DR AYUMI　KOREKAWA (Orcid ID : 0000-0002-4534-8313)

DR TOSHIYUKI　YAMAMOTO (Orcid ID : 0000-0002-8390-2573)

DR HAJIME　NAKANO (Orcid ID : 0000-0001-5160-4929)

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Nagashima-type palmoplantar keratoderma and malignant melanoma in Japanese patients

A. Korekawa[1], E. Akasaka[1], D. Rokunohe[1], T. Fukui[1], T. Kaneko[1], D. Sawamura[1], M. Ishikawa[2], T. Yamamoto[2], H. Nakano[1]

[1] Department of Dermatology, Hirosaki University Graduate School of Medicine, Hirosaki, Japan

[2] Department of Dermatology, Fukushima Medical University School of Medicine

Corresponding author: Hajime Nakano, M.D., Ph.D.

E-mail: dnarna2016@yahoo.co.jp

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Nagashima-type palmoplantar keratoderma (NPPK) is an autosomal recessive type of PPK with non-progressive, diffuse, transgradient hyperkeratosis. Clinical findings usually include mild diffuse palmoplantar hyperkeratosis with well-demarcated diffuse erythema on the dorsal aspects of the hands and feet, forearms, elbows, Achilles tendon, and knees.[1,2]

In 2013, Kubo *et al.*[2] identified mutations in *SERPINB7* that cause complete deficiency of SERPINB7 protease inhibitor activity in the epidermis and NPPK. To date, 221 cases of NPPK have been reported, mainly in Japan, China, and Korea.[1,2]

We previously reported a higher incidence of malignant melanoma (MM) in the hyperkeratotic lesions of Japanese patients with PPK.[3] In our department, 28 patients were diagnosed with NPPK based on distinctive clinical findings and testing for *SERPINB7* mutations in blood samples from 2007 to 2017. The mean age was 26.1 years (range, 0.5 to 85 years). Homozygous *SERPINB7* mutations were identified in 22 (79%) patients. Although the remaining six (21%) patients were heterozygous for *SERPINB7* mutations, they were diagnosed with NPPK based on distinctive clinical findings. Four (14%) developed MM in hyperkeratotic NPPK lesions. We describe the clinical courses of these four cases below.

Patient 1 was a 65-year-old woman who presented with a black macule and red nodule on the nail bed of her left fourth toe (Fig. 1a and b). Tumour resection and left inguinal lymph node dissection were performed. The MM stage was pT4bN2aM0, stage IIIB. Systemic adjuvant chemotherapy consisting of interferon-β was

administered. She survived for over 72 months after resection. Patient 2 was an 85-year-old woman who presented with a black macule on the dorsum of her right hand and in the interdigital area of the right index finger (Fig. 1c and d). Tumour resection and right axillar sentinel lymph node biopsy (SLNB) were performed. The MM stage was pT1aN0M0, stage IA. She survived for over 52 months after resection. Patient 3 was a 55-year-old man who presented with a black macule on his right sole (Fig. 1e and f). Tumour resection and right inguinal SLNB were performed. The MM stage was pT2aN0M0, stage IB. He survived for over 52 months after resection. Patient 4 was a 38-year-old man who presented with a black macule on his right sole (Fig. 1g and h). Tumour resection and right inguinal SLNB were performed. One of three SLNs was positive for micrometastasis. Next, he developed in-transit metastasis on the right thigh. Resection of the in-transit metastasis and right inguinal lymph node dissection were performed. The resected lymph nodes were negative for metastasis. The MM stage was pT4bN3M0, stage IIIC. Subsequently, he developed multiple metastases despite systemic therapy.

All four patients had hyperkeratosis of the palms and soles. All four NPPK patients with MM had pathogenic *SERPINB7* mutations. Patient 1 had a compound heterozygous mutation (c.382C>T, p.Arg128Ter and c.455G>T, p.Gly152Val, at the exon/intron junction of exon 6). Patients 2 and 3 had a homozygous nonsense mutation (c.796C>T, p.Arg266Ter). Patient 4 had a different compound heterozygous mutation (c.796C>T, p.Arg266Ter and c.830C>T, p.Pro277Leu). The nonsense mutation c.382C>T has not been previously reported.

The association between MM and NPPK has been previously described.[4–6] To date, there have been eight patients[4–6] with NPPK and MM, including the four present cases. All eight patients were Japanese. The overall prevalence of MM in the

Japanese population is estimated at approximately 0.002%.[3,7] The percentage of NPPK with MM is 3.6% (8 out of 221 cases), suggesting a high incidence of MM in NPPK lesions. Since it has not been determined whether NPPK lesions are prone to develop into MM, more cases of NPPK with MM are necessary to understand the association.

Some authors[2-4,6,8] have suggested an association between repeated mechanical damage, hyperkeratosis, and the development of MM within NPPK lesions. Kubo *et al*.[2] reported that NPPK skin lesions have a whitish appearance that results from a maceration phenomenon in the stratum corneum after water exposure. They suggested that water permeation into the stratum corneum is enhanced in NPPK lesions. This suggests a tendency towards maceration in NPPK lesions, making the skin in NPPK lesions more fragile and susceptible to repeated mechanical damage.

In addition to hyperkeratosis and repeated mechanical damage,[8] other factors such as immune impairment, suggested by the decrease in the number of Langerhans dendritic cells in the epidermis of NPPK lesions,[6] might play a role in the development of MM within NPPK lesions. Further clinical and histological case studies and genetic studies of NPPK are necessary to identify the pathogenic mechanism of MM-associated NPPK.

References

1 Kabashima K, Sakabe J, Yamada Y, *et al*. “Nagashima-type” keratosis as a novel entity in the palmoplantar keratoderma category. *Arch Dermatol* 2008; **144**:375-9.

2 Kubo A, Shiohama A, Sasaki T, *et al*. Mutations in SERPINB7, encoding a member of the serine protease inhibitor superfamily, cause Nagashima-type palmoplantar keratosis. *Am J Hum Genet* 2013; **93**:945-56.

3 Nakajima K, Nakano H, Takiyoshi N, *et al*. Papillon-Lefèvre syndrome and malignant melanoma. A high incidence of melanoma development in Japanese palmoplantar keratoderma patients. *Dermatology* 2008; **217(1)**:58-62.

4 Takahashi T, Tokuzumi M, Matsuyama K, *et al*. A case of malignant melanoma occurred in an area of palmoplantar keratoderma (Nagashima-type). *Proceedings: conference on disorders of keratinization* 2016: 94-8.

5 Adachi A, Komine M, Maekawa T, *et al*. Multiple primary acral lentiginous melanoma on the feet developing in lesions of Nagashima-type palmoplantar keratoderma. *Acta Derm Venereol* 2017; **97(6)**:756-58.

6 Tsutsumi R, Yoshida Y, Yamada N, *et al*. Nagashima-type palmoplantar keratosis with melanoma: absence of epidermal Langerhans cells in hyperkeratotic skin. *Eur J Dermatol* 2017; **27(2)**:210-2.

7 Ishihara K, Saida T, Yamazaki N, *et al*. Statistical analysis of malignant melanoma: clinical features and therapeutic survival rate in terms of patients’ age difference. *Skin Cancer* 2009; **24**:258-66. (in Japanese)

8 Minagawa A, Omodaka T, Okuyama R. Melanomas and Mechanical Stress Points on the Plantar Surface of the Foot. *N Engl J Med* 2016; **374**: 2404-6.

Figure legends

Fig. 1 (a) Patient 1. Diffuse hyperkeratosis and mild erythema on the palms and soles (the palms are not shown in (a)). The erythematous lesions extended to the dorsal aspects of the hands, forearms, and feet. The nails on all fingers were thickened and opaque. She did not have palmar or plantar hyperhidrosis.

(b) Patient 1. A 10 mm × 10 mm reddish nodule accompanied by a black macule on the nail bed of the left fourth toe. The toenail was broken by the nodule.

(c) Patient 2. A black macule on the dorsum of the right hand and interdigital area of the right index finger.

(d) Patient 2. Diffuse hyperkeratosis and mild erythema on the palms and soles (the palms are not shown in (d)). The erythematous lesions extended to the dorsal aspects of the hands and feet. She did not have palmar or plantar hyperhidrosis.

(e) Patient 3. Diffuse hyperkeratosis and diffuse mild erythema on the soles. The erythematous lesions extended to the dorsal aspects of the hands and feet. He had palmar and plantar hyperhidrosis.

(f) Patient 3. A black macule on the right sole.

(g) Patient 4. A black macule on the right sole and diffuse hyperkeratosis and diffuse mild erythema on the soles.

(h) Patient 4. Diffuse hyperkeratosis and mild erythema on the right palms. The erythematous lesions extended to the inner surface of the wrists.