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CASE REPORT

Allogeneic bone marrow transplantation possibly induces a localized type of porokeratosis

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ABSTRACT

A 15-year-old girl underwent allogenic bone marrow transplantation for neuroblastoma. A few years later, she noticed a round lesion on her left buttock. Since the lesion had been asymptomatic and never grown, more than 20 years had passed before she saw a local doctor to consult about it. Although the lesion was suspected to be tinea corporis, no fungi were found on microscopic examination. Subsequently, administered topical corticosteroids were not effective. She was referred to our hospital for further evaluation, and a skin biopsy confirmed the diagnosis of porokeratosis. There was a possibility that chemotherapy, total body radiation, or immunosuppressive therapy associated with allogeneic bone marrow transplantation was involved in the development of porokeratosis. Numerous cases of acquired porokeratosis in immunocompromised status have been observed; as for those after allogenic bone marrow transplantation, 12 cases have been reported in the English literature, 4 of which had only one or a few lesions on a limited area of body surface. Our case was relatively uncommon in that the lesion was solitary and comparatively large. In a localized type of porokeratosis, it was suggested that a malignant skin tumor developed earlier than in other types. Careful follow-up for malignant transformation is especially required.

Keywords: Porokeratosis; Localized Type; Bone Marrow Transplantation; Immunosuppression; Malignant Transformation

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1. Introduction

Porokeratosis is a rare hyperkeratotic disorder arising from abnormal clones of keratinocytes. The risk factors for its genesis include inheritance, trauma, and ultraviolet light[1]. Since MacMillan reported a case of porokeratosis after renal transplantation in 1974[2], immunosuppression has also been believed to be a risk factor. Immunosuppression-associated porokeratosis is more often characterized by multiple lesions rather than a single lesion[3]. We herein report a case of localized porokeratosis after allogeneic bone marrow transplantation for neuroblastoma.

2. Case presentation

A 42-year-old woman presented with an asymptomatic round lesion on her left buttock. She consulted a local doctor, and the lesion was suspected to be tinea corporis, but no fungi were found by microscopy. Although topical corticosteroids were prescribed, the lesion did not improve, and she was referred to our hospital for further evaluation. She had a solitary, 6.5 × 3.5 cm, annular erythematous patch with a brownish hyperkeratotic border (**Figure 1**). She noticed it at the

age of 17 or 18. Since then, its size had not changed for more than 20 years. No rash was found on other areas. She denied any family history. A biopsy of the brownish border of the lesion showed a cornoid lamella, which was a column of tightly fitted parakeratotic cells in the upper epidermis (**Figure 2**). She was diagnosed with porokeratosis. The lesion has been followed up clinically without any specific therapy.

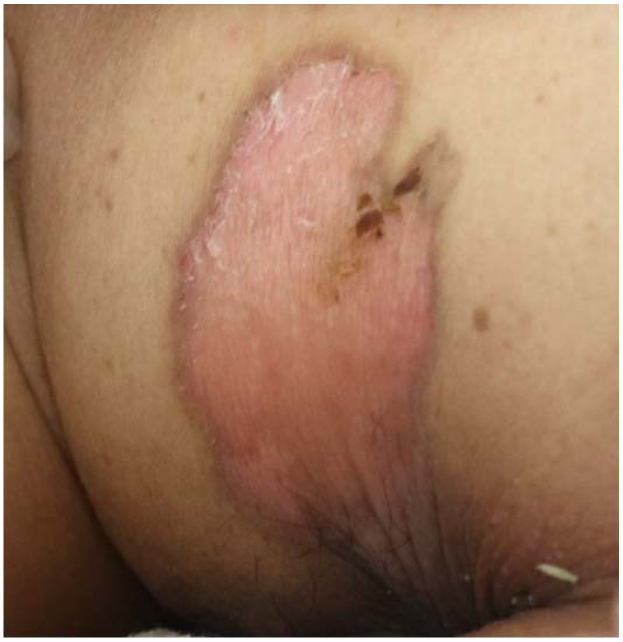

Figure 1. An annular erythematous patch with a brownish hyperkeratotic border on the left buttock**.**

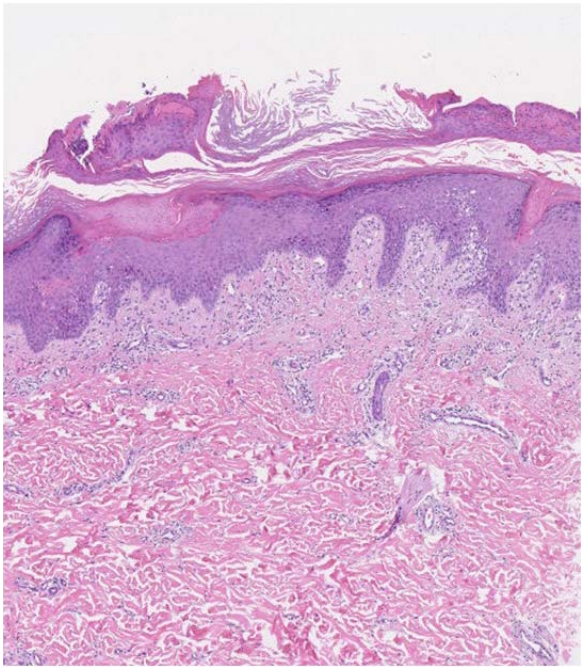

Figure 2. A column of tightly fitted parakeratotic cells in the upper epidermis, which is consistent with a cornoid lamella (hematoxylin and eosin ×10)**.**

According to her medical record obtained in our hospital, she was diagnosed with neuroblastoma at the age of 14 by close examination of abdominal pain. Surgical operation and adjunctive chemotherapy were performed the following year. In addition, she underwent allogeneic bone marrow transplantation, with high-dose chemotherapy and total body radiation as preparative therapy. Immediately after allogeneic bone marrow transplantation, the immunosuppressive agent cyclosporine was initiated. Two months later, chronic graft-versus-host disease developed, for which treatment with prednisolone 45 mg daily was started. A good clinical response was obtained, and prednisolone was tapered over 5 months.

3. Discussion

Porokeratosis was first described by Mibelli in 1893[4]. It is a disorder of epidermal keratinization and characterized by a distinct peripheral keratotic ridge that corresponds histologically to the cornoid lamella. Although no unified classification standard for it is yet to be created, it has been classified in Japan, on the basis of its clinical characteristics as follows: classical porokeratosis, localized porokeratosis, linear porokeratosis, disseminated superficial porokeratosis, and disseminated superficial actinic porokeratosis[5]. In our case, a single lesion of 6.5 × 3.5 cm was observed only on the left buttock, and it was therefore considered to be localized porokeratosis.

Porokeratosis has been observed in various types of immunosuppression, including that after solid organ transplantation[2,6], systemic corticosteroids[7], electron beam radiation[8], and biological agents[9]. The development of porokeratosis during the course of human immunodeficiency virus infection has also been reported[10]. That is to say, genetic predisposition and a variety of triggers such as immunosuppressive drugs may be associated with the occurrence of porokeratosis. Recently, causal mutations of several genes (MVK, PMVK, MVD, and FDPS) have been identified[11,12], and it has been shown that approximately one per 400 Japanese individuals is estimated to have a pathogenic mutation in MVD[13]. Each skin lesion of disseminated superficial actinic porokeratosis origi-

nates from a postnatal keratinocyte clone with a different second-hit genetic event in the wild type allele of the corresponding gene, and linear porokeratosis derives from a single prenatal clone of keratinocytes with a second-hit genetic event[13].

Although the exact timing of porokeratosis onset in our case is unknown, the patient noticed the lesion on her left buttock within a few years after allogeneic bone marrow transplantation. There is a possibility that chemotherapy or total body radiation before bone marrow transplantation, or immunosuppressive therapy after bone marrow transplantation led to porokeratosis, but the identification of the causative one is difficult because the combined effects of these therapies may have been involved. We speculate that the patient exhibits monoallelic germline mutations in genes encoding mevalonate pathway enzymes such as MVD, and total body radiation triggers an individual second hit genetic change in the wild-type allele of the corresponding gene specifically in the epidermis. In addition, loss of immunosurveillance caused by chemotherapy or immunosuppressive therapy may facilitate the proliferation of abnormal keratinocyte clones. However, further studies are required to elucidate that localized porokeratosis is caused by a similar mechanism to that of disseminated superficial actinic porokeratosis. Alexis and colleagues argued that, in the case of bone marrow transplantation, the frequent lack of concurrent immunosuppressive therapy at the time of diagnosis of porokeratosis suggests a more complex association with immunosuppression than that after solid organ transplantation[3].

We summarized cases of porokeratosis after allogeneic bone marrow transplantation that have been reported in the English literature (**Table 1**)[3,6,14-18]. In 4 of 12 cases, only one or a few lesions were present on a limited area of body surface as in our case[3,6]. The lesion size of our case was much larger than any reported lesion sizes shown in **Table 1**.

Table 1. Cases of porokeratosis after allogenic bone marrow transplantation reported in the English literature

Age/Sex	Anatomic location	Number of lesions	Size (cm)	Post-transplantation time (years)	Reported year [reference]
19/M	Leg, buttock	A small number	0.5–1.0	1	1985[14]
38/M	Arm	1	Not stated	Not stated	1992[6]
32/M	Thigh, buttock, flank	Not stated	Not stated	Not stated	1995[15]
37/M	Flank, thigh, buttock	3	1.0, n/a for thigh and buttock	3, 4	2006[3]
62/M	Leg	1	1.5	6	2006[3]
58/M	Preauricular region, antihelix, thigh, calf	5	0.4, 0.5, n/a for thigh and calf	3, 4, 5	2006[3]
42/F	Popliteal fossa	2	0.8, 1.0	13	2006[3]
42/M	Thigh	1	0.5	1	2006[3]
38/M	Both extremities, trunk	Multiple	0.5–2.5	3	2010[16]
13/M	Leg, arm, abdomen, face	Multiple	0.5–1.5	1	2012[17]
1/M	Thigh, axilla	2	Not stated	Not stated	2015[18]
12/M	Popliteal fossa, cervical region	5	Not stated	Not stated	2015[18]

It has been reported that administration of cyclosporine led to malignant disorders[19,20]. Some immunosuppressive agents used after bone marrow transplantation may be associated with cancer progression. A possible complication of porokeratosis is Bowen's disease, squamous cell carcinoma or basal cell carcinoma. A study showed that a localized type of porokeratosis developed a malignant skin tumor in an average of 22.3 years, which was significantly earlier than other types[5]. The lesion in our case is relatively large, and we carefully follow-up the patient so as not to overlook malignant transformation.

Conflict of interest

The authors declare no potential conflicts of interest.

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