Received: 8 February 2018 | Accepted: 22 February 2018

DOI: 10.1002/cia2.12011

ORIGINAL ARTICLE

WILEY Journal of Cutaneous Immunology and Allergy

An adolescent case of xeroderma pigmentosum variant confirmed by the onset of sun exposure-related skin cancer during Crohn's disease treatment

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Abstract

The patient was a 16-year-old boy who was diagnosed with Crohn's disease at 13 years of age, who was treated with mesalazine, azathioprine, and infliximab. Concurrently, the patient developed small freckle-like pigmented spots on sun-exposed areas, which gradually increased in number. At 14 and 16 years of age, a blue-gray macule and a nodule appeared on his face, respectively. A histopathological examination revealed that the macule had only postinflammatory pigmentation, while the nodule was basal cell carcinoma. The sensitivity to UV-killing by colony formation of the patient's cells was normal but was enhanced by caffeine treatment. In addition, a pathologic mutation in the *POLH* gene was identified and a diagnosis of xeroderma pigmentosum variant (XP-V) was established. XP-V is a cutaneous type of XP that is commonly diagnosed from middle age after the induction of skin cancer on sun-exposed areas. Our patient had a genetically sensitive background (XP-V), and we considered that immunosuppressive agents for Crohn's disease may have enhanced the photocarcinogenesis at a young age. This finding implies that we should be careful about a skin cancer production and that protection from UV may be essential when pediatric patients with a genetic background of UV sensitivity take immunosuppressive agents.

KEYWORDS

child, Crohn's disease, immunosuppressive agent, photocarcinogenesis, xeroderma pigmentosum variant

1 | INTRODUCTION

Xeroderma pigmentosum variant (XP-V) is a highly carcinogenic photosensitivity disease that occurs due to a defect of the DNA polymerase η (POLH), which conducts translesion synthesis during the replication of DNA with ultraviolet (UV)-induced damage. Patients with XP-V have skin manifestations alone and the disease causes no sunburn. In addition, their dyschromatosis on the sun-exposed skin is milder in comparison with other groups of XP (XP groups A–G) with deficient nucleotide excision repair (NER). Furthermore, without appropriate sun protection, they usually develop skin cancers after middle age. Thus, it is difficult to make a definitive diagnosis of XP-V in childhood.[1–3]

Crohn's disease is an inflammatory bowel disease and is usually treated with corticosteroids, biologic agents, or immunosuppressive

agents. Crohn's disease is more common in adults than in children, but frequency of Crohn's disease among children has been reported to be increasing and pediatric patients with Crohn's disease should start taking medications earlier and should continue taking them for longer in comparison with adult patients with Crohn's disease.[4,5]

We herein report an interesting case of a Japanese adolescent patient of XP-V, in which the diagnosis of XP-V was confirmed by the onset of a sun exposure-related skin cancer during Crohn's disease treatment. In the present case, immunosuppressive agents, which were administered for Crohn's disease over a few years, were thought to have increased the risk of UV-induced skin cancer in a patient whose genetic background of XP-V made him photosensitive and more cancer-prone than a patient without XP.

2 | CASE REPORT

A 16-year-old Japanese boy, born from nonconsanguineous parents, has developed diarrhea, remittent fever, and stomatitis at age of 13. A local physician found a longitudinal ulcer in the terminal ileum via endoscopy. Consequently, this patient was diagnosed with Crohn's disease and treatment was initiated with mesalazine (Pentasa®), azathioprine (Imuran®), and infliximab (Remicade®). Concurrently, the patient developed small freckle-like pigmented spots on the sun-exposed skin, including the face, the dorsal aspect of both hands and the lateral sides of both forearms: The number of these spots gradually increased. At 14 years of age, a black macule appeared in the right preauricular region. At 16 years of age, the patient newly noticed a nodule at the root of his nose and was referred to our department for the evaluation and treatment of these skin problems. At his first visit to our clinic, he had multiple small freckle-like pigmented spots on sun-exposed skin areas, a black nodule at the right root of his nose and a blue-gray macule in the right buccal region (Figure 1A,B). A physical examination revealed no neurological symptoms. We performed incisional biopsies of the nodule and macule. The histopathological examination of the specimens revealed that the nodule at the nose root was basal cell carcinoma (Figure 2A,B), while the macule in the right buccal region was postinflammatory pigmentation (Figure 2C,D). Further evaluation was performed because XP was suspected as a background factor, based on the fact that he had developed basal cell carcinoma on the face in his teens and had multiple small freckle-like pigmented spots on his sun-exposed skin. A host cell reactivation assay using an ultraviolet irradiation (UV)-irradiated reporter gene in the cultured primary fibroblasts derived from the patient suggested that he had normal NER capacity. The evaluation of UV sensitivity by colony formation was also normal; however, this sensitivity was enhanced by caffeine treatment. Finally, a compound heterozygous mutation (c.c907t [p.R303X] and c.c1643a [p.S548X]) was identified in the *POLH* gene. These genetic changes, which are novel in XP-V patients, resulted in decreased POLH protein expression (Figure 1C). At this point, a definitive diagnosis of XP-V was established in this patient.

3 | DISCUSSION

XP is an autosomal recessive photosensitive genodermatosis with failures in the mechanisms of UV-induced DNA damage repair.[1] It is classified into 8 different types (A–G groups and a variant) according to the responsible gene. *XPV* is the responsible gene in approximately 25% of the XP patients in Japan. It is the second common form of XP after XP group A (XP-A) which affects 55% of the XP patients in Japan.[3] In XP-V patients, the freckle-like pigmented spots on the sun-exposed skin are relatively mild and progress slowly without neurological abnormalities. XP-V is usually suspected based on the clinical findings and laboratory findings of tests of the patients' primary fibroblasts which reveal that the NER capacity with slightly high or normal sensitivity to killing by UV that is enhanced by caffeine treatment. After obtaining these results, we next try to analyze the *XPV* gene to detect genetic abnormalities. Because the cutaneous symptoms are obscure and the onset of skin cancers in childhood is rare, the diagnosis of XP-V is usually established in adulthood. Thus, a definite diagnosis tends to be made later in the XP-V patients in comparison with the patients in the other XP

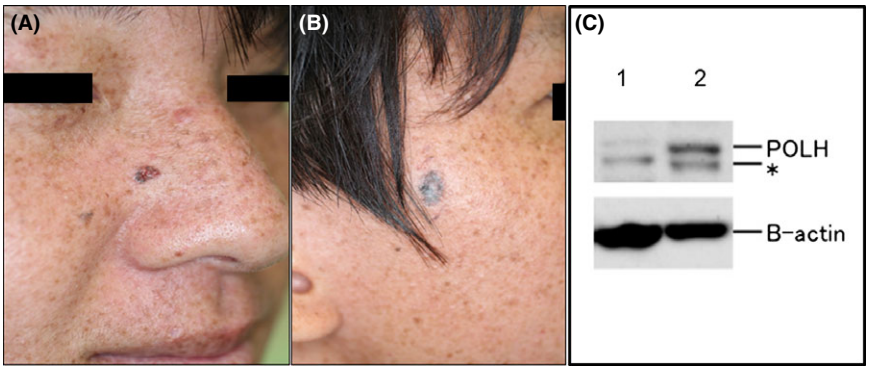

FIGURE 1 The image at the initial visit to our department shows a black nodule of 4 mm in diameter centered on a small ulcer on the nose root of the right side (A) and a blue-gray macule of 10 mm in diameter with mild cornification in the buccal region on the right side of the face (B). Later, the diagnosis of XP-V was confirmed with Western blot analysis, showing decreased level of POLH protein (C) (lane 1; this case, lane 2; normal subject, *; nonspecific band)

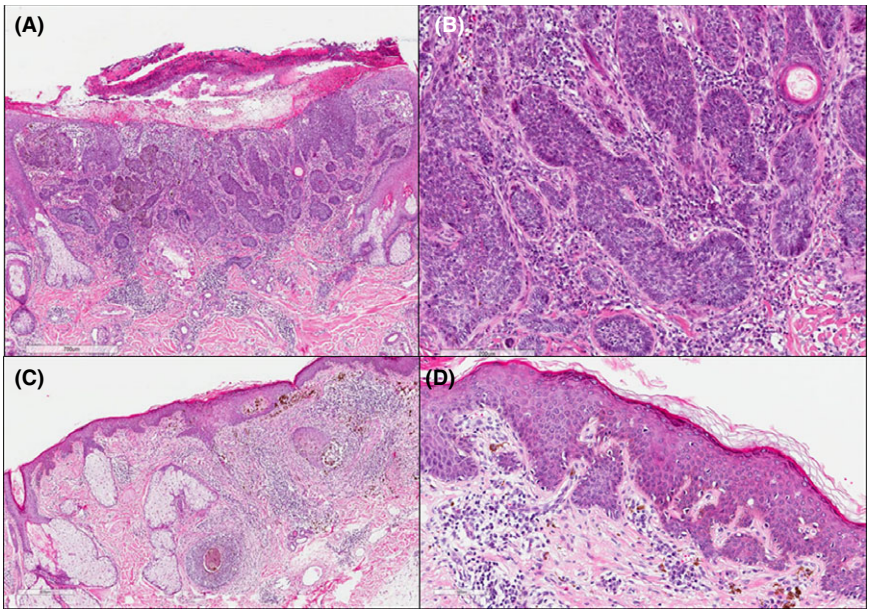

FIGURE 2 The histopathological findings of the nodule at the right root of the nose (A, B) and the macule in at the right buccal region (C, D). A, Focal growth of the tumor cells surrounded by a fissure in the dermis (hematoxylin and eosin staining, ×40); B, The tumor cells had a circular to oval nucleus that was enriched with chromatin, and a palisaded alignment was found at the margins of the tumor lesion (hematoxylin and eosin staining, ×200); C, Dense infiltrate of mononuclear cells with scattered small lumps of melanin were observed in the upper dermis (hematoxylin and eosin staining, ×40); D, An increased number of epidermal melanocytes was observed and an the accumulation of melanin in the melanophages (incontinentia pigmenti hsitologia) in the upper dermis was obvious. No atypical cells were found in the epidermis (hematoxylin and eosin staining, ×100)

groups. According to a report by Tanioka et al, the mean age at the initial presentation of BCC was 41.5 years in patients with Japanese XP-V, which is much earlier than that in healthy Japanese subjects.[2,3] However, our patient developed BCC at the age of 16, which indicates that he developed skin cancer at a considerably younger age in comparison with most XP-V patients.

The patient's genetic background (XP-V) and the effects of immunosuppressive therapy for Crohn's disease are thought to have influenced the development of BCC during adolescence in the present case. In addition, the patient had been a member of a soccer club until 13 years of age; thus, he had a history of a high degree of sun exposure. Nishigori et al[6] reported on 2 patients with XP-V who developed BCC at 12 and 27 years of age, and who had a habit of swimming and windsurfing, respectively, and who thus had a high degree of sun exposure before the diagnosis of XP-V. In our patient, treatment for Crohn's disease was initiated at 13 years of age with the oral administration of azathioprine and mesalazine. The intravenous infusion of infliximab was added 2 years later, and only the administration of azathioprine was discontinued at 15 years of age.

There has been no evidence to support that mesalazine increases the carcinogenic risk until now. On the other hand, there are several reports indicating that the incidence of skin cancer was increased by azathioprine through interaction with ultraviolet radiation.[7,8] Azathioprine is metabolized in vivo into 6-thioguanine nucleotides (6-TGNs), which corresponds with chromophores and absorb UVA, leading to the generation of reactive oxygen species. The generation of reactive oxygen species induces oxidative DNA damage, such as 8-oxoguanine, which may relate to the mutagenesis.[9] On the other hand, our patient showed defective translesion synthesis because of his genetic disease (XP-V). Thus, photoproducts such as cyclobutane pyrimidine dimer and 6-4-photoproduct, due to UVB, form easily and also promote mutation.[1] In addition, if TNF-α is inhibited by infliximab, adverse effects may occur with regard to the immune function against the tumor. In our patient, azathioprine was administered for only 2 years. However, it was thought that these multiple, complicated effects led to BCC in childhood.

It is still unclear how the long-term use of biological drugs affects the risk of development malignant tumors.[10] In patients who received immunosuppressive agents for underlying diseases from childhood, the risk of skin cancers may be high. When for children receive immunosuppressive therapy for inflammatory bowel disease or after renal transplantation, it is important to provide thorough education on the prevention of skin cancer from a young age as they are likely to receive such therapy for longer periods of time than adult patients. When children receiving immunosuppressive therapy develop freckle-like pigmented spots, dermatologists should immediately examine the patient to determine whether they have developed XP and provide the patient with appropriate education on protection from UV light, and to regularly screen the patient for skin cancer in the clinic.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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How to cite this article: Terada A, Aoshima M, Tanizaki H, et al. An adolescent case of xeroderma pigmentosum variant confirmed by the onset of sun exposure-related skin cancer during Crohn's disease treatment. *J Cutan Immunol Allergy*. 2018;1:23–26. https://doi.org/10.1002/cia2.12011