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Title: Melanoma in a patient with neurofibromatosis 1: A single institutional study in Japan

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Neurofibromatosis 1 (NF1) is an autosomal genetic disorder caused by mutations in the *NF1* gene that affects approximately 1 in 3000 people.[1] Melanoma has been found in 0-5.4% of NF1 patients.[2] However, the incidence of melanoma in patients with NF1 in Japan has not been elucidated. Herein, we report a case of melanoma with NF1 and the incidence in our institution.

A 95-year-old Japanese woman was referred to us for evaluation of a black nodule on her left hand. She had been diagnosed as having NF1 because of multiple cutaneous neurofibromas in addition to her family history. Physical examination revealed a black nodule, 3 × 2.5 cm in size, within a pigmented macule on the dorsal side of her left hand (Fig. 1a). Numerous cutaneous neurofibromas were also seen (Fig. 1b). Histopathology of the black nodule showed a proliferation of atypical tumor cells containing melanin granules invading into the deep dermis (Fig. 1c). Based on these findings, a diagnosis of acral melanoma (low to no chronic sun-induced damage) in a patient with NF1 was made. *BRAF* mutation was not found in the tumor cells. However, we could not perform mutation analysis for the *NF1* gene because the patient was lost to follow-up.

A retrospective study was conducted to reveal the relationship between melanoma and NF1 in Japan. We investigated the numbers of both NF1 patients and melanoma patients

at the Dermatology Department of Tottori University Hospital from 2007 to 2019. The study protocol was approved by the Ethics Committee (1704A005). During the period, there were 170 NF1 patients (mean age, 27.25 years; age range, 0-95 years) and 157 melanoma patients (mean age, 70.59 years; age range, 26-95 years). We identified only one patient with both diseases. The incidence in Japanese patients was about 0.6% in our institution.

Since melanoma develops in approximately 1 or 2 in 100000 individuals in Japan, the incidence of melanoma in NF1 patients seems to be higher than that in normal individuals. However, the sample size in our study was relatively small because the data were obtained from a single institution. Guillot et al. reported the following features of melanoma with NF1: predominance for women, younger age (mean age, 33 years), large tumor thickness (mean thickness, 3.2 mm) and development from congenital nevus in 9 of 37 patients.[3] However, the prognosis is still unknown. In the present case, melanoma occurred on an unknown preceding lesion in an elderly woman. Recently, it has been reported that *NF1* is one of the driver genes for melanoma.[4] Allelic loss of the *NF1* gene (loss of heterozygosity) is likely to be related to the genesis of melanoma.[5] In the present case, the melanoma cells did not have *BRAF* mutation. Therefore, inactivation of both copies of the *NF1* gene could be related to the development of melanoma. However, it seems

that the risk of melanoma genesis is relatively low in individuals with NF1 in Japan. We speculate that racial differences might be related to the development of melanoma with NF1.

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<Figure legends>

Figure 1.

a) A black nodule in a pigmented macule.

b) Multiple cutaneous neurofibromas were also seen.

c) Histopathology showed a proliferation of atypical tumor cells containing melanin granules in the basal layer of the thickened epidermis invading into the deep dermis (tumor thickness, 3mm; HE, bar=500 μ m).