

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

short title: melanoma with NF1

The total number of words 499, figure 1, and references 5.

Yuichi YOSHIDA¹, Yuko EHARA¹, Osamu YAMAMOTO¹

¹Division of Dermatology, Department of Medicine of Sensory and Motor Organs,
Faculty of Medicine, Tottori University, Yonago, Japan

Correspondence to: Yuichi Yoshida, M.D.

Division of Dermatology, Department of Medicine of Sensory and Motor Organs, Faculty
of Medicine, Tottori University, 86 Nishi-cho, Yonago-shi, Tottori 683-8503, Japan

E-mail: xyhifu1@med.tottori-u.ac.jp

Key words: NF1, melanoma, epidemiology, mutation, gene

Funding source: This work was supported by Health Labour Sciences Research Grant (Y.Y) from the Ministry of Health, Labour and Welfare and by AMED (Y.Y) under Grant Number 17ek019082h0003.

Conflicts of interest: The authors have no conflict of interest to declare.

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.

References

1. Ehara Y, Yamamoto O, Kosaki K, Yoshida Y. Clinical severity in Japanese patients with neurofibromatosis 1 based on DNB classification. *J Dermatol* 2017; **44**: 1262-1267.
2. Seminog OO, Goldacre MJ. Risk of benign tumours of nervous system, and malignant neoplasms, in people with neurofibromatosis: population-based record-linkage study. *Br J Cancer* 2013; **108**: 193-198.
3. Guillot B, Dalac S, Delaunay M, et al. Cutaneous melanoma and neurofibromatosis type 1. *Melanoma Res* 2004; **14**: 159-163.
4. The cancer genome atlas network. Genomic classification of cutaneous melanoma. *Cell* 2015; **161**: 1681-1696.
5. Rubben A, Bausch B, Nikkels A. Somatic deletion of the NF1 gene in a neurofibromatosis type I-associated malignant melanoma demonstrated by digital PCR. *Mol Cancer* 2006; **5**: 36.

<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).