



## Spindle Cell Carcinoma: A Rare Malignant Transformation in Neurofibromatosis (NF1): A Case Study

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### Abstract

*Neurofibromatosis (von Recklinghausen disease) is an autosomal dominant disorder that occurs about once in three thousand live births. Patients with NF1 have an increased risk of developing malignant tumors, in particular a tendency for some NFs to undergo malignant transformation to a malignant peripheral nerve sheath tumor (MPNST). The reported incidence of malignant transformation of neurofibromas in this condition ranges between 2.4% and 16.5%. We report a patient in which this malignant transformation was observed to occur in to spindle cell carcinoma which is very rare and not yet reported. Spindle cell carcinoma (SpCC) or sarcomatoid carcinoma is a highly malignant variant of squamous cell carcinoma. It is a rare tumor with a reported incidence of 2% to 3% of all cutaneous cancers.*

*Keywords- Neurofibromatosis, von Recklinghausen disease, malignant transformation of neurofibroma, Spindle cell carcinoma, squamous cell carcinoma, sarcomatoid carcinoma,*

### INTRODUCTION

Neurofibromatosis (von Recklinghausen disease) is an autosomal dominant disorder that occurs about once in three thousand live births.[1] Diagnostic criteria for NF1 include two or more neurofibromas (NFs) of any type or one plexiform

NF, cafe´ -au-lait macules, axillary or inguinal freckles, optic glioma, Lisch nodules, distinctive osseous lesions, and/or a first-degree relative with NF1.[2] Patients with NF1 have an increased risk of developing malignant tumors, in particular a tendency for some NFs to undergo malignant

transformation to a malignant peripheral nerve sheath tumor (MPNST).[3][4] The reported incidence of malignant transformation of neurofibromas in this condition ranges between 2.4%' and 16.5%.[5]

We report a patient in which this malignant transformation was observed to occur in to spindle cell carcinoma which is very rare and not yet reported.

### CASE REPORT

A 62 years old male patient, presented to us with complaints of a non healing ulcer in the right thigh .The patient was a case of neurofibromatosis type I (von Recklinghausen disease) and the ulcer was on one of the large cutaneous neurofibromas on the upper third of the thigh on the right lower limb. The patient had undergone excision of another neighboring cutaneous manifestation six months back (no records or biopsy available). The swelling was stony hard and not adherent to the fascia or the muscles. The ulcer had everted edges and there was marked induration.

A diagnosis of Neurofibromatosis (von Recklinghausen disease) with malignant transformation was made clinically and wide excision biopsy was taken. The biopsy was reported as spindle cell carcinoma.

### DISCUSSION

In a case of multiple neurofibromatosis malignant transformation should be suspected if there is progressive enlargement and pain related to a neurofibroma. Those in who malignant transformation occurs have a poor prognosis with

a few long-term survivors. [6] Radical ablative surgery appears to offer the only hope of cure and results would probably be improved if diagnosis could be made earlier. MRI scanning is the most useful investigation in evaluating suspicious deep seated lesions and there have been reports of the value of gallium scanning in detecting malignant transformation.[7] [8] Predisposition to malignant transformation has been reported following surgical intervention [9]

Some reports have suggested that malignant transformation is more likely to occur in internal tissues than in superficial cutaneous lesions. [10]

Estimation of the frequency of malignancy in NF1 is made difficult by bias of ascertainment and admixture of malignancies that might occur in affected individuals but which are not related to NF1 [11]. Blatt et al. reviewed the types of malignant tumors seen in 121 children with neurofibromatosis. Sarcomas were seen in three; 17 had brain tumors, including nine optic gliomas and three malignant astrocytomas; two had acute myelogenous leukemia. The presence of two children with bilateral vestibular schwannomas indicates admixture of NF2 in this study population. The study also was likely to have been biased by ascertainment at a major pediatric cancer center. [12] A population-based study done by Huson et al. provides the data set least likely to be biased towards ascertainment of cancer. The frequency of glioma (excluding optic glioma) was 1.5% and of non-central nervous system (CNS) malignancy (mainly sarcomas) 2.9%, for a combined frequency of 4.4%.[13]

Using an international NF1

database, Friedman and Birch reported a frequency of CNS neoplasms (excluding optic gliomas) of 2.0% in probands and 1.2% in NF1-affected relatives, and of non-CNS neoplasms (excluding neurofibromas) of 4.9% in probands and 3.2% in affected relatives. [14] Sørensen et al. reported a long-term follow-up of 212 Danish patients with NF1. The relative risk of malignancy in this population was 4.0 (95% confidence limits 2.8-5.6). [15]

Another approach to study the risk of cancer in NF1 is to search for NF1 cases among a large population of cancer patients. Matsui et al. reviewed data from 26,084 Japanese children with cancer and found 56 with NF1, 6.45 times the expected number. Tumor types in the NF1-affected children included optic glioma, other CNS glioma, MPNST, rhabdomyosarcoma, and leukemia. [16] Baptiste et al. found a dramatically increased relative risk of brain tumor in individuals with NF1 in a New York population-based case-control study of CNS tumors. [17]

Patients with NF1 have a defect in the NF1 gene, which is located on the long arm of chromosome 17 (17q11.2). [18]

Given the predilection of NF1 patients to develop NFs, it is likely that inactivation of the NF1 gene predisposes patients to the formation of benign NFs. Indeed, biallelic inactivation of the NF1 gene has been documented in some NFs from NF1 patients. [19]

Spindle cell carcinoma (SpCC) or sarcomatoid carcinoma is a highly malignant variant of squamous cell carcinoma. It is a rare tumor with a reported incidence of 2% to 3% of all cutaneous cancers [20]. Spindle cell carcinoma is considered to be a biphasic tumor that is composed of a squamous cell carcinoma (in situ or invasive) and spindle cell carcinoma with sarcomatous appearance. SpCC is also considered to be a monoclonal epithelial neoplasm with the sarcomatous component derived from squamous epithelium with divergent mesenchymal differentiation [21].

Although the exact cause of SpCC is not known, it is strongly associated with a history of cigarette smoking and alcohol abuse. It has also been suggested that SpCC is associated with radiation exposure although the determination of radiation risk may be complicated by the dose and duration of radiation exposure [22]. SpCC is more predominant in men compared to females (12: 1 ratio) although it is becoming more common in females, and it is usually seen in the 6<sup>th</sup> and 7<sup>th</sup> decades of life [23]. In addition to histological studies, immunohistochemical studies of epithelial and mesenchymal markers are used to diagnose the tumor. Epithelial markers include keratin (AE1/AE3, CK1, 8, 9), epithelial membrane antigens, KI, and K18. Mesenchymal markers include vimentin, desmin, S-100, Osteopontin, and BMP (2, 4) [24]. For spindle cell carcinomas with poorly differentiated epithelial tumor components Lewis et al. have shown that p53, a transcription factor that is important for epithelial proliferation and differentiation, is particularly

useful for diagnosing SpCC of the head and neck region [25].

A spindle cell carcinoma in a case of neurofibromatosis is an extremely rare variant of malignant transformation which has not yet been reported.



Fig.1 Cutaneous nodules with the ulcerating growth.



Fig.2 Ulcerating growth with everted edges

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