Segmental Neurofibromatosis: A Rare Case and Review of the Literature

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Abstract
Segmental neurofibromatosis is a very rare subtype of the neurofibromatoses. Affected individuals have a segmental distribution of neurofibromas or pigmented changes including café-au-lait macules or axillary freckling. It is an example of somatic mosaicism caused by a post-zygotic mutation in the NF1 gene. Familial transmission and systemic complications are rare. We report a case of a 42-year-old female with no family history of neurofibromatosis diagnosed with segmental neurofibromatosis on her right neck and shoulder.

Introduction
Segmental neurofibromatosis (SN) is a rare subtype of the neurofibromatoses. The most recent literature reports only 150 documented cases.1 The prevalence ranges from 0.0014% to 0.002%.2 The first reported cases of segmental neurofibromatosis were published in 1931 by Gammel and in 1956 by Crowe et al.1 Due to the heterogeneous nature of NF, Riccardi created a classification system that divided NF into eight different subtypes (Table 1). SN became labeled neurofibromatosis type V and was defined as café-au-lait macules and/or axillary freckling, and/or neurofibromas distributed in a single unilateral segment of the body, without midline crossing, family history, or systemic involvement.3,4 In 1987, Roth observed that the diverse clinical presentations of SN would not fit into the rigid classification system created by Riccardi, and he therefore divided SN into four subtypes: true segmental, localized with deep involvement, hereditary, and bilateral.1 Herein, we report a case of a patient with true segmental neurofibromatosis.

Case Report
A 42-year-old female with a past medical history significant only for anxiety presented to our dermatology office complaining of “moles” on her right neck extending to her right shoulder. The patient stated that the bigger lesions had been there since birth, and approximately 10 years ago, smaller lesions had erupted in the same region. The patient denied any symptoms, including pruritus or pain. She denied any prior treatments. A complete review of systems was negative, including any visual, hearing, or neurological complications. The patient denied any family history of neurofibromatosis.

Physical examination showed multiple pink-brown, dome-shaped papules and nodules extending unilaterally from her right lower neck to her right shoulder, varying in size from 0.3 cm to 0.8 cm (Figures 1, 2). The patient did not have any signs of axillary freckling, café-au-lait macules, or Lisch nodules.

An excisional biopsy of her right shoulder was performed. Histologic examination showed a well-circumscribed nodule composed of delicate wavy fibrils of neural origin with elongated fibroblasts and some mucoid change in the stroma with a slightly irregular epidermis (Figures 3, 4), consistent with true segmental neurofibromatosis transmitted to offspring in a familial pattern have been reported.1 There have been two case reports of offspring affected with generalized NF with the history of one parent having NF. The large majority of SN cases can be explained by a post-zygotic somatic mutation on the NF1 gene present on chromosome 17.7 The somatic mutation occurs during late embryonic development and results in mosaicism. Mosaicism occurs when cells in the body are of more than one genotype. Somatic mosaicism is not transmitted to offspring because it does not affect gonadal cells. On the contrary, post-zygotic gonadal mosaicism occurs during the early embryonic period in cells that are not terminally differentiated.8,9 Gonadal mosaicism is believed to be the origin of the rare cases of familial transmission that can result in offspring with generalized NF1. Interestingly, the risk of generalized NF1 transmission from a parent with SN has been found to be proportional to the percentage of body involvement in the parent.10 Additional research needs to be undertaken to examine the relationship between more severe presentations of SN and gonadal mosaicism.

Discussion
Genetics
Segmental neurofibromatosis (SN) is a rare clinical subtype of the neurofibromatoses. While neurofibromatosis type 1 (NF1) is primarily inherited in an autosomal-dominant fashion, the majority of SN patients have no consistent pattern of genetic transmission. It is generally considered a non-inheritable disorder. A literature review of 82 cases of SN showed that 93% of patients had no family history.3 However, exceptions to this rule exist, and nine cases of SN
Clinical Presentation

The clinical presentation of SN is fairly standard between patients. However, rare presentations have been reported in the literature. The largest case review of SN was done by Hager in 1997. He examined the clinical presentation of 82 patients with biopsy-proven SN. He found that the median age of onset was 28 years and that the incidence was higher in women (58%). Out of the 82 patients, 100% had neurofibromas, 26% had café-au-lait macules, and 10% had axillary freckling. Most neurofibromas were located unilaterally; however, five patients had bilateral neurofibromas. Most patients had only a single dermatome affected. Interestingly, recent case reports have documented patients with SN present on multiple dermatomes.10 The cervical (38%), thoracic (40%), and lumbar (24%) dermatomes were the most commonly affected regions. Facial involvement is rare but has been reported in five cases.1 Only 21% of patients had any additional systemic involvement. The most common systemic complaints in this study were painful neurofibromas (seven patients) and pruritic neurofibromas (four patients). Another clinical finding appreciated in SN patients is an increase in clinical severity during puberty and pregnancy.2 The increase in severity during pregnancy is directly related to increased activity of progesterone receptors on NF1 tumors cells.3

The increase in severity during pregnancy is directly related to increased activity of progesterone receptors on NF1 tumors cells.3 The clinician should approach suspected SN as a phenotypic subtype of NF1 so as not to miss crucial physical findings more commonly present in generalized disease (NF1). The appearance of Lisch nodules in patients with SN is extremely rare. There has been one documented case of Lisch nodules in a patient originally diagnosed with SN.11 While the exact significance of Lisch nodules in SN is unknown, the absence of Lisch nodules most likely lessens the risk of transmission to offspring.12 Another clinical finding that needs to be examined in patients presenting with suspected SN is asymptomatic internal neurofibromas.3 Patients with internal neurofibromas need further imaging, and depending on the results might need to be reclassified into another subtype of NF.3 Sloan et al. suggests waiting until after puberty to discuss genetic counseling because the absence of Lisch nodules and internal neurofibromas becomes more significant to prognosis at that point, as they usually do not appear until this age.

Association with Malignancy

Recent literature has shown that patients with SN have an increased risk of developing malignant tumors. Ten patients with both SN and malignancies have been reported to date. The incidence of malignancies in patients with SN is 5.3%, compared to the 7% life-time risk for cancer in documented in patients with NF1.12 The two most common malignancies in patients with SN are malignant peripheral nerve sheath tumors and malignant melanoma.13 Malignant peripheral nerve sheath tumors are also the most common malignancy in NF1 patients, revealing the close relationship between these two variants. Other tumors reported include breast cancer, colon cancer, gastric cancer, lung cancer, and lymphoma. SN was diagnosed prior to cancer in half of the cases (5/10), while three of the 10 patients were diagnosed with SN after being diagnosed with cancer.13 This demonstrates the importance of surveillance of SN patients for any suspicious cutaneous lesions or systemic symptoms.

Differential Diagnoses

It is crucial to consider other skin disorders that may present clinically as dermatomal nodules. Infections, benign tumors, malignant tumors, and numerous other mucocutaneous conditions are known causes of dermatomal nodules (Table 1).6 The primary infection that can present in a localized nodular distribution is syphilis. A recent case report examined an unusual presentation of secondary syphilis that followed a localized pattern as two granulation tissue-like nodules.18 The benign tumors that can present similar to SN are linear syringocystadenoma papilliferum (SP) and trichoepithelioma. SP is an uncommon cutaneous adnexal tumor of uncertain etiology. Most cases of SP present as solitary lesions around the head and neck region. It often occurs in association with nevus sebaceous.19 Trichoepithelioma is a facial hair follicle tumor that presents after puberty. It can appear similar to facial SN. On occasion it is associated with rare genetic conditions such as Brook-Spiegler syndrome and Cowden syndrome.20 Other malignant tumors that resemble SN include basal cell carcinoma, squamous cell carcinoma, lymphoma, plasmacytoma, and cutaneous metastases. Other lesions that can mimic SN include sarcoidosis, pseudolymphoma, granuloma annulare, and rheumatic nodules. All of these differentials need to be excluded before the diagnosis of SN is made.

Treatment

The management of cutaneous manifestations of SN can provide immeasurable benefit to the patient. Current treatments are limited, and there is presently no consensus on standard therapy.4 Cutaneous neurofibromas and café-au-lait macules that are bothersome to the patient can be removed. The most common technique to remove neurofibromas is simple surgical excision.15 This may be time-consuming and can result in pain and scarring. Laser ablation and electrocautery have been used on numerous smaller cutaneous neurofibromas; however, recurrences are possible.15 Recent research has shown that CO2 laser treatment for neurofibromas can be effective and provide a high level of patient satisfaction and minimal pain. In one study using Lumenis 30c CO2 laser, more than 90% of the 106 patients in the study were pleased with the treatment. The drawback to the treatment was a 15% local infection rate and hypertrophic scarring.16 Another study using a combination of shave excision and laser photothermocoagulation with 1,444 nm Nd:YAG laser showed excellent results. A seven-month follow-up showed no visible recurrence of neurofibromas or scars.14 Similarly, treatment of neurofibromas with electrocautery was effective. Electrocautery allows for quick treatment of numerous lesions with instant hemostasis and minimal thermal damage to surrounding tissue. In one study, all 97 patients treated with electrocautery were satisfied with the results and had minimal scarring.17

Conclusion

SN is a rare and atypical variant of neurofibromatosis. Our case represents a typical clinical presentation of SN without generalization. The patient denied any familial history of neurofibromatosis or systemic complaints. The patient has one healthy offspring with no signs of neurofibromatosis. Close monitoring is vital for all patients with SN. Additionally, the cutaneous manifestations of SN can inflict emotional distress on patients. Counseling and cosmetic treatments should always be offered to patients. In addition to counseling, our patient had shave removal of the larger neurofibromas and electrocautery of the smaller lesions with no complications.
References


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