

Squamous Cell Carcinoma of the Sole of the Foot in Neurofibromatosis Type 1

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Abstract. *Neurofibromatosis (NF1) is an autosomal dominant tumour predisposition syndrome. A plethora of tumours are described in the literature associated with NF1. These tumours usually develop earlier in life. Some tumours show a close association with NF1, e.g. malignant peripheral nerve sheath tumour and optic nerve glioma, others are only rarely diagnosed in the context of this disease. This report focuses on the diagnosis and therapy of a squamous cell carcinoma (SCC) of the sole of the foot arising in a 67-year-old male patient with NF1. The lesion was initially misdiagnosed as an abscess. Wide excision of the highly differentiated SCC was followed by conditioning of the deep wound by a vacuum dressing. After achievement of bulky granulation tissue covering the defect at the level of the adjacent skin, a full-thickness skin graft was obtained from the abdominal skin and fixed on the defect. Healing of the defect was almost achieved by primary intention; two small lesions healed within weeks. The patient was repeatedly investigated. Five years after primary surgery, the patient had developed a corn on the medial side of the former defect. This lesion was completely excised and the defect was closed by primary intention after creating a small rotation flap. The lesion proved to be inflamed skin of the sole of the foot with no dedifferentiation of the epithelia. NF1 is a complex hereditary disease that displays an abundance of signs and symptoms. SCC may affect individuals with NF1. However, SCC account only for a small number of malignancies in NF1 compared to malignancies arising in connective tissue and brain. To the best of our knowledge, this is the first report on an SCC of the sole diagnosed in*

NF1. Vacuum dressing as an adjunct to surgery allowed reduced reconstructive measures.

Neurofibromatosis type 1 (NF1) is an autosomal dominant inherited tumour predisposition syndrome (1). Benign nerve sheath tumours are the hallmark of this disease (2). However, a number of other tumours, predominantly of mesenchymal origin, are associated with NF1 (3). The higher incidence of tumours in NF1 compared to the normal population is the main reason for reduced life-span of affected individuals (3). The majority of tumours arising in NF1 appear to be derived from nerve sheath cells (3). Carcinoma may also be registered in NF1 and diagnosis may be hampered due to the presence of neurofibromas (4).

NF1-associated neurofibromas of the foot occur in two phenotypes, namely cutaneous or plexiform. Plexiform neurofibroma of the foot may show extensive expansion causing functional and severe aesthetic problems (5). Cutaneous neurofibromas are small, nodular tumours of the skin. It is believed that cutaneous neurofibroma do not dedifferentiate into malignant peripheral nerve sheath tumours, whereas plexiform neurofibromas are a risk factor for such development (6). There are reports on malignant tumours arising in the foot in NF1 (7). Squamous cell carcinoma (SCC) of the foot is rarely diagnosed (8-10). We report on a patient with NF1 who developed a SCC in this region. This appears to be the first report of diagnosis of SCC of the sole of the foot in a patient with NF1.

Case Report

The 67-year-old patient was admitted to our Outpatient Clinic in order for us to take over the treatment of a lesion of the sole of the foot. Several months earlier, a lesion of the sole of the right foot had been noted and had continued slowly growing. The lesion was painless in the early phase of growth and the skin was unaffected over months. During the previous weeks, walking had become severely impaired due to increasing pain. The skin covering the lesion had become reddish. The patient sought for medical advice.

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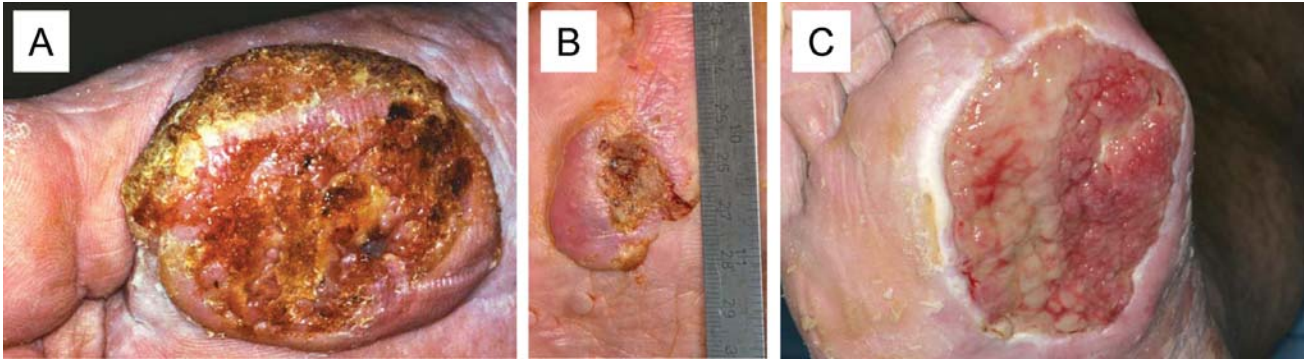


Figure 1. A: Squamous cell carcinoma of the right sole of the foot (10/2006). B: Local recurrence following excision and closure of the skin defect by full thickness skin graft (9/2007). C: Aspect of the defect following wide excision and vacuum therapy of the wound. Granulation tissue has covered the skin surface (10/2007).

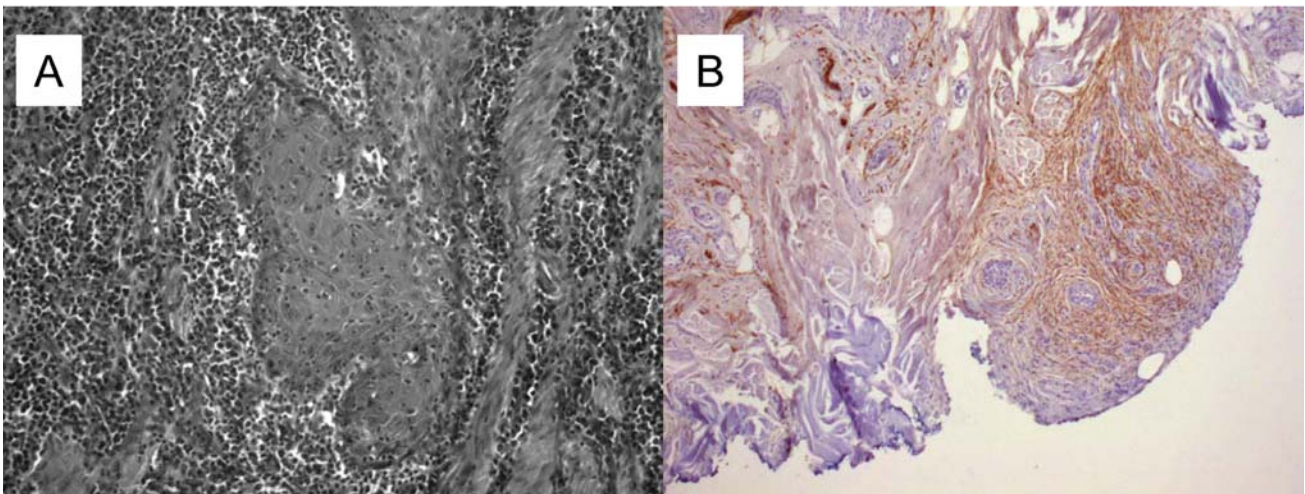


Figure 2. A: Biopsy of the ulcer of the sole of the right foot. A highly differentiated squamous cell carcinoma is invading connective tissues, haematoxylin-eosin stain. B: Diffuse plexiform neurofibroma with extensive scar formation demonstrated in a biopsy of the sole of the right foot. Anti-S-100-positive staining of neurofibroma. Original magnification, $\times 100$.



Figure 3. A: Full thickness skin graft of the sole of the foot (10/2007). B: Aspect of the sole of the foot more than three years later (2/2011), showing a small ulcer that proved to be a simple corn. C: The full-thickness skin graft has adapted to the recipient site and allows wound closure after local excision (3/2011).

Initially, the lesion was diagnosed as an abscess and incised under local anaesthesia. The medical report described that an abscess cavity could not be demonstrated and that the ill-defined lesion appeared to be necrotic in part. The initial diagnosis was recanted and the patient was advised to seek further surgical treatment.

On admission we saw a patient with NF1 with reduced general status and more than one hundred cutaneous, mushroom-like tumours covering the whole body including both soles of the feet. The patient had more than six café-au-lait spots and inguinal and axillary freckling (11). Even before the development of the tumour, the walking distance of the patient was reduced to about 50 m due to reduced physical strength.

In the sole of his right foot, an exophytic, oval tumour mass of about 2.5×3 cm² covered the metatarsal region of the first and second digit (Figure 1A). According to the patient, the lesion had increased in size after the local incision. The lesion bled on gentle pressure. The tentative diagnosis was a malignant tumour with local infection.

Under general anaesthesia, the lesion was excised. The histological diagnosis was of a highly differentiated SCC with tumour invasion in all margins (Figure 2A). The malignant epithelial tumour contained no parts indicative of a plexiform neurofibroma. Two further resections were necessary to achieve resection margins with no evidence of carcinoma. The defect extended to about 6 x 5 cm². In order to avoid a loading reconstructive surgery with a microvascular flap we opted for generation of connective tissue by applying a vacuum bandage (KCI Medizinprodukte, Wiesbaden, Germany). After 14 days, the wound tissue had reached out to the level of the surrounding skin. A full-thickness skin graft was placed on the wound. Healing was uneventful despite two regions of secondary wound healing, where intentionally, skin incisions had been placed to avoid haematoma below the transplant. The patient was regularly seen at our Outpatient Clinic. Seven months after the initial surgery, a small lesion appeared at the site of the graft. This lesion was excised and proved to be a small local recurrence of SCC (Figure 1B). Again, a wide excision was performed (7×6 cm²) to achieve tumour-free resection margins, followed by vacuum dressing that generated a thick layer of granulation tissue (Figure 1C). In one marginal resection, parts of a diffuse plexiform neurofibroma were noted (Figure 2B). The defect was closed with a skin graft (Figure 3A). Four years later, the patient returned to our Outpatient Clinic, presented a callous lesion in the middle of the metatarsal. This lesion was excised and the defect was closed by primary intention with the aid of a small rotation flap (Figure 3B and C). This lesion was a corn in the transplanted skin with no signs of atypia. Healing was uneventful and our follow-up investigation five years after diagnosis of primary tumour revealed no tumour recurrence.

Discussion

This report details the diagnosis and treatment of a highly differentiated SCC of the sole of the foot in NF1. SCC of the sole of the foot is a rare diagnosis (8-10). Tumours in NF1 are predominantly derived from connective tissues, *e.g.* malignant peripheral nerve sheath tumours (12-14). Carcinomas of the sole are usually not associated with actinic damage to the skin. The pathogenesis of SCC arising in this region is presently unclear and current studies are focusing on the effect of oncogenic viruses (10).

Differential diagnosis of this lesion may be difficult in NF1 patients with numerous cutaneous tumours (4, 15). Infection of cutaneous neurofibroma may occasionally occur and can be treated by antibiotics and local drainage. Indeed, this patient had cutaneous neurofibromas of the sole. Infection of the sole may mimic a neurofibroma (15). However, a cutaneous neurofibroma is only rarely painful and the integrity of the epidermis is usually not affected by the tumour. Indeed, it is accepted in general that the identification of a growing and painful tumour in NF1 needs to be investigated thoroughly (16). Despite tremendous efforts in NF1 diagnostics, these clinical findings are still a major indication in the diagnosis of a malignant tumour in NF1 (16).

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