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Case Report
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Desmoplastic Melanoma and Neurofibromatosis Type 1: More Than a Coincidence

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Abstract

A 62-year-old man, who was diagnosed with neurofibromatosis type 1 at the age of 30, presented with a nodular lesion on the sole of his right foot. Physical examination revealed a nodular, indurated lesion with a regular pigmented border, located on the inner side of the heel. No lymph node areas showed any signs of involvement, and radiological assessment did not reveal any secondary locations. An initial biopsy of the lesion confirmed the diagnosis of desmoplastic melanoma, leading to subsequent wide tumor resection and sentinel lymph node biopsy. Desmoplastic melanoma is a rare subtype of melanoma that exhibits similar or better survival rates compared to common melanoma of similar thickness. It has been observed that NF1 mutations work in conjunction with oncogenic BRAF mutations to promote melanomagenesis. The frequency of mutations in the *NF1* gene in desmoplastic melanoma further strengthens the potential association between neurofibromatosis type 1 and this specific subtype of melanoma.

Keywords: Desmoplastic melanoma; Neurofibromatosis type 1; NF1 mutation

Introduction

Desmoplastic Melanoma (DM) is a rare subtype of melanoma characterized by a higher susceptibility to local recurrence and a lower rate of lymph node metastasis [1]. Accounting for less than 4% of all melanoma types, desmoplastic melanoma poses diagnostic challenges for both clinicians and pathologists [2]. A potential link between neurofibromatosis and melanoma was suggested in the literature [3,4]. However, desmoplastic melanoma in NF1 patients has only been described once previously [5].

Case Presentation

A 62-year-old man presented with a lesion on the sole of his right foot. The lesion had been present for 1 year and had gradually increased in size, resulting in ulceration and bleeding due to repeated trauma. The patient had a significant medical history of Neurofibromatosis type 1 (NF1) diagnosed at the age of 30, characterized by the presence of café-au-lait spots (Figure 1), axillary and inguinal freckling, neurofibromas (Figure 2), and Lisch nodules. Physical examination found a rounded nodular indurated lesion measuring 3 cm × 2.7 cm located in the inner side of the heel (Figure 3). The lesion had a regular pigmented border and was surrounded by hyperkeratotic perilesional skin. No lymph node areas showed signs of involvement. Radiological assessment did not reveal any secondary locations. He initially underwent a biopsy of the lesion that revealed a desmoplastic melanoma and then had a large resection of the tumor, and a sentinel lymph node biopsy. Histopathological examination of the lesion revealed a malignant tumor proliferation characterized by cells with irregular enlarged hyperchromatic nuclei and eosinophilic cytoplasm. These cells were dispersed within a dense collagen fibrotic stroma. Immunohistochemistry showed positive staining for S-100 protein and negative staining for MelanA, HMB45, and CKAE1/AE3. The melanoma had a level V of invasion with a maximum thickness of 14 mm, ulceration and vascular embolus were present, and deep and lateral margins were reported as negative. Methylene blue dye infiltrated into the lesion identified one sentinel lymph node; the biopsy of this node was reported negative. Subsequently, the patient received a flap surgery.

Discussion

DM is divided into two distinct subtypes: Pure Desmoplastic Melanoma (PDM) with more

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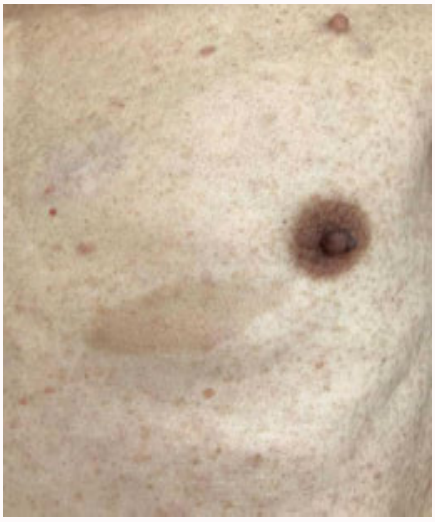

Figure 1: Café-au-lait spot.

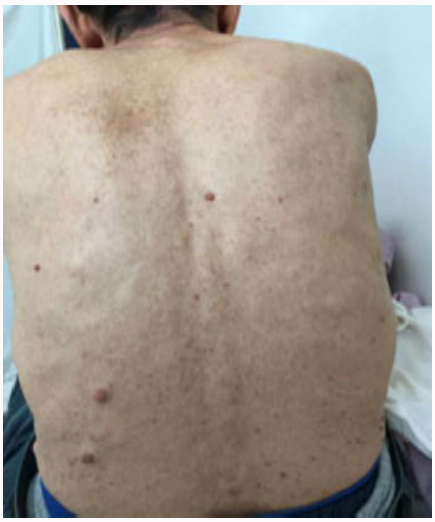

Figure 2: Cutaneous neurofibromas.

than ninety percent of the tumor volume showing significant desmoplasia and Mixed Desmoplastic Melanoma (MDM) with a desmoplastic composition between ten and ninety percent of the tumor. These two types are not only different in morphology, but also in immunohistochemical profile and prognosis [6]. Our patient had a mixed desmoplastic melanoma. Clinically, DM may be achromic [2]. This tumor behaves more like a soft tissue neoplasm than cutaneous melanoma [7]. Histologically, it is a low abundant proliferation of fusiform malignant melanocytes in an abundant collagen stroma [8]. S-100 immunostaining is typically positive, HMB-45 is only positive in about 9% of cases [9]. In our case, only S-100 protein was positive. Recent studies have shown that the survival of patients with DM is either identical or superior to that observed in patients with common melanoma of comparable thickness. The histological subtype seems to influence recurrence and lymph node metastasis rates, with significantly higher rates of nodal and distant metastasis in mixed DM compared to pure DM, although this has not been consistently demonstrated in all studies [10]. Therefore, the strategy of local management of DM should be reconsidered due to the consistently high rates of local recurrence.

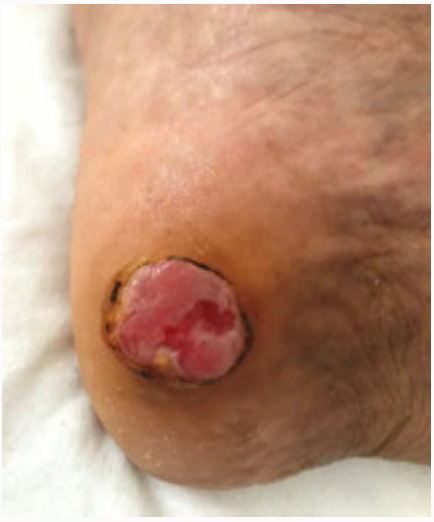

Figure 3: Nodular indurated lesion of the heel.

Table 1: NF1 mutations in desmoplastic melanoma and common melanoma.

Reference	NF1 mutation in DM (number and %)	NF1 mutation in non-DM (number and %)
[3]	54 of 78 (69.2%)	29 of 54 (53.7%)
[11]	14 of 15 (93%)	4 of 20 (20%)
[13]	10 of 15 (67%)	1 of 20 (5%)

In 2014, Maija et al. identified inactivating mutations of NF1 in a combined tumor of desmoplastic and dedifferentiated sarcomatoid melanoma. They also stated that NF1 mutations are not unique to this case but are very common in desmoplastic melanoma. NF1 mutations were found in 14 out of 15 (93%) cases of DM [11]. NF1 codes for neurofibromin 1, a protein that provides the protective state known as Oncogene Induced Senescence (OIS) by stimulating the GTPase activity of RAS, converting it to the non-active form, and preventing the activation of BRAF. NF1 mutations have been shown to work cooperatively with concomitant oncogenic BRAF mutations to promote melanomagenesis [12]. It is likely not a coincidence that this patient had both NF1 and desmoplastic melanoma. Previous studies have found a higher rate of loss of heterozygosity at the NF1 locus in desmoplastic melanoma compared to common melanoma (Table 1), indicating that the dysfunction most likely involves the expression of the *NF1* gene product [3,11,13].

Conclusion

This case serves as an illustration of the occurrence of rare and potentially related diseases in a single patient. The potential link between NF1 and desmoplastic melanoma is reinforced by the findings of several studies, which have reported an increased frequency of mutations in the *NF1* gene in patients with desmoplastic melanoma. Furthermore, the differences in prognosis between desmoplastic melanoma and common melanoma highlight the importance of identifying more cases of desmoplastic melanoma to facilitate the development of improved treatments.

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