Neurofibromatosis Type 1 in the Setting of Systemic Lupus Erythematosus

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PRACTICE **POINTS**

- Patients with neurofibromatosis type 1 (NF-1) benefit from early diagnosis and long-term follow-up.
- Patients with systemic lupus erythematosus (SLE) may develop different malignancies given the immune dysregulation. We recommend that patients with SLE undergo detailed skin examinations to check for subtle clues for NF-1.
- Similarly, patients with NF-1 can develop SLE later in life.

To the Editor:

Patients with concurrent neurofibromatosis type 1 (NF-1) and systemic lupus erythematosus (SLE) rarely have been reported in the literature. Neurofibromatosis type 1 is one of the most common genetic disorders, with a worldwide birth incidence of 1 in 2500 individuals and prevalence of 1 in 4000 individuals.[1] The incidence and prevalence of SLE varies widely depending on race and geographic location. Estimated incidence rates for SLE range from 1 to 25 per 100,000 individuals annually in North America, South America, Europe, and Asia.[2,3] The reported worldwide prevalence is 20 to 150 cases per 100,000 individuals annually.[2,4,5]

Given the high prevalence of both conditions, the association between SLE and NF-1 likely is underrecognized; therefore, identifying more patients with concurrent SLE and NF-1 and describing the interplay between the 2 conditions may have important therapeutic implications. We present the case of a middle-aged woman with a history of SLE who had cutaneous lesions characteristic of NF-1 to further the understanding of these concurrent conditions.

A middle-aged woman presented to our academic dermatology clinic for evaluation and removal of dark spots that had been present diffusely on the trunk and extremities since birth. She reported a history of SLE with lupus nephritis, hypertension, and a nodular goiter following a partial thyroidectomy. She noted that she did not seek treatment for the skin findings sooner because she was more concerned about her other medical conditions; however, because she felt these conditions were now stable, she decided to seek treatment for the "rash." Physical examination revealed hundreds of café au lait macules and numerous neurofibromas diffusely distributed on the trunk and extremities (Figure 1) as well as bilateral axillary freckling. A clinical diagnosis of NF-1 was made.

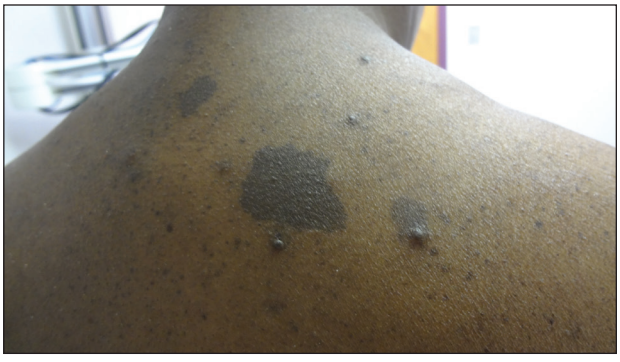

FIGURE 1. Café au lait macules and neurofibromas on the upper back.

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When questioned, the patient reported that she may have been diagnosed with NF-1 in the past by another physician, but she did not recall it specifically. The patient was advised that there were no treatments for the café au lait macules. We notified her other physicians of the NF-1 diagnosis so she could be monitored for systemic conditions related to NF-1, including optic gliomas, pheochromocytoma, renal artery stenosis, and internal neurofibromas. We also referred the patient for genetic counseling; of note, the patient reported she had 4 children without any evidence of similar skin lesions or chronic health problems.

A PubMed search of articles indexed for MEDLINE using the terms *systemic lupus* and *neurofibromatosis* yielded 8 cases of patients having both SLE and NF-1 (including our case).[6-11] Our patient reported having multiple lesions since birth, decades before the onset and diagnosis of SLE. In 3 other cases, patients were diagnosed with SLE and then presented with neurofibromas, leading to NF-1 diagnosis. In the discussion of those 3 cases, it was proposed that immune system alterations caused by SLE leading to viral illness may have predisposed the patients to the development of tumors and other collagen diseases, or it could be coincidental.[6,7] In another case, a patient with NF-1 developed SLE, which was thought to be coincidental.[8] Akyuz et al[9] described the case of a pediatric patient with NF-1 who subsequently was diagnosed with SLE. The authors suggested that the lack of neurofibromin contributed to the development of SLE, an autoimmune condition. Under normal circumstances, neurofibromin acts as a guanosine triphosphatase–activating protein for RAS in T cells.[10] $CD8^+$ T-cell function also is impaired in patients with SLE.[9] Additionally, it has been reported that anti–double-stranded DNA antibodies and immune complexes were present in NF-1 patients, even though there were low titers.[12] Thus, the authors proposed that the lack of neurofibromin led to dysregulation of the RAS pathway and impairment of T cells, creating an immune milieu that predisposed the patient to development of SLE. Our case gives additional credence to this theory, as our patient had a similar clinical course: the café au lait macules were present since birth and the symptoms of SLE surfaced much later in her late 20s and 30s. Another case by Makino and Tampo[10] described a patient with a history of SLE who was later diagnosed with NF-1 based on choroidal findings highly specific for NF-1 but did not have other classic findings of NF-1. The authors mentioned that there might be a potential relationship between these two disorders but did not speculate any theory in particular for their case.[10]

The interplay between an autoimmune condition such as SLE and NF-1, a condition traditionally thought to be due to a genetic mutation, may have greater clinical and therapeutic implications beyond just these two disorders. Although it is well established that RAS pathway

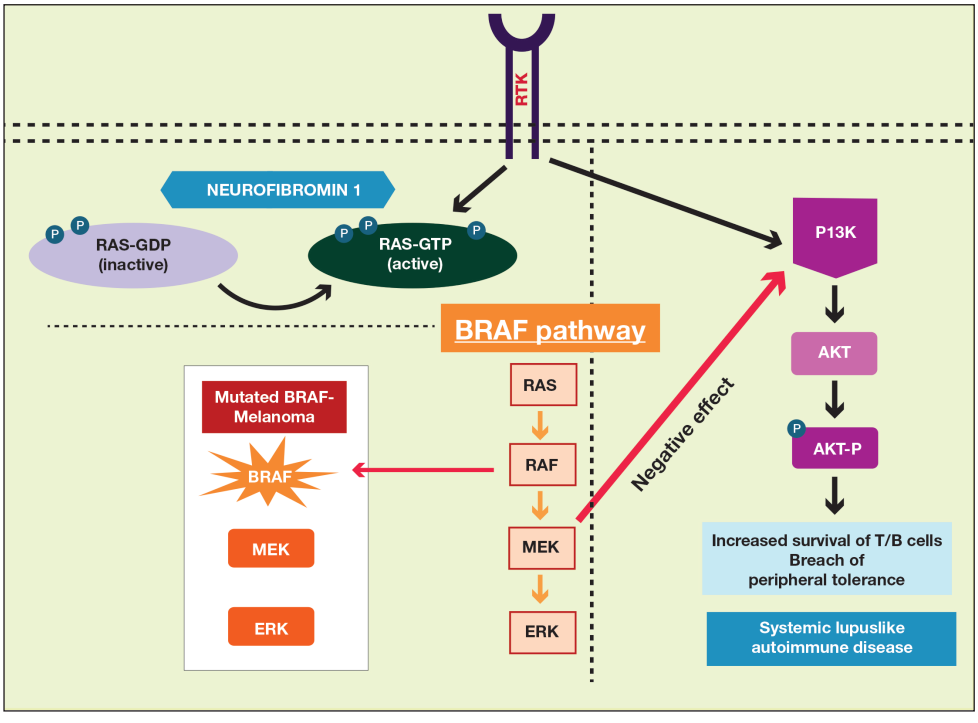

FIGURE 2. MAPK pathways and potential interplay between neurofibromatosis type 1, systemic lupus erythematosus, and melanoma. Mutated BRAF leads to activation of the MEK/ERK pathway and development of melanoma. MEK-1 inhibition results in activation of P13K/AKT signaling and breach of peripheral tolerance and development of lupuslike autoimmune disease. Both neurofibromatosis type 1 and systemic lupus erythematosus are related to activated RAS. Neurofibromin 1 *(NF1)* leads to phosphorylation of RAS-GDP, resulting in the activated form of RAS (RAS-GTP).

Diagnostic Criteria for Neurofibromatosis Type 1[24,a]

6 or more café au lait macules over 5 mm in greatest diameter in prepubertal individuals and over 15 mm in greatest diameter in postpubertal individuals
2 or more neurofibromas of any type or 1 plexiform neurofibroma
Freckling in the axillary and/or inguinal regions
Optic glioma
2 or more Lisch nodules (iris hamartomas)
A distinctive osseous lesion (eg, sphenoid wing dysplasia or thinning of long bone cortex), with or without pseudoarthrosis
First-degree relative (eg, parent, sibling, child) with NF-1 diagnosed according to the above criteria

Abbreviation: NF-1, neurofibromatosis type 1.
[a]Two or more findings must be present for diagnosis.

disruption causes NF-1, it has been uncovered that dysfunction in the RAS pathway also can contribute to melanoma oncogenesis.[13,14] These insights have led to the development of and approval of targeted drugs designed to inhibit the RAS pathway (eg, vemurafenib, dabrafenib, trametinib).[14-17] Melanoma also is considered a "model" tumor for studying the relationship between the immune system and cancer.[18] AKT is a signal transduction pathway that promotes cell survival and growth in various cancers.[15] In addition, deactivation of MEK (part of the RAS pathway) can cause activation of AKT (protein kinase B) signaling and lupuslike autoimmune conditions[19] (Figure 2). Likewise, an understanding of the RAS pathway and T-cell function in patients with both SLE and NF-1 may give us more information about melanoma and other cancers.

Our case also is instructive in another point: our patient had never sought treatment for her skin lesions, as she said she had other more serious health conditions. Closer evaluation of her skin condition may have led to earlier diagnosis of NF-1, which has important health implications. The average lifespan of patients with NF-1 is 10 to 15 years lower than the general population, with cancer being the leading cause of death.[20] Malignant peripheral nerve sheath tumors are the most common malignant tumors observed in such patients.[21-23] Other cancers that are associated with NF-1 include rhabdomyosarcomas, gastrointestinal stromal tumors, neuroectodermal tumors, pheochromocytomas, and breast carcinomas.[23]

To make a clinical diagnosis of NF-1, a patient must have 2 of 7 cardinal clinical features as defined by the National Institutes of Health (Table).[24] In our patient with hundreds of café au lait macules and dozens of neurofibromas, the diagnosis was clear; however, in other patients, the skin findings of NF-1 may not be as prominent. A patient could meet criteria for NF-1 diagnosis with the inconspicuous presentation of 6 café au lait macules and either 1 plexiform neurofibroma or 2 neurofibromas (of any type) on the entire body.

We recommend that patients with SLE undergo skin examinations to look for more subtle presentations of NF-1. Earlier diagnosis will help to initiate close monitoring of the disorder's associated systemic health risks. In addition, the identification of more patients with both NF-1 and SLE may help shed light on the etiology of both conditions.

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