Segmental Neurofibromatosis Associated With Renal Angiomyolipomas

Kim-Tan Nguyen, BS; Melvin Chiu, MD

Segmental neurofibromatosis (SN) is a rare disorder characterized by neurofibromas or neurofibromas with café-au-lait spots limited to one region of the body without crossing the midline. Renal angiomyolipomas (AMLs) are rare benign neoplasms usually found in association with tuberous sclerosis (TS). Similar to neurofibromatosis (NF), TS has a high spontaneous mutation rate and a family history often is absent. Although both are autosomal dominant diseases with neural involvement, there are few reports in the literature demonstrating a link between the 2 disorders. We report a case of SN associated with renal AMLs. To our knowledge, there has been only 1 prior report of renal AML associated with NF type 1 (NF1), and there have been no prior reports of SN associated with AML.

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Case Report

A 49-year-old black woman presented with multiple cutaneous nodules on her face that had progressively developed during the past 10 years. Physical examination revealed 3 discrete flesh-colored nodules distributed on the right superior, anterior, and posterior cheek, as well as 1 nodule on the right side of her chin (Figure 1). On palpation, lesions were soft in consistency and slightly tender to touch. There were no telangiectases, ulcerations, or other surface changes noted. Her general physical examination was otherwise unremarkable, including intelligence, speech, and auditory functions. The patient had a history of a right renal angiomyolipoma (AML) that caused flank pain and hematuria, necessitating a nephrectomy. Four years after the nephrectomy, left renal AMLs were diagnosed by ultrasound. The patient denied any history of systemic diseases, seizures, or other neurologic disorders or similar disease in the family. None of the patient's 4 children had any neurologic or cutaneous disease. Biopsy of the facial lesions showed dermal proliferation of loose spindle cells with some formation of fascicles consistent with neurofibromas (Figure 2).

Comment

Segmental neurofibromatosis (SN) is a rare condition that is estimated to affect 1 in 36,000 to 40,000 individuals in the general population, or 0.0027%.[1] von Recklinghausen[2] first described neurofibromatosis (NF) in 1882. In 1931, Gammel[3] made the first reference to SN, and in the 1970s, Miller and Sparkes[4] proposed the term *segmental neurofibromatosis*. In the 1980s, Riccardi[5] classified the different clinical presentations of NF into 7 different types and a "not otherwise specified" category (Table). Segmental neurofibromatosis was classified as type 5.[5] In 1987, Roth et al[6] further classified SN into 4 subtypes: true segmental, localized cases with deep involvement (nonfamilial), hereditary segmental (no deep involvement, familial), and bilateral segmental (no deep involvement, nonfamilial). Segmental neurofibromatosis is thought to be caused by a postzygotic mutation in the NF type 1 (NF1) gene, *NF1*, resulting in a phenotype of gene mosaicism.[7] The term *mosaic NF1* was later proposed to replace SN because of cases involving body segments that were not clearly unilateral, bilateral, or generalized and thus displayed a gene mosaic structure.[1]

The neurofibromas of SN present as soft flesh-colored nodules grouped in a dermatomal distribution. They most commonly occur in a cervical or thoracic dermatome and are usually unilateral.[8] The incidence of neurofibromas on the face with the distribution of the trigeminal nerve is rare, with only a few cases described.[7,9-11] The median age of onset is 28 years, with a higher incidence in

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From the Division of Dermatology, David Geffen School of Medicine at the University of California, Los Angeles.
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Correspondence: Melvin Chiu, MD, Division of Dermatology, David Geffen School of Medicine at UCLA, 52-121 Center for the Health Sciences, Los Angeles, CA 90095 (mchiu@mednet.ucla.edu).

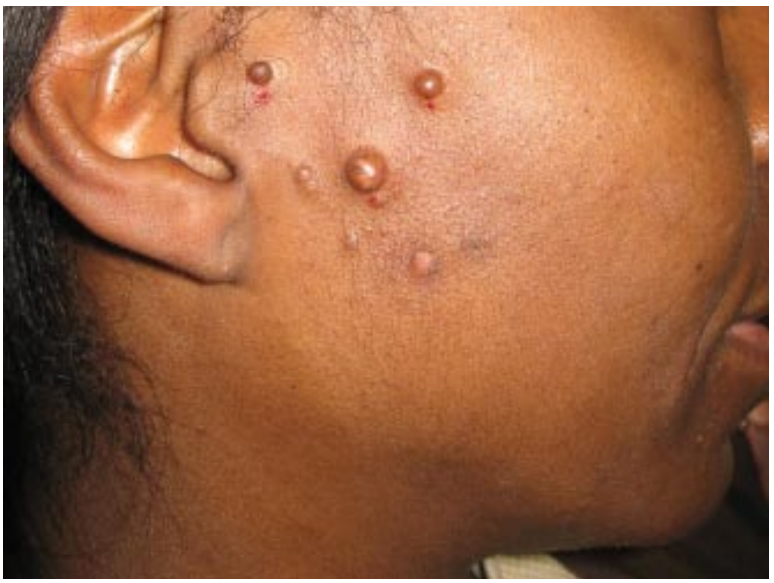

Figure 1. Flesh-colored nodules on the right cheek.

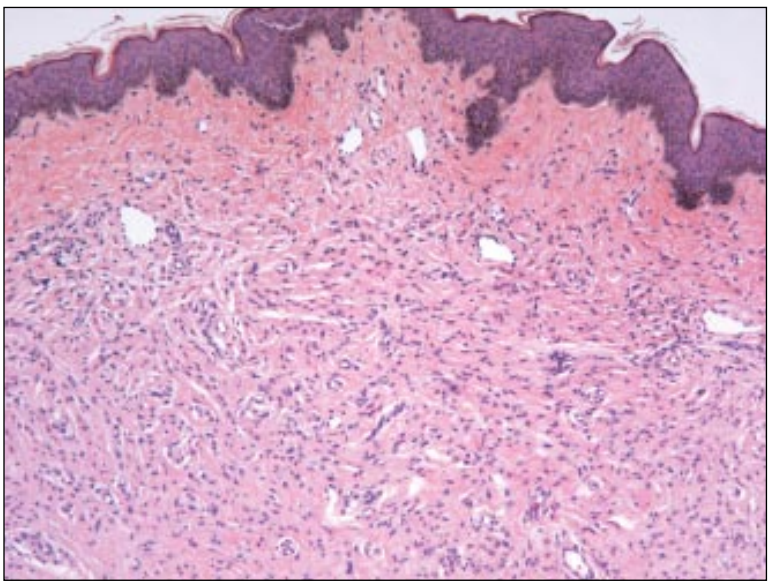

Figure 2. Histopathology of a neurofibroma, showing wavy spindle cells in a pink stroma (H&E, original magnification ×100).

women (58%).[8] Histologically, the neurofibromas in SN are exophytic lesions with an unaffected or atrophied overlying epidermis. They often consist of spaced spindle cells and wavy collagenous strands arranged in the shape of a whirlpool, surrounding vessels.

Other clinical findings normally seen in NF1 are rarely seen in SN. Axillary freckling is described in very few patients.[8] Most patients do not have a family history of NF, and disease-associated systemic involvement is uncommon.[8] There have been reports of SN associated with extracutaneous manifestations, such as soft-tissue hypertrophy, skeletal abnormality, visceral neurofibromas, and unilateral renal agenesis.[12] Segmental neurofibromatosis has been linked to other internal neoplasms. Kim et al[13] linked SN to colon cancer. Kajimoto et al[14] described the concomitant development of SN and gastric carcinoma. Yalcin et al[15] reported a case of SN and bronchoalveolar lung carcinoma and suggested that the neoplastic processes might promote the development of SN.

Renal AMLs are benign tumors of the kidney that contain variable amounts of fatty, muscular, and vascular components. Renal AML was first identified by Fischer[16] in 1911 and designated in 1951 by Morgan et al.[17] Its pathogenesis is still unknown, but approximately 20% of AMLs are found in patients with tuberous sclerosis (TS), a disorder clinically characterized by a triad of mental retardation, epilepsy, and adenoma sebaceum.[18] Previously, most AMLs were diagnosed only after symptomatic presentation. The most feared complication of AML found in 10% of patients is massive retroperitoneal hemorrhage.[18] Common signs and symptoms include flank

Riccardi Classification of Neurofibromatosis (NF)

NF Type	Clinical Features
1	≥6 café-au-lait spots (>5 mm in prepubertal individuals, or >15 mm in postpubertal individuals)
	≥2 neurofibromas of any type or 1 plexiform neurofibroma
	Freckling in the axillary or inguinal regions (Crowe sign)
	Optic glioma
	≥2 Lisch nodules (iris hamartomas)
	Distinctive osseous lesion, such as sphenoid wing dysplasia or thinning of long-bone cortex with or without pseudoarthrosis
	First-degree relative (parent, sibling, or offspring) with NF1 diagnosis by the above criteria
2	(1) Bilateral vestibular schwannomas; (2) family history of NF2 (first-degree relative) plus unilateral vestibular schwannoma and any 2 of the following: meningioma, neurofibroma, glioma, schwannoma, posterior subcapsular lenticular opacities; (3) multiple meningiomas plus unilateral vestibular schwannoma or 2 schwannomas, gliomas, neurofibromas, posterior subcapsular lenticular opacities; or (4) unilateral vestibular schwannoma plus 2 meningiomas, schwannomas, gliomas, neurofibromas, posterior subcapsular lenticular opacities
3	Mixed
4	Variant form (café-au-lait spots in the absence of neurofibromas)
5	Segmental form
6	Café-au-lait spots, absence of neurofibromas
7	Late onset form
8	Not otherwise specified

Abbreviations: NF1, neurofibromatosis type 1; NF2, neurofibromatosis type 2.

Data from Riccardi[5]

pain, hematuria, palpable mass, and hypovolemic shock. More subtle presentations of AML include anemia and hypertension. More recently, AMLs have been incidentally found on abdominal imaging studies.[19] The typical finding of AML on ultrasonography is a well-circumscribed, highly echogenic lesion associated with shadowing. The presence of fat within a renal lesion on computed tomographic scan is diagnostic of AML.[20] Based on reviews, 82% of AMLs 4 cm or greater in diameter were symptomatic.[21] Most patients with life-threatening hemorrhage require nephrectomy, while selective embolization is considered for patients with small symptomatic AMLs or TS or for those patients with alteration in renal function.[22]

The association of SN and renal AML is rare, and to our knowledge, no prior cases have been reported. However, Stone et al[23] reported a case of renal AML associated with NF1 and primary carcinoid of mesentery. There have been few reported cases of simultaneous occurrences of NF1 and TS. Alaraj et al[24] reported a case of NF1 and TS in a 24-year-old man, Phillips and Rye[25] reported a case in a 35-year-old man, and Lee et al[26] reported a case in a 16-year-old adolescent boy. Wheeler et al[27] reported a case of a young girl who inherited

NF1 and TS from her mother and father, respectively. While a chance occurrence between SN and AML may exist here, it is possible that there is an association. The TS genes, *TSC1/TSC2*, which code for hamartin and tuberin, respectively, act as tumor suppressors and inhibit the mammalian target of rapamycin (mTOR), which is involved in tumor growth.[24,28] In TS, aberrant *TSC1/TSC2* release inhibition for mTOR, allowing for tumor growth. With respect to NF, neurofibromin also acts as a tumor suppressor by inhibiting ras signaling. Aberrant neurofibromin activates ras signaling and increases phosphoinositide 3-kinase (PI3-kinase)/Akt signaling, which causes phosphorylation of tuberin and in turn leads to increased mTOR signaling. Similarly, in TS, a loss of inhibition from *TSC1/TSC2* leads to increased mTOR signaling and tumor growth.[27,29] The mechanisms for NF and TS are complex and the nature of their relationship is unknown and speculative at this point, but it is possible that they may be linked by the mTOR signaling pathway.

Conclusion

We report a case of SN associated with renal AMLs. Given the high frequency of spontaneous mutations of NF1 and its link to *TSC1/TSC2* inactivation via ras and PI3-kinase/Akt signaling, it is possible that patients with NF1 and TS are underreported and there may be a greater association than once believed.

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