Unusual Bilateral Distribution of Neurofibromatosis Type 5 on the Distal Upper Extremities

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PRACTICE **POINTS**

- Segmental neurofibromatosis, or neurofibromatosis type 5 (NF5), is a rare subtype of neurofibromatosis type 1 (NF1)(also known as von Recklinghausen disease).
- Individuals with NF5 are born mosaic with 2 genotypes—one normal and one abnormal—for the neurofibromin 1 gene, *NF1*. This is in contrast to the autosomal-dominant and systemic characteristics of NF1, which has the *NF1* gene mutation in all cells.

To the Editor:

Segmental neurofibromatosis, or neurofibromatosis type 5 (NF5), is a rare subtype of neurofibromatosis type 1 (NF1)(also known as von Recklinghausen disease). Phenotypic manifestations of NF5 include café-au-lait macules, neurofibromas, or both in 1 or more adjacent dermatomes. In contrast to the systemic features of NF1, the dermatomal distribution of NF5 demonstrates mosaicism due to a spontaneous postzygotic mutation in the neurofibromin 1 gene, *NF1*. We describe an atypical presentation of NF5 with bilateral features on the upper extremities.

A 74-year-old woman presented with soft pink- to flesh-colored growths on the left dorsal forearm and hand that were observed incidentally during a Mohs procedure for treatment of a basal cell carcinoma on the upper cutaneous lip. The patient reported that the lesions initially appeared on the left dorsal hand at approximately 16 years of age and had since spread proximally up to the mid dorsal forearm over the course of her lifetime. She denied any pain but claimed the affected area could be itchy. The lesions did not interfere with her daily activities, but they negatively impacted her social life due to their cosmetic appearance as well as her fear that they could be contagious. She denied any family history of NF1.

Physical examination revealed innumerable soft, pink- to flesh-colored cutaneous nodules ranging from 3 to 9 mm in diameter clustered uniformly on the left dorsal hand and lower forearm within the C6, C7, and C8 dermatomal regions (Figure, A). A singular brown patch measuring 20 mm in diameter also was observed on the right dorsal hand within the C6 dermatome, which the patient reported had been present since birth (Figure, B). The nodules and pigmented patch were clinically diagnosed as cutaneous neurofibromas on the left arm and a café-au-lait macule on the right arm, each manifesting within the C6 dermatome on separate upper extremities. Lisch nodules, axillary freckling, and acoustic schwannomas were not observed. Because of the dermatomal distribution of the lesions and lack of family history of NF1, a diagnosis of bilateral NF5 was made. The patient stated she had declined treatment of the neurofibromas from her referring general dermatologist due to possible risk for recurrence.

Segmental neurofibromatosis was first described in 1931 by Gammel,[1] and in 1982, segmental neurofibromatosis was classified as NF5 by Riccardi.[2] After Tinschert et al[3] later demonstrated NF5 to be a somatic mutation of *NF1*,[3] Ruggieri and Huson[4] proposed the term *mosaic neurofibromatosis 1* in 2001.

While the prevalence of NF1 is 1 in 3000 individuals,[5] NF5 is rare with an occurrence of 1 in 40,000.[6] In NF5, a spontaneous *NF1* gene mutation occurs on chromosome 17 in a dividing cell after conception.[7] Individuals with NF5

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The authors report no conflict of interest.

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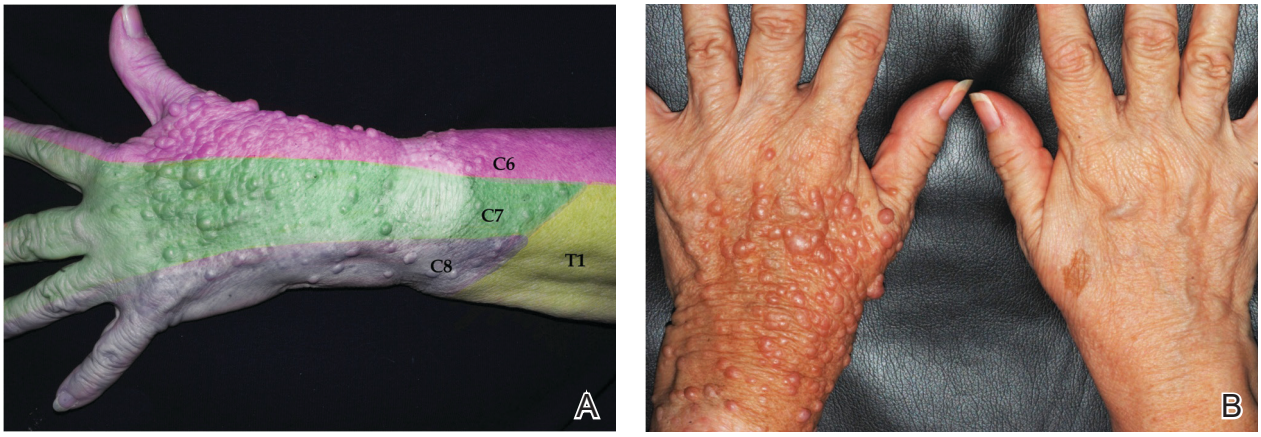
doi:10.12788/cutis.0634



A, Neurofibromas were distributed segmentally on the left dorsal hand and lower forearm in the C6, C7, and C8 dermatomes. B, A 20-mm café-au-lait macule on the right dorsal hand had been present since birth.

are born mosaic with 2 genotypes—one normal and one abnormal—for the *NF1* gene.[8] This contrasts with the autosomal-dominant and systemic characteristics of NF1, which has the *NF1* gene mutation in all cells. Patients with NF5 generally are not expected to have affected offspring because the spontaneous mutation usually arises in somatic cells; however, a postzygotic mutation in the gonadal region could potentially affect germline cells, resulting in vertical transmission, with documented cases of offspring with systemic NF1.[4] Because of the risk for malignancy with systemic neurofibromatosis, early diagnosis with genetic counseling is imperative in patients with both NF1 and NF5.

Neurofibromatosis type 5 is a clinical diagnosis based on the presence of neurofibromas and/or café-au-lait macules in a dermatomal distribution. The clinical presentation depends on when and where the *NF1* gene mutation occurs in utero as cells multiply, differentiate, and migrate.[8] Earlier mutations result in a broader manifestation of NF5 in comparison to late mutations, which have more localized features. An *NF1* gene mutation causes a loss of function of neurofibromin, a tumor suppressor protein, in Schwann cells and fibroblasts.[8] This produces neurofibromas and café-au-lait macules, respectively.[8]

A large literature review on segmental neurofibromatosis by Garcia-Romero et al[6] identified 320 individuals who did not meet full inclusion criteria for NF1 between 1977 and 2012. Overall, 76% of cases were unilaterally distributed. The investigators identified 157 individual case reports in which the most to least common presentation was pigmentary changes only, neurofibromas only, mixed pigmentary changes with neurofibromas, and plexiform neurofibromas only; however, many of these cases were children who may have later developed both neurofibromas and pigmentary changes during puberty.[6] Additional features of NF5 may include freckling, Lisch nodules, optic gliomas, malignant peripheral nerve sheath tumors, skeletal abnormalities, precocious puberty, vascular malformations, hypertension, seizures, and/or learning difficulties based on the affected anatomy.

Segmental neurofibromatosis, or NF5, is a rare subtype of NF1. Our case demonstrates an unusual bilateral distribution of NF5 with cutaneous neurofibromas and a café-au-lait macule on the upper extremities. Awareness of variations of neurofibromatosis and their genetic implications is essential in establishing earlier clinical diagnoses in cases with subtle manifestations.

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