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【 CASE REPORT 】

Secondary Skin Cancer in a Case with Long-term Voriconazole after Allogeneic Hematopoietic Stem Cell Transplantation for Acute Myeloid Leukemia

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Abstract:

Secondary malignancies that develop after allogeneic-hematopoietic stem cell transplantation (allo-HSCT) have become serious issues. A 47-year-old man who developed acute myeloid leukemia in 2009 and subsequently underwent allo-HSCT twice: in 2009 and 2011. In 2015, voriconazole for lung aspergillus was started. In 2018, chronic graft-versus-host disease (GVHD) and multiple actinic keratoses manifested at his head. In 2020, some lesions were diagnosed as squamous cell carcinoma, so voriconazole was withdrawn, and subsequent surgery and radiation led to remission. Long-term administration of voriconazole in addition to allo-HSCT and chronic GVHD may be closely related to secondary skin cancer.

Key words: secondary skin cancer, allo-HSCT, voriconazole, chronic GVHD

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Introduction

Allogeneic-hematopoietic stem cell transplantation (allo-HSCT) is performed for chemotherapy-resistant/refractory hematological malignancies in patients with a preserved organ function provided an acceptable donor is available (1). In recent years, the onset of secondary malignancies has become a serious issue with the increase in numbers of long-term survivors after allo-HSCT (2-9).

The clinical characteristics of secondary malignancy can be divided into three categories (2). Post-transplant lymphoproliferative disease (PTLD) usually occurs within a peak of two to three months after allo-HSCT (2), treatment-related myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) develops with a peak of two to three years after allo-HSCT (2), and solid tumors begin to develop at one year after allo-HSCT (2). In Japan, Atsuta et al. identified the onset of secondary malignancy in 269 cases among 17545 allo-HSCT patients from 1997 to 2007 in a Japanese data center for allo-HSCT (2). These authors also reported that the frequency was 0.7% at 5 years after allo-HSCT and 2.4% at 10 years after allo-HSCT (2).

Regarding the position of solid tumors, oral tumors, esophageal/colon tumors, and skin tumors have reported as the most common sites of solid tumors (2). In general, one of the risk factors for skin cancer is a history of sun exposure. Furthermore, radiation before HSCT and chronic graft-

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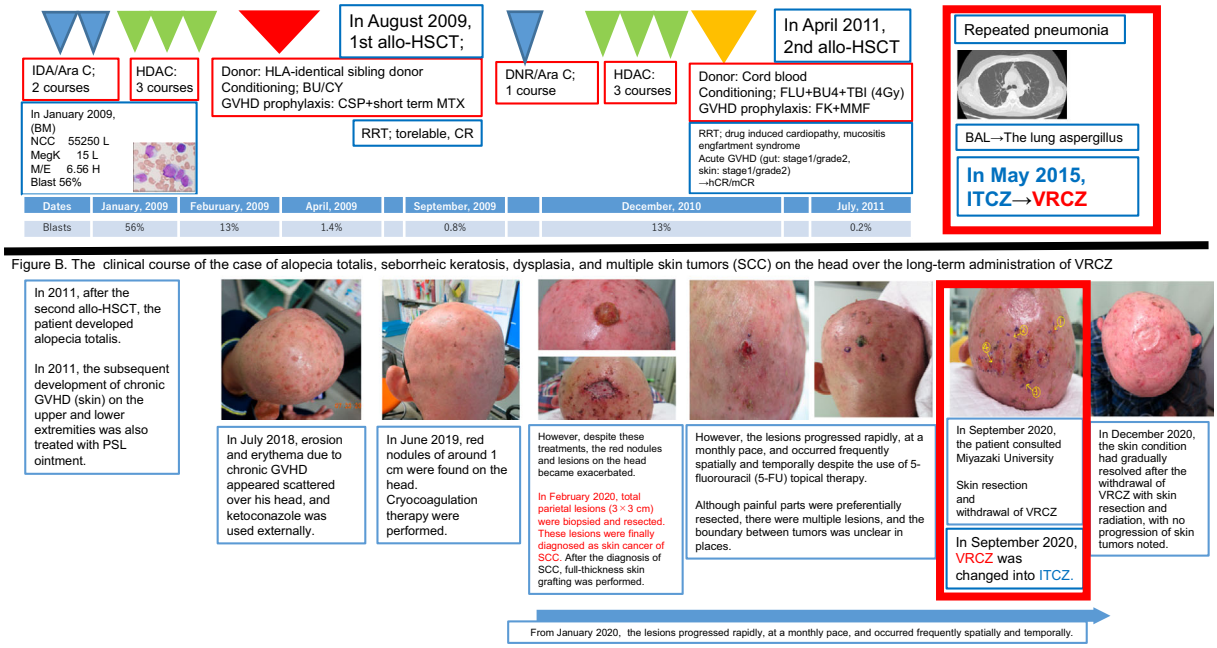

Figure. **A: The clinical course of AML. B: The clinical course of alopecia totalis, seborrheic keratosis, dysplasia, and multiple skin tumors [squamous cell carcinoma (SCC)] on the head over the long-term administration of VRCZ.**

versus-host disease (GVHD) are also reported as repeatedly identified risk factors for secondary solid tumors after allo-HSCT. Given the above, secondary solid tumors are considered multifactorial. Reports of skin tumors after allo-HSCT are limited (2-5), so the clinical features and outcomes remain unclear.

We herein report a case of skin cancer in a patient with long-term voriconazole (VRCZ) administration and repeated allo-HSCT.

Case Report

A 47-year-old man developed AML (M2) with mixed-lineage leukemia (MLL) rearrangement in January 2009 (Figure A). After achieving his first complete remission (CR) by induction therapy and post-remission therapy, we performed allo-HSCT with the conditioning regimen of busulfan (BU)/cyclophosphamide (CY) plus short-term methotrexate (MTX) and cyclosporin (CSP) as GVHD prophylaxis. After allo-HSCT, regimen-related toxicity (RRT) was tolerable. However, recurrence was noted in December 2010. Subsequent re-induction therapy and post-remission therapy led to second CR. In April 2011, umbilical cord blood transplantation (CBSCT) was performed under the conditioning regimen of fludarabine (FLU), BU (4), and total body irradiation (TBI) (4 Gy) with tacrolimus (FK) and mycophenolate mofetil (MMF) as GVHD prophylaxis. RRT was again tolerable, but acute GVHD developed (gut: stage 1/grade 2 and skin: stage 1/grade 1). Chronic GVHD (upper and lower extremities) was pathologically diagnosed by an evaluation of a skin specimen from the upper extremities in 2011. The patient was treated with prednisolone (PSL) ointment. The patient then maintained CR with a long-term survival of over 10 years.

We present below the clinical course of the skin, including alopecia totalis, seborrheic keratosis, dysplasia, and multiple skin tumors [squamous cell carcinoma (SCC)] on the head (Figure B).

In 2011, after the second allo-HSCT, the patient developed alopecia totalis. In 2011, the subsequent development of chronic GVHD (skin) on the upper and lower extremities was also treated with PSL ointment. As it is generally known that one of the risk factors for skin cancer is a history of sun exposure, the patient shaded his face and head with a hat and sunscreen when leaving the house after suffering hair loss in 2011. In July 2018, erosion and erythema due to chronic GVHD appeared scattered over his head, and ketoconazole was used externally.

In June 2019, red nodules of around 1 cm were found on the head. Cryocoagulation therapy were performed; however, despite these treatments, the red nodules and lesions on the head became exacerbated. Therefore, in February 2020, total parietal lesions (3×3 cm) were biopsied and resected. These lesions were finally diagnosed as skin cancer of SCC.

After the diagnosis of SCC, full-thickness skin grafting was performed. However, the lesions progressed rapidly, at a monthly pace, and occurred frequently spatially and temporally despite the use of 5-fluorouracil (5-FU) topical therapy. Although painful parts were preferentially resected, there were multiple lesions, and the boundary between tumors was unclear in places.

In September, 2020, the patient consulted Miyazaki University (the department of dermatology) for a further examination. He presented with limited clinical symptoms of

Table. Previous Reports of Secondary Skin Tumor after Allo-HSCT.

References	Skin cancers	Underlying disease	Allo-HSCT	Administration of VRCZ	The development of secondary skin tumors after allo-HSCT
(2)	13 cases	Not described	+	Not described	1.7% at 10 years
(3)	6 cases	Not described	+	Not described	2.4% at 10 years
(4)	1 case (65, male)	MDS	+	+	6.5 years
(5)	1 case (36, female)	Not described	+	-	2.5 years, 3 years
Our present case	1 case (47, male)	AML	+	+ (5 years)	11 years

MDS: myelodysplastic syndrome, AML: acute myeloid leukemia, Allo-HSCT: allogeneic-hematopoietic stem cell transplantation, VRCZ: voriconazole

chronic GVHD (extremities) for over seven years before the development of skin manifestations (head) in 2018, which led to the diagnosis of SCC the following year (2019). Of note, this clinical course involved a rather irregular pattern of skin chronic GVHD manifestations after allogeneic HSCT. Thus, in this situation, various effects, including the involvement of the administered drugs, needed to be considered. Notably, based on previous reports of secondary skin tumors after allo-HSCT (2-5), the case was suspected of being associated with the long-term administration of VRCZ for deep lung mycosis and pulmonary aspergillosis (over five years) and SCC. Thus, in our case, VRCZ was changed into ITCZ in September 2020. In December 2020, the skin condition had gradually resolved after the withdrawal of VRCZ with skin resection and radiation, with no progression of skin tumors noted.

In clinical practice, the concentration of VRCZ in peripheral blood may be useful to adjust the appropriate dose of VRCZ for deep lung mycosis and pulmonary aspergillosis. However, in our case, we did not measure the blood concentration of VRCZ. Thus, the concentration of VRCZ may need to be monitored in patients after allo-HSCT.

Discussion

We described a patient who developed alopecia totalis, seborrheic keratosis, dysplasia, and multiple SCCs over the long-term administration (five years) of VRCZ after repeated allo-HSCT for AML. Our case and previous reports (2-5) suggest the clinical impact of VRCZ on the risk of skin cancer in addition to allo-HSCT and chronic GVHD.

Regarding secondary malignancies after allo-HSCT, Atsuta et al. reported that risk factors for secondary malignancy after allo-HSCT included very low or very high age (under 10 years old and elderly populations), chronic GVHD, and irradiation (2). However, other risk factors for secondary malignancy after allo-HSCT have been unclear. In allo-HSCT patients, fungal infection is a lethal complication treated with anti-fungal agents, including VRCZ or ITCZ (2). In 2019, Tang et al. reported a meta-analysis of 8 studies including 3710 cases of lung transplantation and allo-HSCT, revealing the onset of SCC in 405 cases (10). Of note, the authors also suggested that the longer-term use of VRCZ (≥180 days) might increase the risk of SCC (10).

Regarding previous reports and the literature concerning secondary malignancies after allo-HSCT (2-9), 22 cases of skin tumors after allo-HSCT have been reported (Table) (2-5). Among those 22 cases, 2 were administered VRCZ during the development of secondary skin cancer after allo-HSCT. A 65-year-old man with MDS after allo-HSCT being treated with VRCZ developed SCC 6.5 years after allo-HSCT (4), and a 36-year-old woman similarly developed SCC 2.5 and 3 years after allow-HSCT (5).

Our patient, consistent with the above previous reports, had a history of repeated allo-HSCT and a history of oral administration of VRCZ for five years. VRCZ withdrawal and subsequent skin resection and radiation prevented the further onset and development of actinic keratosis and SCC. These findings also resulted in a therapeutic diagnosis and supported a close relationship between VRCZ and SCC. Consequently, our case and previous reports (2-9) suggest clinical risk factors of VRCZ for skin cancers in addition to allo-HSCT and chronic GVHD. The phototoxicity induced by VRCZ is suspected to be related to seborrheic keratosis, dysplasia, and multiple skin tumors (SCC) on the head during long-term administration (10).

In conclusion, our case suggests that long-term administration of VRCZ may be closely related to carcinogenesis of the skin in patients with a history of allo-HSCT and chronic GVHD.

The authors state that they have no Conflict of Interest (COI).

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Noriaki Kawano, Shunou Nakamura, Kousuke Mochida contributed equally to this work.

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