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Successful Use of Anti-PD-1 Antibody to Treat Multiple Metastatic Carcinomas in a Patient with Xeroderma Pigmentosum: Case Report and Literature Review

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Abstract

Xeroderma pigmentosum (XP) is a hereditary photosensitive disease in which skin cancers frequently develop in sun-exposed areas. Several reports on the use of immune checkpoint inhibitor (ICI) therapy in patients with difficult-to-treat XP indicate that ICIs have the potential to improve survival outcomes in these patients. This report describes a Japanese man with XP and multiple systemic metastases of carcinoma in whom ICI therapy achieved a favorable outcome. He was diagnosed with XP at the age of about 30 years. Unresectable distant metastases appeared, despite numerous cryotherapy and excisional procedures for recurrent skin tumors. Irinotecan, 5-fluorouracil, carboplatin, and cetuximab were ineffective. Finally, he was treated with nivolumab, which had a marked therapeutic effect. A literature review revealed 10 cases of XP-related cancer that had responded well to ICI. ICI therapy may be an effective tool in patients with XP and unresectable malignant lesions.

Keyword: Dermatologic oncology; Skin cancer; Head and neck cancer; Xeroderma pigmentosum; Immune checkpoint inhibitor

Introduction

Xeroderma pigmentosum (XP) is an autosomal recessive photosensitive disease that is associated with development of skin cancers in sun-exposed areas [1]. The first report on XP as a serious photosensitivity disease with dyschromia was published at the end of the 19th century by Kaposi et al. [2,3].

Photosensitivity in patients with XP is attributed to failure to repair ultraviolet (UV)-induced DNA lesions by nucleotide excision repair or translation synthesis. In 1968, Cleaver observed that cells in patients with XP were abnormal in terms of their ability to repair DNA damage caused by UV light [4]. To date, eight genes, namely, XPA, XPB (ERCC3), XPC, XPD (ERCC2), XPE (DDB2), XPF (ERCC4), XPG (ERCC5), and XPV (POLH), have been implicated in XP. Accordingly, XP is classified into eight subtypes, from XP-A to XP-G and XP-V, each of which has characteristic clinical symptoms [5].

The prevalence of XP is low in Western Europe, with an incidence of 2-3 per million live births [6]. In Japan, on the other hand, the incidence of XP is 1 per 22,000 live births; 55% of affected individuals with XP-A, and there are about 1 million carriers of the XPA founder mutation [7-9]. In 2015, the Japanese Ministry of Health, Labor and Welfare classified XP as an intractable disease that is eligible for government support [9]. It is known that patients with XP have a 2,000-fold increased incidence of melanoma and a 10,000-fold increased incidence of non-melanoma skin cancer [1]. The recommendations for management of carcinogenic risk in patients with XP are (i) as follows: early diagnosis; (ii) lifelong protection from UV radiation, including avoidance of unnecessary UV exposure, wearing UV-blocking clothing, and use of topical sunscreens; and (iii) surgical resection of skin cancers [5,9]. However, there is still no curative treatment for XP and no consensus has been reached regarding standard treatment for unresectable XP lesions. There have been several reports suggesting that immune checkpoint inhibitor (ICI) therapy has the potential to improve survival outcomes in patients with difficult-to-treat XP.
In this report, we describe our experience using ICI to treat a patient with XP and multiple systemic metastases of carcinoma.

Case

The patient was a Japanese man with no known abnormalities at birth. By the age of 5 years, he was observed to be prone to sunburn, but the cause was unknown at that time. At the age of 30 years, a skin lesion on his face was resected and diagnosed as keratoacanthoma. He was subsequently diagnosed as having XP based on his clinical symptoms but had lived for a further 30 years without avoiding UV exposure. He had no medical history other than XP, no known allergies, and had never smoked.
After XP was diagnosed, numerous skin lesions were resected, all of which were diagnosed as squamous cell carcinoma (SCC). Skin grafting or local flap reconstruction was occasionally required after these resections. Cryotherapy was administered periodically for a basal cell carcinoma on the left ala of the nose that relapsed repeatedly (Figure 1). At the age of 36 years, the lesion on the left ala of the nose was treated by proton beam therapy, and at 56 years, a metastasis to the left orbit was treated by radiotherapy with a total of 54 Gy.

At the age of 60 years, computed tomography (CT) and positron emission tomography scan (PET) revealed multiple metastases to the mediastinum, pleura, liver, bones, and tongue base. Irinotecan, which is approved in Japan for skin cancer, was selected as first-line chemotherapy. At the time of a total of four doses of irinotecan (100mg/m2) at weekly intervals, CT shown that all lesions were in an increasing trend, and we decided that irinotecan was ineffective. After discussion in a multidisciplinary team meeting, it was decided that he should be treated using the therapeutic strategy for recurrent or metastatic head and neck squamous cell carcinoma (RM-HNSCC). A previous report suggested that platinum agents such as cisplatin were highly toxic in patients with XP [10]. Therefore, 5-fluorouracil, carboplatin, and cetuximab were administered as second-line chemotherapy with a considerable reduction of the dose of carboplatin. However, progression of bone metastases was observed after one course. Therefore, we have decided to started n nivolumab, the anti-PD-1 monoclonal antibody, as third-line chemotherapy.

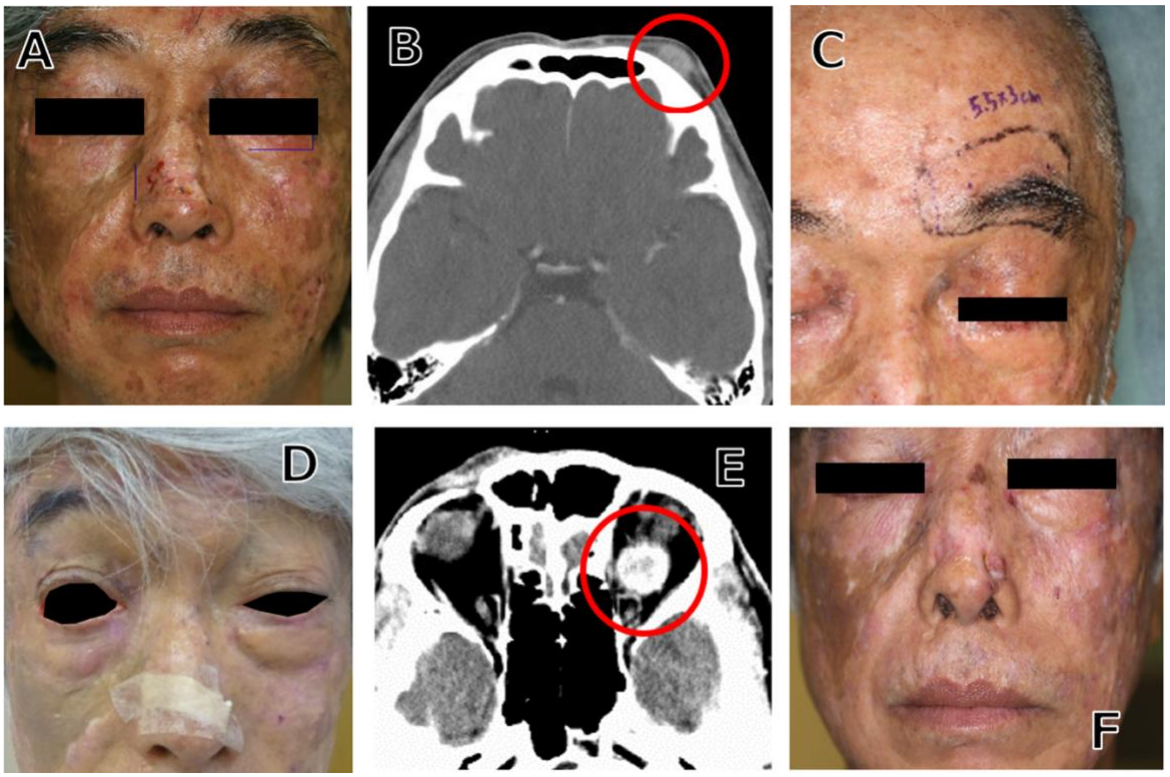

Figure 1: Changes in facial appearance and patterns of recurrence and metastasis. **(A):** Clinical photograph obtained in 2011 after several resections and cryotherapy sessions. **(B):** Computed tomography scan obtained in 2012 showing a subcutaneous metastasis of squamous cell carcinoma in the left frontal region. **(C):** Clinical photograph obtained in 2013 after the lesion in the left frontal region was resected and the defect was reconstructed using a local flap. **(D):** Clinical photograph obtained in 2015 when the patient developed left eyelid ptosis and exophthalmos. **(E):** Computed tomography scan obtained in 2015 showing a metastasis in the left orbit that was treated by irradiation. **(F):** Clinical photograph obtained in January 2019 after the lesion on the left ala of the nose was treated with cryotherapy.

Genomic Analysis

Although the previously resected metastatic left frontal subcutaneous SCC was deemed unsuitable due to the lack of tumor invasion there, the combined positive score (CPS) was checked using PD-L1 IHC 22C3 pharmDx and the result was negative (<1). The same sample was also subjected to next-generation sequencing using OncoGuide™ NCC Oncopanel System version 2.01, which was designed to examine somatic and germline mutations and copy number alterations within the entire coding region of 124 genes, fusions of 12 oncogenes, tumor mutational burden (TMB), and microsatellite instability (MSI). Next-generation sequencing revealed multiple genomic alterations (AXL, ERBB2, NOTCH2, ROS1, and TSC1), all of which are rare genetic polymorphisms but not oncogenetically important. The TMB, which includes all mutations, including synonymous mutations, within the entire targeted region was low at 2.30 mutations per megabase. High-level microsatellite instability (MSI-H) which is a form of genetic instability caused by mismatch repair deficiency, was not detected. In conclusion, next-generation sequencing did not detect genetic abnormalities which related to the predictive value of drug effectiveness.

It was difficult to identify the type of XP in this case. In Japan, 55% of patients with XP-A, which leads to severe cutaneous and neurological symptoms, followed by XP-V, which leads only to cutaneous symptoms [7-9]. Our patient had no neurological symptoms, so a genetic test for POLH was performed on the suspicion that he with XP-V, but the result was negative. In Japan, genetic testing for XP is covered by health insurance but only for one causative gene. Therefore, after obtaining approval from the institutional review board of Kobe University and securing informed consent, we measured the patient's UDS (unscheduled DNA synthesis) ability, using a previously described method [11]. Fibroblasts cultured from an intact skin specimen from his medial side of left upper arm were compared with those from a 2-year-old patient with XP-A (XP173KO) and those from a healthy 27-year-old control. His UDS was found to have decreased to 19% that of the healthy control (Figure 2). He was diagnosed with XP based on his clinical symptoms and the decrease in UDS. However, his XP subtype could not be identified.

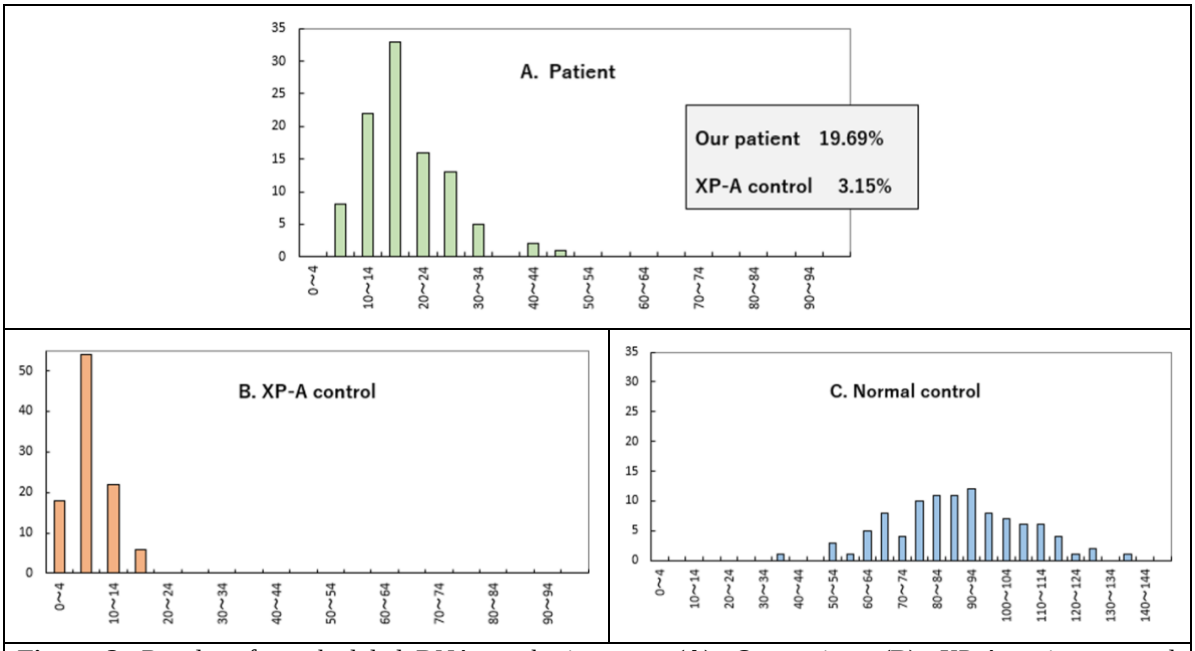

Figure 2: Results of unscheduled DNA synthesis assay. **(A):** Our patient. **(B):** XP-A patient control (XP173KO). **(C):** Normal control. The X and Y axes indicate Number of tritiated thymidine taken up per cell nucleus and number of irradiated cells, respectively. Compared to normal control data, our patient showed a decrease in USD to about 19% and about 3% in XP-A patient.

Treatment Outcomes

Five months after diagnosis of multiple distant metastases, nivolumab was started at a dosage of 240mg/body weight intravenously every 2 weeks. Palliative irradiation was also provided for painful bone metastases. After four doses of nivolumab, CT showed marked shrinkage of his metastatic lesions (Figure 3). After 14 doses, the lesion on the left ala of the nose, which had recurred repeatedly, had almost disappeared. After 20 doses, there was improvement in the condition of the skin on the face (Figure 4). After 21 doses, the dosage of nivolumab was changed to 480mg/body weight every 4 weeks. Mild leukoplakia appeared around the time of the 26th dose of nivolumab. To date, a total of 50 doses of nivolumab have been administered, and complete remission of metastatic lesions has been maintained for 3 years and 10 months after diagnosis of multiple distant metastases with no severe immune-related adverse events.

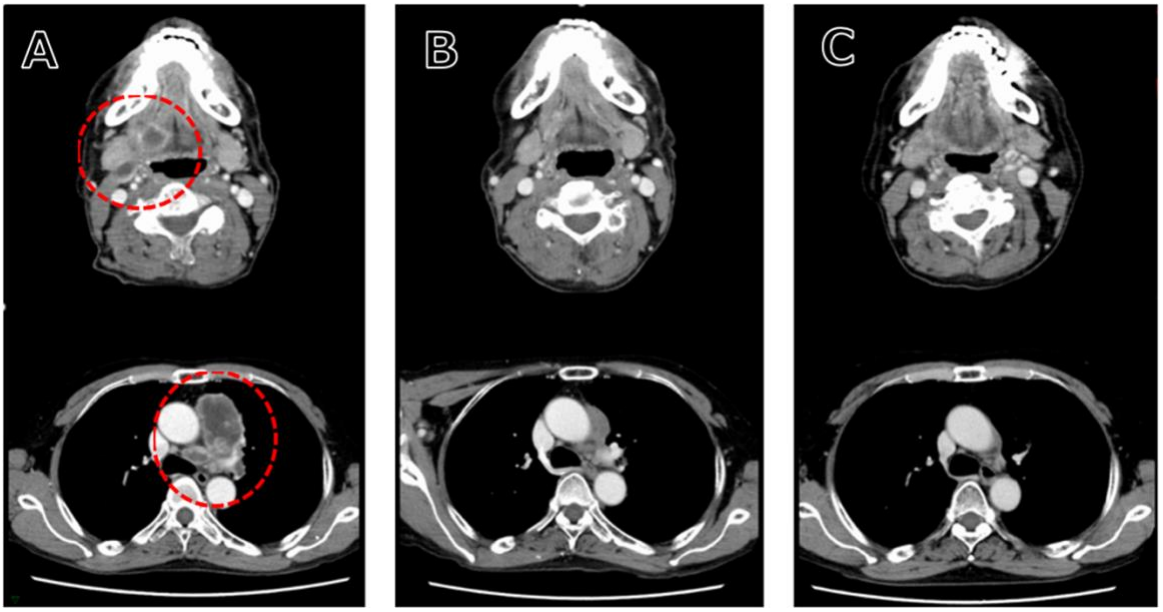

Figure 3: Computed tomography images obtained before and after introduction of nivolumab. **(A):** In July 2019, before the first infusion of nivolumab. **(B):** In November 2019, a considerable decrease in tumor size was observed after four infusions of nivolumab. **(C):** In January 2022, after over 30 infusions of nivolumab, a good clinical and radiologic partial response had been achieved.

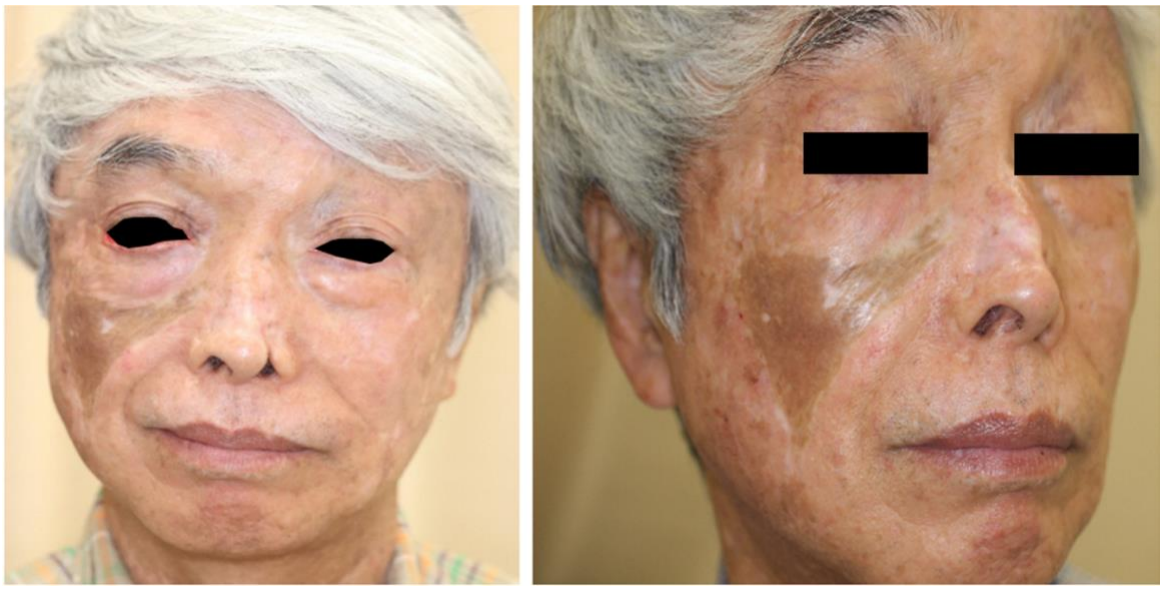

Figure 4: Facial appearance after introduction of an immune checkpoint inhibitor. After 20 infusions, the condition of the skin on the entire face had improved.

Discussion

This case report describes a patient in whom multiple metastases of SCC emerged against a background of XP that was confirmed by a DNA repair test. Nivolumab achieved dramatic tumor shrinkage in this patient, despite the fact that his TMB, MSI, and CPS were not high.

Table 1:

Case	Reference	Country	Sex	Age at diagnosis years	XP subtype	Tumor histology	CPS/TPS*	TMB	MSI-status	Age at time of starting ICI	Type of ICI	Tumor response/duration of response
1	Hauschild A et al	Germany	M	N.S.	E	SCC, BCC, MM	N.S.	High	N.S.	51	Pem	PR/10 courses
2	Deinlein T et al	Austria	F	N.S.	N.S.	SCC	TPS=20%	N.S.	N.S.	48	Pem	PR/3 courses
3	Chanbon F et al	France	F	0	C	SCC, BCC, MM, sarcomatoid carcinoma	N.S.	N.S.	N.S.	7	Nivo	PR/16 courses (temporarily used with cetuximab)
4	Salomon G et al	France	M	2	C	SCC, MM	N.S.	N.S.	N.S.	17	Pem	PR/12 courses for 6 months
5	Steinneck A et al	USA	F	2	C	SCC	N.S.	High	Stable	7	Pem	PR/24 months
6	Momen S et al	England	M	N.S.	C	Angiosarcoma	TPS=60%	High	N.S.	32	Pem	PR/11 courses
7	Ameri AH et al	USA	F	N.S.	C	SCC, BCC	N.S.	N.S.	N.S.	18	Pem	PR/26 months
8			M	N.S.	E	SCC	N.S.	N.S.	N.S.	19	Pem	PR/18 months
9			F	N.S.	V	SCC	N.S.	N.S.	N.S.	20	Ipi →Pem	PR/48 months for Ipi, PR/31 months for Pem
10	Boutros C et al	France	M	N.S.	C	Angiosarcoma, BCC, SCC	N.S.	High	N.S.	32	Nivo	PR/34 courses
11	Itoyama M et al	Japan	M	30	**	BCC, SCC	CPS <1	Low	Stable	60	Nivo	PR/42 courses

*CPS/TPS are both indicators of PD-L1 expression.

**A genetic test for POLH was performed on suspicion that the patient with XP-V, but the result was negative.

He was diagnosed with XP based on his clinical symptoms and a decrease in unscheduled DNA synthesis.

Abbreviations: BCC: basal cell carcinoma; **CPS:** combined positive score; **ICI:** immune checkpoint inhibitor; **Ipi:** ipilimumab (anti-CTLA-4 monoclonal antibody); **MM:** malignant melanoma; **MSI-H:** high-level microsatellite instability; **Nivo:** nivolumab (anti-PD-1 monoclonal antibody); **N.S.:** not shown; **Pem:** pembrolizumab (anti-PD-1 monoclonal antibody); **PR:** partial response; **SCC:** squamous cell carcinoma; **TMB:** tumor mutational burden; **TPS:** tumor proportion score.

Table 1 summarizes the reports in the literature on patients treated with ICI for malignant lesions arising against a background of XP [12-19]. The first report was published by Hauschild et al., who described the clinical outcome in a patient with XP treated with pembrolizumab, another type of anti-PD-1 monoclonal antibody [12]. Eleven cases (including our present case) with variable histology, including SCC, basal cell carcinoma, and angiosarcoma, have been described. Six of the previous cases with XP-C, two with XP-E, and one with XP-V; the subtype was not mentioned in one case. Three patients (3, 10, and 11) were treated with nivolumab, seven (1, 2, and 4-8) with pembrolizumab, and one (patient 9) with ipilimumab (the CTLA-4 monoclonal antibody) followed by pembrolizumab. The overall response rate was 100%, and 9 of the 11 patients (82%) achieved durable responses during the observation period. None of the patients experienced serious adverse events. Concomitant skin lesions decreased in size after introduction of ICI in five patients (1, 7-9, and 11). Therefore, all metastatic lesions or concomitant skin lesions were successfully treated with ICI in these cases.

It is thought that the high mutational burden in XP-associated SCC accumulated by years of sun exposure might respond well to ICI therapy [18]. The KEYNOTE-158 study in 2020 found that patients with a high TMB had a good response to pembrolizumab [20]. Therefore, TMB could be a useful predictor of the response to pembrolizumab in patients with previously treated recurrent or metastatic advanced solid tumors given that the indications for pembrolizumab have been expanded to include patients with high TMB. Not all of the 11 patients in this report underwent next-generation sequencing, but at least four patients (1, 5, 6, and 10) were reported to have a high TMB. Our case (patient 11) was the only one with a low TMB. However, it is not clear how accurately the submitted samples reflected the status of relapsed tumors. This is one of the limitations of our report.

Solid MSI-H tumors are also an indication for pembrolizumab. However, although most MSI-H tumors have a high TMB, not all tumors with a high TMB are MSH-H [21,22]. The coexistence of MSI-H and high TMB is often observed in gastrointestinal cancer; however, in malignant melanoma, SCC, and lung cancer, high TMB is relatively common, whereas MSI-H is not [23]. Indeed, MSI-H was not found in any of the 11 patients in the present report. Therefore, the relationship between MSI-H and the therapeutic effect of ICI in patients with XP is not clear.

CPS is an index of PD-L1 expression and, like TMB and MSI-H, is used to predict the therapeutic effect of pembrolizumab. Several virus-related cancers, including nasopharyngeal carcinoma (caused by Epstein-Barr virus), oropharyngeal carcinoma (caused by human papillomavirus), and Merkel cell carcinoma (caused by Merkel cell polyomavirus) are considered to arise as a result of PD-L1 expression against a background of chronic inflammation [24-26]. Chronic inflammation in response to UV exposure may also increase the CPS in patients with XP. PD-L1 expression was detected in three patients (2, 6, 11) in our series; however, case 11 (our patient) had a low CPS. As mentioned earlier in relation to the TMB in our patient, the samples submitted for analysis may not have been fully representative in cases with tumor recurrence.

When our patient developed multiple distant metastases, nivolumab was the only ICI covered by the Japanese health insurance system for platinum-refractory RM-HNSCC. Pembrolizumab was not approved for platinum-sensitive RM-HNSCC at that time. Therefore, platinum-based chemotherapy was administered before nivolumab. However, the dose of carboplatin was reduced considerably for the following reasons. An in vitro study suggested that cisplatin may have enhanced cytotoxic effects on normal cells in XP, reflecting the deficiency of DNA repair systems [27-29]. Sumiyoshi et al. also reported that two patients with XP died from severe adverse events attributed to cisplatin [10]. One of these patients with XP-V and developed severe hearing impairment, renal dysfunction, and febrile neutropenia after treatment with cisplatin and vinorelbine for stage IIIA non-small cell lung cancer. The other patient, a family member of the first case, was treated with cisplatin and 5-fluorouracil for stage IIB esophageal basaloid SCC and developed severe hearing impairment, renal/hepatic dysfunction, and myelosuppression. Both patients died as a result of multiple organ failure, one at 59 days and the other at 21 days after initiating platinum-based chemotherapy. Therefore, extreme care should be taken when using a platinum agent in a patient with XP. Fortunately, the indications for pembrolizumab have now been expanded to allow patients with head and neck cancer as well as those with TMB-H to be treated with this agent without the need for treatment with platinum in Japan.

In this report, we described a patient with XP who was successfully treated with nivolumab and showed a marked and durable response. Apart from factors such as MSI, TMB, and CPS, a decrease in UDS may also be a predictor of ICI response. Although the limitation of this report is that it is a single case report, it is a valuable report because of the rarity of this disease. If available, an anti-PD1 antibody should be used first for unresectable carcinoma caused by XP. To our knowledge, this is the first report of successful use of ICI to treat XP in Japan.

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