A Rare Case of SCC in a Pediatric Patient with NF-1

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Abstract
We present a case of a pre-adolescent female with neurofibromatosis type 1 (NF1) who developed squamous cell carcinoma (SCC) on the dorsum of the nose. This rare presentation has been reported in the literature only twice, and both instances involved adult patients. SCC itself is very rare in children and is usually seen in those with a predisposing condition like immunosuppression, radiation exposure or genodermatoses, none of which our patient had. We also discuss the possible pathogenesis of epithelial tumor development in patients with NF1, a historically non-epithelial tumor-producing disorder.

Introduction
Neurofibromatosis type 1 is an autosomal-dominant genetic disorder characterized by the presence of café-au-lait macules (CALMs), neurofibromas, nerve sheath tumors, Lisch nodules and freckling in the axillary or inguinal region. Almost every organ system in the body can be affected by renal dysfunction, from essential hypertension and learning difficulties to scoliosis. Skin manifestations like CALMs and plexiform neurofibromas will usually appear congenitally or within the first year of life, whereas other skin findings, like simple neurofibromas, appear later in childhood. Generally, all criteria for diagnosis of NF1 are met in 97% of patients by age 8 and in 100% of patients by age 20. Patients are at increased risk of developing a number of different central nervous and non-epithelial neoplasms. It is very rare for patients with NF1 to develop cutaneous squamous cell carcinoma.

Case Report
An 11-year-old female with a past medical history of NF1 and positive family history of NF1, including mother and sibling, presented to the dermatology clinic for evaluation of a lesion on her nose that was present for the past six months. There was no bleeding, pain or change in size. She denied similar lesions elsewhere. On physical examination, the patient had a smooth, pink papule measuring 7 mm in diameter on the dorsum of the nose with overlying scale-crust (Figure 1), as well as multiple well-defined brown patches and macules on the trunk and extremities. Differential diagnosis included: verruca vulgaris, irritated molluscum contagiosum, and pyogenic granuloma. Cryotherapy using liquid nitrogen was performed on the lesion for presumed verruca vulgaris. Three weeks later, the patient returned to the dermatology clinic with the lesion having grown since the last visit. The patient then had a shave biopsy of the nasal lesion, which showed atypical squamous cell proliferation invading the dermis, consistent with SCC (Figures 2, 3).

Our patient underwent Mohs micrographic surgery for complete surgical removal, full examination of tumor margins and best cosmetic outcome. After several months, she has shown no signs of recurrence and is happy with the appearance of tumor margins and best cosmetic outcome. Our patient has been offered genetic counseling for her underlying NF1. We recommended yearly follow-up for full skin exams to monitor for further skin cancer development.

Discussion
NF1 is an autosomal-dominant genetic disorder resulting from mutations in the NF1 gene at chromosome 17q11.2. Tumors in NF1 are predominantly derived from connective tissue, and neurofibromas are the most common type of benign tumor in these patients. Patients with NF1 are at increased risk of developing non-epithelial tumors including optic gliomas, astrocytomas and malignant peripheral nerve sheath sarcomas. The NF1 gene codes for neurofibrin, a protein that acts as a GTPase-activating protein. This leads to negative regulation of Ras-mitogen-activated protein kinase, which is involved in cell survival and proliferation. Neurofibrin acts as a tumor suppressor by hastening the transition from GTP to GDP, causing Ras to be nonfunctional. With Ras nonfunctional, tumor formation does not occur.

While evidence linking NF1 to epithelial tumors is scant, there have been some studies investigating a possible role for the gene in their carcinogenesis. It is known that neurofibrin can be found in normal human epidermis. A Finland study by Hermonen et al. used reverse transcriptase PCR, immunohistochemistry, and molecular hybridizations to characterize the expression of NF1 within keratinocytes. They found evidence that neurofibrin acts as a regulator of the basal keratinocytes in normal skin and that dysregulation could potentially cause the development of epithelial tumors like basal cell carcinoma and squamous cell carcinoma. Another study in mice by Atit et al. showed further evidence for NF1's role in epithelial carcinogenesis. They studied mice who were heterogeneous for null mutations in NF1 and exposed them to known carcinogens. Heterogeneous mice developed papillomatous growths as well as sustained increases in keratinocyte proliferation, while wild types with the same exposure did not. In addition, all mice with papillomas were shown to have activation of Ras, a crucial step in the process of carcinogenesis, supporting its involvement in epidermal tumors.

There are very few reported cases of epithelial tumors, specifically cutaneous squamous cell carcinoma (SCC), in patients with NF1. Ishida and Okabe reported a case of SCC of the forehead in an 80-year-old female patient with a history of NF1. Friedrich et al. reported a case of SCC arising on the sole of the foot in a 67-year-old male patient with NF1. Squamous cell carcinoma is the second most common cutaneous malignancy in adults. Classically, it occurs in older adults on chronically sun-exposed areas as well as in those with radiation exposure, chronic wounds, arsenic exposure and immunodeficiency. Children rarely develop any cutaneous cancers, with an incidence of 1.4 per
1,000 patients. One study by a large pediatric hospital showed that out of about 36,000 dermatology patients, 53 cutaneous malignancies were diagnosed. Of that number, 6% were squamous cell cancer. In children, cutaneous malignancies are mainly seen in association with underlying skin conditions like albinism, xeroderma pigmentosum, nevus sebaceous, and Gorlin syndrome, although all of the classic predisposing factors can come into play. According to one article, pediatric squamous cell cancer of all types appears to have increased in prevalence over the past two decades. They believe it to be caused by multiple factors, including recurrence of SCC after radiation treatments years later and increased HPV infection prevalence.

Cutaneous malignancy should be considered early on in any child with predisposing factors and atypical presentation. It is important to use a dermatopathologist comfortable with diagnosing pediatric lesions. Clinicians may also consider performing a second, wider biopsy, so as not to miss or delay diagnosis. Treatment of these lesions is recommended, and full excision is warranted, as squamous cell cancers in children have poor prognoses.

**Conclusion**

This is the third reported case of cutaneous SCC in a patient with NF1, and the first reported case in a pre-adolescent patient. To our knowledge, this is also the first documented case of SCC of the nose diagnosed in a patient with NF1. Due to the rarity of the condition, there are no clear guidelines for management of pediatric squamous cell cancer; with its increasing incidence, this issue may be addressed in the future. Our case, along with prior studies, suggest a potential increase in risk for developing epithelial tumors in patients with NF1, warranting further study. With this knowledge, clinicians can be more informed about all the risks pertaining to NF1 and consider SCC when they come across any abnormal lesions in predisposed individuals.

**References**


