Segmental Neurofibromatosis: Report of 3 Cases

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Segmental neurofibromatosis (SNF) is an uncommon variant of neurofibromatosis type 1 (NF-1) that is characterized by café au lait spots, freckles, and/or neurofibromas limited to a body segment. In this report we describe 3 adult patients with SNF who presented with only neurofibromas. Although 2 patients had no systemic involvement, the third patient had hypertrophic cardiomyopathy, a cardiologic abnormality that is associated with neurofibromatosis.

Cutis. 2011;87:45-50.

Segmental neurofibromatosis (SNF) is an uncommon variant of neurofibromatosis type 1 (NF-1) that is characterized by pigmentary lesions (ie, café au lait spots and freckling) and/or neurofibromas limited to one region of the body. In some patients there are some other clues for the diagnosis of NF-1 such as Lisch nodules of the iris, while in many patients cutaneous lesions are the only manifestations.[1]

Case Reports

Patient 1—A 55-year-old man displayed several asymptomatic, slow-growing skin tumors that had been present since birth. His medical history was remarkable for hypertension of 2 years' duration and long-term, heavy smoking (>1 pack daily for approximately 30 years). He reported that his father, who died at the age of 96 years, had similar pedunculated skin lesions of soft texture on the right side of the trunk. The patient's daughter also had some similar lesions, but it was not clear if they were segmental/localized. Physical examination revealed multiple flesh-colored or pink, soft, mostly pedunculated nodules and papules (total number, 14) on the right side of the trunk, both on thoracoabdominal and dorsolumbar areas, that ranged in size from 0.3 to 4 cm (Figure 1A). Axillary freckles, plexiform neuromas, or other clinical signs of NF-1 were not present. The only neurologic concern was intermittent mild headache. There were no mental health, physical development, or speech abnormalities. Mucous membranes, hair, and nails were normal. Ophthalmologic, orthopedic, and neurologic examinations revealed normal findings.

Laboratory investigations including complete blood cell count, erythrocyte sedimentation rate, fasting glucose, hemoglobin A_{1c}, hepatic transaminases, lactate dehydrogenase, amylase, bilirubins, total protein, albumin, electrolytes, calcium, phosphor, cholesterol panel, triglycerides, triiodothyronine (T_3), thyroxine (T_4), thyrotropin (TSH), vitamin B_{12}, folate, ferritin, prothrombin time, activated partial thromboplastin time, C-reactive protein, C3 complement, C4 complement, rheumatoid factor, rapid plasma reagin, carcinoembryonic antigen, prostate-specific antigen, carbonhydrate antigen 19.9, anti–human immunodeficiency virus (HIV), hepatitis B surface antigen, anti–hepatitis A virus, IgM, and anti–hepatitis C virus were within reference range or were negative. Blood urea nitrogen was 25 mg/dL (reference range, 8–23 mg/dL), serum creatinine level was 2.15 mg/dL (reference range, 0.6–1.3 mg/dL), creatinine clearance was 26.27 mL/min/1.73 m^2 (reference range, 75–125 mL/min/1.73 m^2), and urinary protein excretion was 1.11 g/24 h (reference range, 0.04–0.15 g/24 h). Abdominal ultrasonography was normal, except for increased parenchymal echogenicity of both kidneys. Renal doppler as well as radiographs of thoracic and lumbar vertebrae and

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The authors report no conflict of interest.
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crura were normal. Cranial magnetic resonance imaging (MRI) showed chronic lacunar infarcts at the level of centrum semiovale and corona radiata, located at periventricular and periatrial regions. In addition, there were widespread ischemic gliotic foci at the frontoparietal subcortical and bilateral periatrial regions of deep white matter.

Patient 2—A 56-year-old woman presented with several nodules on the right forearm of 10 years' duration. The lesions had gradually increased in number and size. She described intermittent pruritus of the lesions. Her medical history included hypertension of approximately 10 years' duration and medical treatment of cervical hernia 12 years prior. She reported dyspnea and chest pain with exercise. Mental and physical development was normal. Her family history was not remarkable.

Several flesh-colored to tan, 0.3- to 1-cm, dome-shaped papulonodules with soft to firm consistency were located on the dorsal surface of the forearm from immediately below the elbow to 10 cm above the wrist (Figure 1B). Although multiple 1- to 2-mm hyperpigmented macules, compatible with ephelides, were seen over the sun-exposed parts of the body, there was no axillary or inguinal freckling. Mucous membranes, hair, and nails were normal. Ophthalmologic, orthopedic, and neurologic examinations revealed normal findings.

Laboratory examinations including complete blood cell count, erythrocyte sedimentation rate, fasting glucose, aspartate transaminase, bilirubins, creatinine, blood urea nitrogen, lactate dehydrogenase, calcium, electrolytes, total protein, albumin, cholesterol panel, triglycerides, TSH, T_3, T_4, fecal occult blood, urinalysis, VDRL test, C-reactive protein, serology for hepatitis B and C virus, and anti-HIV were within reference range or negative. Alanine transaminase and γ-glutamyltransferase were found to be elevated (43 IU/L [reference range, 8–37 IU/L] and 184 IU/L [reference range, 6–36 IU/L], respectively). Abdominal ultrasonography was normal, except for grade 1 hepatic steatosis. Radiographs of thoracic and lumbar vertebrae and renal doppler were normal. Cranial MRI showed a few ischemic gliotic foci.

Patient 3—A 52-year-old man presented with multiple asymptomatic skin tumors on the right side of the trunk of 10 years' duration. His medical history was otherwise unremarkable and blood pressure was normal, in contrast to the other 2 cases. He had no family history for similar skin tumors. Physical examination revealed multiple, soft, flesh-colored, pedunculated papulonodules (total number, 18) that ranged in size from 0.1 to 1 cm and were distributed on the right

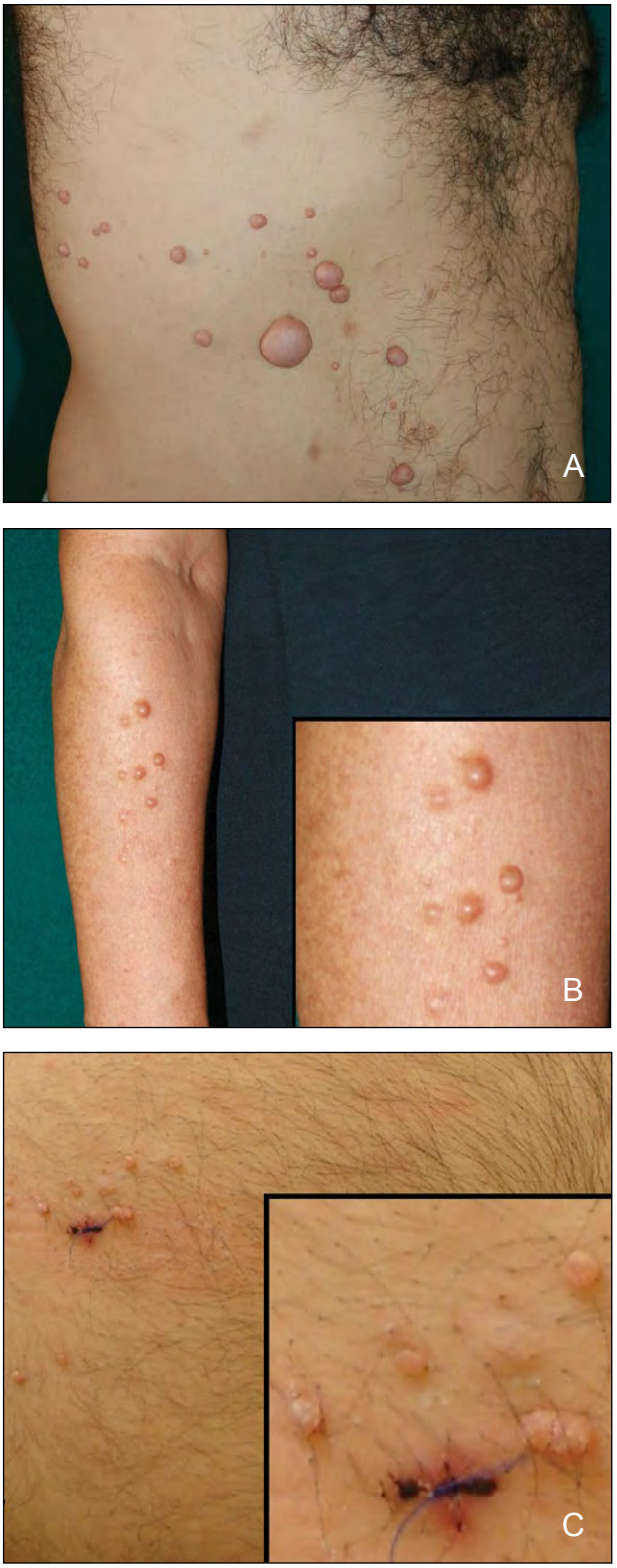

Figure 1. Multiple flesh-colored or pink, soft, mostly pedunculated nodules on the right side of the trunk (patient 1)(A). Flesh-colored to tan, hemispheric papulonodules on the dorsomedial surface of the forearm (patient 2)(B). Similar papules on the right side of the lower abdomen (patient 3)(C).

thoracoabdominal area (Figure 1C). There were no other clinical signs of NF-1 or skin tags. Mental health and physical development as well as mucous membranes, hair, and nails were normal.

Laboratory investigations including complete blood cell count, erythrocyte sedimentation rate, fasting glucose, hepatic transaminases, urea, creatinine, bilirubins, total protein, albumin, globulin, amylase, alkaline phosphatase, T_3, T_4, TSH, vitamin B_{12}, folate, ferritin, C-reactive protein, rheumatoid factor, anti-HIV, hepatitis B surface antigen, and anti–hepatitis C virus were within reference range or negative. Triglycerides, cholesterol, and very low-density lipoprotein were elevated (triglycerides, 472 mg/dL [reference range, <200 mg/dL]; cholesterol, 218 mg/dL [reference range, <200 mg/dL]; very low-density lipoprotein, 94.3 mg/dL [reference range, <40 mg/dL]). Radiographs of thoracic and lumbar vertebrae and crura were normal. Echocardiography was consistent with hypertrophic cardiomyopathy. The patient did not present for further follow-up; therefore, ophthalmologic, orthopedic, and neurologic examinations as well as cranial MRI, abdominal ultrasonography, and renal doppler could not be performed.

Histopathologic Findings—In all 3 patients, histopathologic examination of the skin nodules revealed nodular infiltration of fusiform cells with oval and fusiform nuclei that formed strands crossing with each other (Figure 2A). Immunohistochemical examination in all patients showed positive staining with S-100 protein (Figure 2B) but negative staining for desmin, actin, and CD68. The specimens from neurofibromas and normal skin were evaluated for mast cells in all patients. The comparison of the mean densities of mast cells on 10 microscopic areas of high magnification (toluidine blue, original magnification ×400) is shown in the Table.

Comment

Segmental neurofibromatosis is a rare entity. It is estimated that the prevalence of SNF in the general population from different countries is at least 15 times less frequent than NF-1, with a prevalence of 1 in 36,000 to 40,000 individuals in the general population.[2,3] The criteria for the diagnosis of SNF have not been precisely established. The former description of the disorder by Riccardi[4] in 1981 under the name of NF-5 was too restrictive, requiring the features of café au lait spots, freckling, and neurofibromas without crossing the midline. In 1992, Goldberg[5] proposed that at least 2 features, including café au lait macules, freckles, neurofibromas, Lisch nodules, optic pathway gliomas, and neurofibromatosis-specific bone lesions, were required for the diagnosis of SNF. However,

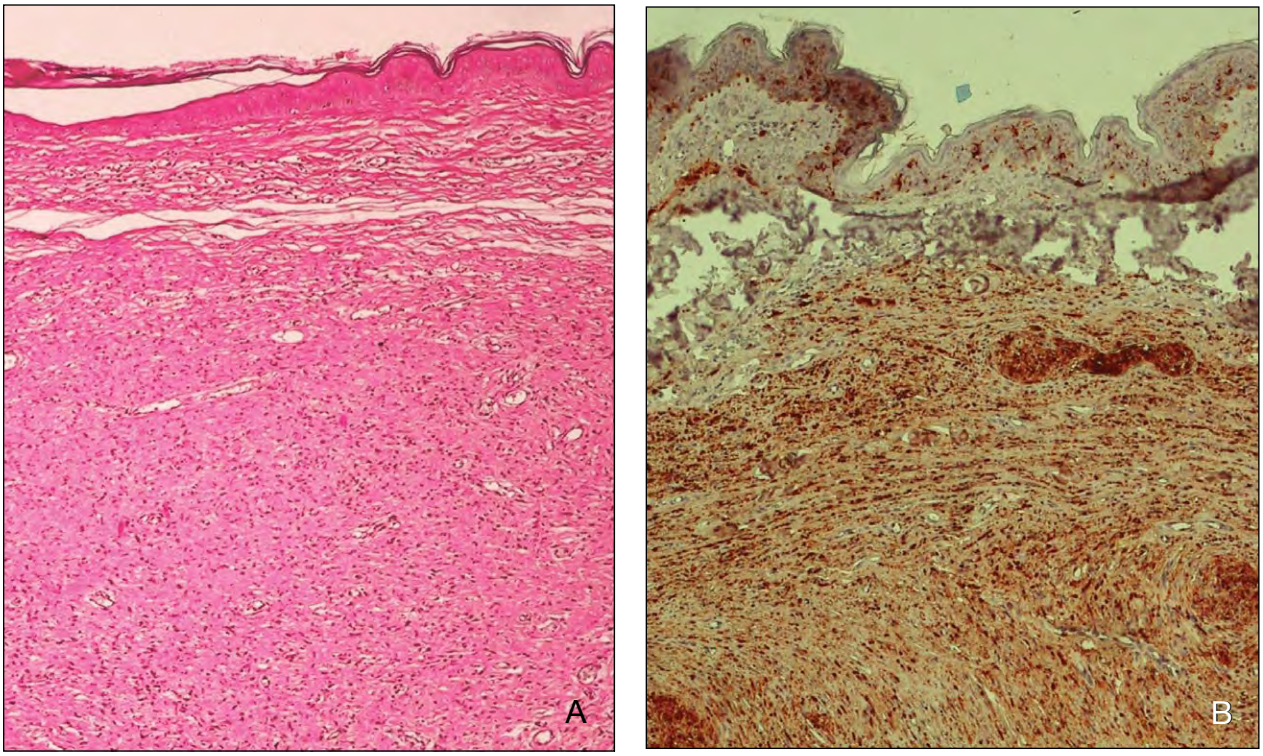

Figure 2. Nodular infiltration of fusiform cells with oval and fusiform nuclei that formed strands crossing with each other (H&E, original magnification ×100)(A). Positive staining of fusiform cells with S-100 protein (original magnification ×200)(B).

Mean Number of Mast Cells

	Pruritus	Mean Lesional Mast Cells, n	Mean Nonlesional Mast Cells, n
Patient 1	Absent	8.8	1.2
Patient 2	Absent	3.6	1.7
Patient 3	Absent	3.2	1.3

since then, many patients not fulfilling these criteria were reported to have SNF. In a study performed by Huet et al,[6] 47 of 83 patients had isolated neurofibromas. In our patients, only neurofibromas in a restricted area were present and the diagnosis of NF-1 was ruled out by the lack of other diagnostic features.

In some early reports, authors regarded SNF as a cutaneous hamartoma that manifested with multiple neurofibromas rather than being related to the generalized type of NF-1.[7,8] However, in recent years, SNF has been considered to be an example of mosaicism, arising from a postzygotic NF-1 gene mutation. Tinschert et al[9] showed the presence of a mutant allele with an NF-1 microdeletion in only the cultured fibroblasts from a café au lait lesion but not in fibroblasts from the normal skin. They proved that the molecular basis of SNF is a mutation in the NF-1 gene.[9] Patients with SNF have a low risk for passing the disorder to offspring because of involvement of gonosomal cell lines. One of our patients indicated a family history of similar lesions, but unfortunately we were not able to examine his relatives.

Clinical manifestations can appear at any age. In a group of 82 patients, the median age of onset was 28 years.[1] It has been reported that clinical features of SNF develop along the same time course as generalized NF-1, with pigmentary changes and plexiform neurofibromas developing in childhood and neurofibromas in adulthood.[2] In a series of 39 children with SNF, only 3 had neurofibromas, indicating the low frequency of these lesions in childhood.[3] Although our first patient's history indicated congenital onset of neurofibromas, contrary to this observation, the other cases conformed to the usual disease course.

Pigmentary changes of SNF include café au lait macules and skin fold freckling, the latter being less common. Axillary freckling was reported in only 9 of 82 patients.[1] Several patients with SNF show clearly demarcated areas of increased pigmentation on which café au lait macules, freckles, and/or neurofibromas are scattered.[2] With respect to skin complexion, our patients showed no difference between the involved and uninvolved areas.

Neurofibromas are the most frequent manifestations of SNF, presenting in 75% of patients. Neurofibromas are the sole manifestation in more than half of patients. They are most commonly found over cervical or thoracic skin, while involvement of the upper extremity is relatively rare. The right side of the body seems to be more commonly affected than the left side,[1] as seen in our cases. In patients with pigmentary changes, the lesions usually follow the lines of Blaschko. Neurofibromas tend to develop in a dermatomal distribution or involve a major peripheral nerve or nerve plexus.[10] On the other hand, differentiating between a dermatomal pattern and lines of Blaschko may not be so easy. In our patients, we were not able to determine if the distribution of the lesions was dermatomal or along the lines of Blaschko. In patients 2 and 3, localization of the lesions along the dermatomal areas of the C6 nerve and the space between T10 and T11 seems possible, but distribution along the lines of Blaschko also may be taken into consideration. However, for patient 1, if we consider a dermatomal distribution, then several dermatomes (T6–T11) should have been involved, which may be less probable. Nevertheless, it is well-known that the area of involvement is highly variable in SNF, from a narrow band of skin to almost half of the body. In most patients, lesions occupy a single dermatome, but some patients have involvement of nearby dermatomes.

Neurofibromas are almost always asymptomatic. Painful neurofibromas rarely have been described,

mostly related with the involvement of a nerve or nerve plexus. Pruritus related to neurofibromas also is rare, occurring in 4 of 82 patients in one report.[1] The exact cause and prognostic importance of pruritic neurofibromas is a matter of debate. Mast cells are proposed to influence the growth of neurofibromas, and ketotifen fumarate, as a mast cell stabilizer, is claimed to reduce proliferation and itching of neurofibromas.[11] Therefore, we assessed the mast cells in neurofibromas of our patients and found a striking increase in mast cell counts in the lesions compared to normal skin. However, in our patients, mast cell density did not appear to be related to the presence of pruritus.

In contrast to NF-1, systemic involvement in SNF is uncommon. Extracutaneous manifestations including visceral neurofibromas, renal agenesis, and visceral carcinomas rarely have been reported. In addition, specific complications of NF-1 such as learning difficulties, optic pathway gliomas, skeletal abnormalities, and pseudoarthrosis have been encountered in some patients with SNF.[1] In our patients, thorough examinations failed to reveal any systemic pathology, except hypertension, hypertrophic cardiomyopathy, hyperlipidemia, and renal insufficiency. In a series of 82 patients with SNF, only 2 were reported to have hypertension.[1] Pheochromocytoma is a rare cause of hypertension in patients with NF-1 with a prevalence of 1%. Although 2 of our patients had a history of hypertension, they had no signs or symptoms suggesting an underlying pheochromocytoma such as attacks with headache, diaphoresis, palpitation, tremor, nausea, and weakness. Moreover, in both of the patients, hypertension was well-controlled and did not show paroxysmal increases. Another cause for hypertension in patients with NF-1 is middle aortic syndrome, which is generated by segmental aortic stenosis; middle aortic syndrome is mostly seen in children and young adults. Typical manifestations of this syndrome include headache, fatigue on exertion, and bilateral lower limb claudication.[12] Neither of our patients experienced these latter clinical findings.

Of note, patient 3 had hypertrophic cardiomyopathy. In a study comprising 48 cases of NF-1 evaluated with echocardiogarphy, 2 patients had this cardiac abnormality.[13] Hypertrophic cardiomyopathy may be associated with neurofibromatosis because both diseases are hereditary defects of neural crest tissue. Another suggested mechanism is the increased nerve growth factors and abnormal catecholamine metabolism leading to ventricular hypertrophy.

In contrast with NF-1, neurologic abnormalities rarely have been encountered in patients with SNF. Cerebrovascular complications, mainly stenosis or aneurysms and more infrequently vertebral arteriovenous fistulas and malformations, may rarely accompany NF-1. Because specific features are absent, cerebral infarcts related to NF-1 cerebral vasculopathy can only be considered after other causative diseases are excluded. Patient 1 had no history of neurologic disease. There was no concern of neurologic involvement, such as vertigo and diplopia. His intermittent mild headache was thought to be related to hypertension. Neurologic examination was completely normal. Therefore, on neurologic consultation, the abnormal cranial MRI findings were mainly attributed to atherosclerosis and hypertension, though the contribution of NF-1 could not be precisely eliminated. Of note, both of our patients who received ophthalmologic examination were free of Lisch nodules. These iris hamartomas rarely are recorded in patients with SNF. In a systematic study investigating the ophthalmologic manifestations in SNF, none of the 72 patients evaluated had Lisch nodules.[14] It has been proposed that Lisch nodules may only be present when the involved dermatome includes the eye. Although there is still some debate on this issue, the current view is that the presence or lack of Lisch nodules in SNF should not be considered a predictor for genetic transmission of NF-1.[14]

Conclusion

Accurate diagnosis of SNF is important. Because of mild and asymptomatic features, it may be easily ignored by both patients and physicians. On the other hand, it may be misdiagnosed as NF-1, causing substantial stigma for the patients, though individuals with this mosaic pattern of NF-1 are less likely to have systemic disease and have lower risk for genetic transmission. In recent years, the number of published cases of SNF has increased. New reports may help physicians become more aware of the disease manifestations so they do not overlook abortive cases.

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