidermis (yellow arrow) and basal layer hyperpigmentation (black arrow) (H&E, 10×); **(B)** Closer view showing basal layer hyperpigmentation (H&E, 40×); **(C)** Non-encapsulated, circumscribed tumor (H&E, 2×); **(D)** Myxoid stroma with spindle-shaped cells (H&E, 10×).

Segmental neurofibromatosis is rare and usually presents with unilateral CALMs, freckling, and/or neurofibromas [11]. Individuals with this variant have a higher risk of developing various malignancies [12], including peripheral nerve sheath tumors, melanoma, and cancers of the breast, colon, stomach, lung, and Hodgkin lymphoma [13,14].

Segmental neurofibromatosis may go undiagnosed as patients often perceive it as a cosmetic issue and are reluctant to seek medical attention. These diagnostic and management challenges are further compounded by the cost of recommended tests and interventions, particularly in patients with limited resources. Such barriers can affect health-seeking behavior, resulting in delayed consultation despite early symptom onset. Consequently, these delays may contribute to the underreporting of NF1 cases and the limited availability of documented data on the condition.

Additionally, the absence of neurofibromas can lead to the condition being overlooked [15]. Feret et al. reported a case of segmental NF1 in a patient presenting with CALMs and right inguinal freckling, without neurofibromas [16]. Similarly, İritaş and İritaş described a 30-year-old woman with segmental neurofibromatosis presenting with CALMs, axillary freckling, and Lisch nodules, but no evidence of neurofibromas. Consequently, segmental neurofibromatosis is likely underreported due to the challenges in achieving an accurate diagnosis [15].

However, in the present case, the patient exhibited neurofibromas, in addition to multiple disseminated CALMs and axillary freckling, thus fulfilling the diagnostic criteria for segmental NF1. The presence of neurofibroma was further confirmed through histopathologic assessment, which revealed an unencapsulated, uniformly symmetrical proliferation of spindle-shaped cells

with wavy nuclei, a characteristic feature of neurofibroma [17].

Various treatment options are available for the management of NF1; however, they primarily address existing manifestations, as tumor development may continue as long as the pathogenic NF1 gene is present. The treatment of cutaneous neurofibromas depends largely on tumor size, with different modalities indicated accordingly: surgery for large tumors (>4 cm), modified biopsy removal for small to medium-sized tumors (up to 2 cm), carbon dioxide (CO_2) ablative laser for small tumors (up to 2 cm), photocoagulation for very small tumors (<1 cm), and electrodessication for very tiny tumors (<5 mm) [18]. Although surgical interventions offer benefits, such as minimal scarring and higher patient satisfaction, resection carries a risk of recurrence and may induce the growth of new neurofibromas [19], making laser-based interventions a preferable option for the patient.

In the present case, the patient was advised to undergo CO_2 ablative laser treatment for the removal of neurofibromas, and QS Nd:YAG laser therapy for lightening the hyperpigmented macules and patches, as the definitive management plan. CO_2 laser ablation provides results comparable to surgical excision for the management of cutaneous neurofibromas [20,21], with the ability to remove multiple lesions in a single procedure [19]. The expected adverse events, including post-operative pain and pruritus, are generally manageable.

While NF1 demonstrates an autosomal dominant pattern of inheritance, the reproductive risk associated with segmental NF1, which involves somatic mosaicism, depends on whether germline cells are affected. This underscores the importance of counseling the patient regarding the genetic and familial implications of NF1. Genetic testing may be performed to identify pathogenic NF1 variants, which can serve as a reference for future prenatal counseling and diagnostic testing [22]. Timely diagnosis and appropriate genetic counseling can enhance patient outcomes [15]. However, genetic testing was not performed, as the patient declined to undergo it.

Conclusion

This case describes a patient with segmental NF1 and partial unilateral lentiginosis, representing an uncommon overlap of these dual presentations. Reporting this rare combination expands the recognized phenotypic spectrum of NF1. While NF1 is typically described in pediatric and young adult populations, this case demonstrates a later onset of neurofibromas, providing insight into the natural history of atypical NF1. The familial occurrence between the patient and her grandmother may reflect either incomplete penetrance, despite NF1 generally showing near-complete penetrance after childhood or familial mosaic inheritance, which could explain the absence of manifestations in the patient's parents; both mechanisms remain underexplored. Additionally, the absence of multisystemic involvement beyond cutaneous lesions raises questions about systemic manifestations in atypical NF1. Future studies reporting atypical NF1 presentations are recommended to further define the phenotypic spectrum and identify features characteristic of other NF1 subtypes.

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Potential Conflict of Interest

The authors declare no conflicts of interest, financial or otherwise, including familial or proprietary considerations.

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