

## Multiple Primary Acral Lentiginous Melanoma on the Feet Developing in Lesions of Nagashima-type Palmoplantar Keratoderma

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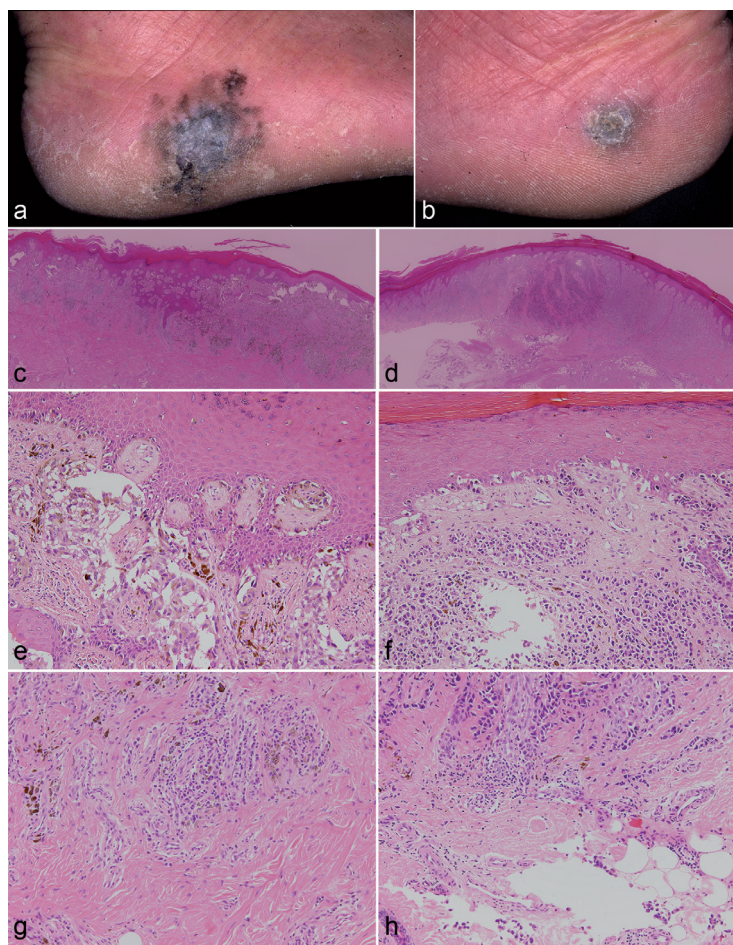
The background of multiple primary melanomas (MPMs) occurring in a patient varies influenced by genetic and environmental factors. Palmoplantar keratoderma (PPK) could be one of such backgrounds. The first cases of Nagashima-type palmoplantar keratoderma (NPPK) were reported in the Japanese literature in 1977 and in the English literature in 1989 (1, 2), respectively. NPPK was suggested to be a distinct entity from other PPKs (3), and this was confirmed by the identification of the causative gene mutations in *SERPINB7*, a gene coding for a skin-specific serine protease inhibitor (4). Twenty cases of malignant melanoma (MM) in skin lesions of PPK have been reported, including the following types of PPK: NPPK, Mal de Meleda (MDM), Papillon-Lefèvre syndrome, and Unna-Thost PPK (5–7). In 2014, the first case of acral lentiginous melanoma (ALM) in skin lesions of NPPK was reported; however, the mutation in the *SERPINB7* gene was not investigated (5).

PPK with no specific diagnosis and no history of familial melanoma. Laboratory tests were within the normal limits, including serum 5-S-cysteinyl-DOPA (5-S-CD) level, which is often used as a marker of disease progression in Japan. Abdominal ultrasonographic test, whole-body computed tomography (CT), and gallium-67 scintigraphy showed no signs of metastasis. Surgery was performed with a 3-cm margin with full-thickness subcutaneous adipose tissue. A medial plantar flap was applied to the left heel and a full-thickness skin graft from his abdomen to both heels. Histopathological examination revealed that atypical spindle to epithelioid cells were proliferated in the spinous and basal layer of the epidermis in nests and in single cells (Fig. 1c–f). They infiltrated the deep dermis and subcutaneous adipose tissue (Fig. 1g, h), and along the ducts of sweat glands. The thickness of the tumours in the right and left heels were 3.0 and 3.4 mm, respectively, with negative surgical margins. Elective bilateral inguinal lymphadenectomy was performed and no residual tumour cells were detected. The patient was diagnosed with multiple primary

### CASE REPORT

A 55-year-old Japanese man with bilateral black macules on both heels presented to our outpatient department in 1999. A macule had developed on his left heel 3 years prior to presentation; and on his right heel 2 months prior to presentation. Both macules were gradually increasing in size. Physical examination revealed poorly demarcated black macules, and a plaque on the right heel, with ulceration and hyperkeratosis, 35×30 mm in size, and a plaque on the left heel, 20×20 mm in size (Fig. 1a, b). The patient was diagnosed with bilateral ALM. The patient had had PPK as a child and had received radiotherapy to his palms and soles during his primary school years. He had unspecified kidney disease at the age of 15 years old for several months, which improved and he had no renal dysfunction after that. His family history had no consanguineous marriages. His mother and grandmother had similar symptoms of

**Fig. 1. The patient's first melanomas on the feet.** (a) Poorly demarcated black macule (35×30 mm) on the right heel in 1999, with hyperkeratosis and ulceration. (b) Black macule on the left heel (20×20 mm). (c–h) Histopathological findings of lesions on the right and left heel on haematoxylin and eosin staining. (c, d) Low-magnification image of the lesions on: (c) right and (d) left heels revealed basophilic nests located in the epidermis and deep dermis (original magnification ×40). (e–h) High-magnification image of the lesions on: (e, g) right and (f, h) left heels revealed atypical cells as single cells and nests in the epidermis (e, f) and infiltrated into the deep dermis (g, h) (original magnification ×200).



ALM, with a tumour disease of stage 2 with T3b N0 M0 (right heel), and stage 2 with T3a N0 M0 (left heel), according to the classification of the 1997 International Union Against Cancer. Eight courses of adjuvant chemotherapy with DAV-Feron was administered (dacarbazine 100 mg/day for 5 days, nimustine 50 mg/day for 1 day, vincristine 1 mg for 1 day and interferon (IFN)-beta 3×10<sup>6</sup> IU/day subcutaneous injection for 10 days). However, this was discontinued because of the side-effects. Fourteen years after the first surgery, a black macule had developed on the patient's right sole, 30 mm distal from the operation scar from the previous lesion (Fig. S1a<sup>1</sup>). Poorly demarcated black macules with various degrees of pigmentation were scattered in an area of 45×40 mm. Dermoscopy revealed that the black macule showed variegation and a parallel ridge pattern. ALM was suspected and surgery was performed with a 10-mm margin and full-thickness adipose tissue. In addition, full-thickness skin graft from the buttock was applied. Histopathological observation revealed that atypical melanocytes proliferated mainly in the epidermal basal layer (Fig. S1b, c<sup>1</sup>). The proliferation into the dermis was prominent, with a tumour thickness of 0.5 mm and tumour disease stage 1 with T1 N0 M0. Whole-body CT and brain magnetic resonance imaging (MRI) revealed no signs of metastasis. We diagnosed the new pigmented macule as primary ALM because its main proliferating portion was in the epidermis. Detailed physical examination revealed hyperkeratosis not only on the palms (Fig. S1d<sup>1</sup>) and soles, but also on the dorsal surfaces of the hands and feet, elbows, knees, ankles, and Achilles tendon area. The patient reported that his hands and feet developed whitish spongy appearance on bathing for 10 min. We suspected that this case could be Nagashima-type palmoplantar keratoderma (NPPK) and performed genetic analysis using Sanger sequencing, which revealed a compound heterozygous gene mutation due to a nonsense mutation in the gene encoding c.796C>T alteration (p.Arg266\*) in the last exon of the *SERPINB7* and splice mutation encoding c.455-1G>A alteration (p.Gly152Valfs\*21) in the exon 6 of *SERPINB7*, which were reported to be the most frequent mutation sites in Japanese patients with NPPK (4).

Gene analysis was also performed for *BRAF* p.V600E mutation with samples from the tumour tissue, and for *CDKN2A* and *CDK4* by using blood samples. Tissue sections from formalin-fixed and paraffin-embedded blocks were sent to SRL Inc. (Tokyo, Japan), where they were subjected to analysis with the cobas<sup>®</sup> 4800 *BRAF* V600 mutation test. Genomic DNA was purified from blood samples, and coding regions of *CDKN2A* and *CDK4* were amplified by PCR and directly sequenced at the Health Sciences Research Institute Inc. (Kanagawa, Japan). No mutations were detected in *BRAF* V600, *CDKN2A* or *CDK4*.

## DISCUSSION

Various risk factors associated with MM, such as skin immunity, genetic predisposition, and trauma, have been reported (8, 9). Previous reports suggest that the hyperkeratotic palms and soles, which were easily damaged by mechanical stimuli, might be a possible cause of ALM (7). In our case, the ALMs observed at first admission developed on the outer lateral arch of the feet, which are areas prone to mechanical stimuli. Radiotherapy in the patient's primary school years may also be a risk factor for developing MM (10). These stimuli may cause gene amplification, which has been reported in ALM using

comparative gene hybridization and fluorescent *in situ* hybridization (11). Bastian et al. reported that gene amplification was already present in the surrounding normal skin of acral melanoma (11), which may have occurred in our case. We assume that NPPK might be a susceptible genetic background for melanoma; however, the incidence rate and cause of melanoma in NPPK remains to be determined.

To the best of our knowledge, this is the first case of MPMs arising in lesions of NPPK. MPMs develop between 0.6% and 12.7% of melanoma patients and its incidence is higher in patients with a family history of melanoma and gene mutation of the cell cycle regulatory genes *CDKN2A* and *CDK4* (12, 13). Several cases of multiple primary ALMs were reported by Hutcheson et al. in 2007 and Lacruz et al. in 2014 (14, 15). Lacruz et al. (15) reported that *BRAF* mutation was detected in patients with MPM and that it may be a potential risk factor for MPM. The current case did not show *BRAF* p.V600E mutation in either of the specimens excised in 1999. Furthermore, we evaluated *CDKN2A* and *CDK4* gene mutation according to the previous study, but found no mutations in the coding regions. Accumulation of cases and further studies are needed to clarify the possible relationship between PPK and melanoma.

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