

# Cutaneous T-Cell Lymphoma in a Patient With Neurofibromatosis Type 1

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## GOAL

To understand neurofibromatosis type 1 (NF1)

## OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Explain the clinical presentation of NF1.
2. Describe the genetics of NF1.
3. Recognize the tumors associated with NF1.

**CME** Test on page 38.

This article has been peer reviewed and approved by Michael Fisher, MD, Professor of Medicine, Albert Einstein College of Medicine. Review date: June 2003.

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Drs. Herbert and McBurney report no conflict of interest. The authors report no discussion of off-label use. Dr. Fisher reports no conflict of interest.

*A variety of neoplasms may occur in association with neurofibromatosis type 1 (NF1). We describe a patient with NF1 and mycosis fungoides. Recommendations for the initial and long-term evaluations of patients with neurofibromatosis are presented.*

*Cutis.* 2003;72:27-30.

Accepted for publication May 19, 2003.

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Neurofibromatosis type 1 (NF1), also known as von Recklinghausen disease, is an autosomal-dominant syndrome with no racial, gender, or ethnic predilection.<sup>1</sup> It has an estimated incidence of 1 in 3000 to 1 in 7800 people.<sup>1,2</sup> Although there are at least 7 types of neurofibromatosis, NF1 is the most common form. Numerous malignancies have been linked to NF1 including pheochromocytoma, thyroid carcinoma, leukemia, and melanoma.<sup>3,4</sup> Over the past 30 years, there has been one case report of the coexistence of the leukemic phase of cutaneous T-cell lymphoma and NF1.<sup>5</sup> We report the occurrence of the plaque variant of cutaneous T-cell lymphoma in a patient with NF1.

## Case Report

A 72-year-old white man with a lifelong history of NF1 presented for evaluation of an erythematous plaque on his left hip. It had been present for 3 months and had slowly increased in size. The lesion had been treated with econazole cream without improvement. The patient's medical history included atrial fibrillation necessitating daily treatment with amiodarone and acetylsalicylic acid. His family history was significant for a mother with NF1. Although currently retired, he had worked as a professor for more than 20 years.

Physical examination revealed an erythematous scaly plaque 14×16 cm in diameter over his left hip extending to his left flank (Figure). The patient had hundreds of flesh-colored nodules varying in size from 0.5 to 3.0 cm distributed over his entire body. In addition, he had 2- to 3-mm hyperpigmented macules in the axilla and inguinal areas, scattered larger café-au-lait macules, and iris hamartomas (Lisch nodules).<sup>6</sup> There was no palpable lymphadenopathy or organomegaly.

Laboratory data included a complete blood count, which consisted of a hemoglobin level of 16 g/dL; hematocrit level of 46.5%; and normal blood differential and white blood cell counts. The lymphocyte profile was remarkable for an absolute CD4 count of 340 mm<sup>3</sup> (reference range, 359–1519 mm<sup>3</sup>) and the percentage of CD4<sup>+</sup> lymphocytes equal to 26.2% (reference range, 30.8%–58.5%). His chest x-ray revealed moderate pulmonary fibrosis and changes consistent with chronic obstructive pulmonary disease, but no active lung disease. A computed tomographic scan of the abdomen and pelvis was unremarkable for any lymphadenopathy, but there was displacement of the left kidney and bowel into the left hemithorax and a foramen of Bochdalek hernia.

The results of a 3-mm punch skin biopsy of the plaque on the patient's left flank demonstrated psoriasiform acanthosis with a mild to moderate atypical epidermotropic lymphocytic infiltrate and a subjacent neurofibroma. Immunophenotyping revealed prominent epidermotropism of CD3<sup>+</sup> lymphocytes. Fewer intraepidermal lymphocytes marked with CD4 and CD5 immunostains. No CD7 deletion was present, but a T-cell gamma gene rearrangement was identified. The patient was diagnosed with stage 1A cutaneous T-cell lymphoma (CTCL)(T1N0M0).

## Comment

NF1 is the most common of the neurocutaneous disorders.<sup>3</sup> At present, National Institutes of Health criteria for diagnosis include 2 or more of

the following: 6 or more café-au-lait macules larger than 5 mm in greatest diameter in prepubertal patients and larger than 15 mm in greatest diameter in postpubertal patients; 2 or more neurofibromas of any type or one plexiform neurofibroma; freckling in the axillary or inguinal area; optic nerve glioma; 2 or more Lisch nodules; a distinctive osseous lesion such as sphenoid wing dysplasia or thinning of the bone cortex with or without pseudoarthrosis; a first-degree relative (parent, sibling, or offspring) with NF1 by the above criteria.<sup>1,2,6,7</sup> Different criteria appear at various stages of the patient's development (ie, café-au-lait macules appear at birth and neurofibromas emerge at adolescence).<sup>8</sup> Lisch nodules have been regarded as pathognomonic.<sup>4</sup> Intertriginous freckling is highly suggestive of the diagnosis but also may be seen in Watson syndrome. The 5 subtypes of neurofibromas are cutaneous, subcutaneous, nodular, plexiform, and diffuse.<sup>4</sup> Other associated findings include vision changes, cognitive disorders, growth problems, and musculoskeletal disorders.<sup>4</sup> Our patient fulfilled the criteria for NF1 by having neurofibromas, café-au-lait macules, Lisch nodules, intertriginous freckling, and a positive family history.

The gene defect for NF1 has been mapped to chromosome 17. The NF gene acts as a tumor-suppressor gene that dampens the production of the ras proto-oncogene.<sup>9</sup> Therefore, the mutation of this gene contributes to tumor progression.<sup>6,8</sup>

One in 4 patients with NF1 will develop a secondary tumor throughout his or her lifetime. Tumors found with NF1 include those of neural crest origin such as pheochromocytoma, neuroblastoma, and melanoma.<sup>10</sup> Non-neural crest tumors include Wilms tumor, rhabdomyosarcoma, granular cell tumors, malignant nodular hidradenoma, and leukemia.<sup>11,12</sup> Patients with both NF1 and juvenile xanthogranuloma appear to be at increased risk for leukemia. Malignant peripheral nerve sheath tumors are associated with NF1 and are a potential cause of mortality in adult patients with NF1. Typically, the malignancy will occur before age 38 years, arising in a longstanding neurofibroma. Multiple malignancies occur in 12% of patients.<sup>3</sup> To our knowledge, plaque-stage mycosis fungoides has not been previously reported.

As is the case with NF1, mycosis fungoides has been associated with secondary malignancies, most commonly lymphoproliferative disorders. It is postulated that the increase in immune dysfunction and T-cell dysregulation fosters tumor growth in these other locations.<sup>10</sup> The cancer incidence in patients with CTCL is deemed 2.4 times greater than the general population and 3.3 times greater than in



An erythematous scaly plaque 14×16 cm in diameter on the left hip extending to the left flank.

white males alone.<sup>13</sup> An excess of lung and colon cancer, as well as non-Hodgkin's lymphoma has been found in these patients.<sup>10</sup>

One study from Duke University revealed that 15.9% of patients with CTCL will have a second malignancy.<sup>9</sup> Other studies have quoted risks as high as 74% following the first 5 years of diagnosis of CTCL.<sup>9,14,15</sup> It appears that secondary malignancies are more likely if a CTCL patient has received chemotherapy and has a positive family history for other malignancies. The incidence of mycosis fungoides is 0.4/100,000 people. Based on currently accepted incidence data for mycosis fungoides and NF1, we would expect the combined incidence to be  $0.4/25 \times 10^7$  to  $0.4/78 \times 10^7$ .

It is important that clinicians thoroughly investigate all suspicious lesions in patients with neu-

rofibromatosis because cutaneous malignancies may be erroneously diagnosed as tinea corporis or contact dermatitis.

*Acknowledgments*—The authors would like to offer gratitude to Richard Marshall, MD, from the Department of Pathology at Touro Hospital in New Orleans, and to Alun Wang, MD, PhD, from the Department of Pathology and Dermatopathology at the Tulane University Medical Center, for their assistance and patience in corroborating this manuscript.

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