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MINIREVIEW

Immune checkpoint inhibitors for children with xeroderma pigmentosum and advanced cutaneous squamous cell carcinoma: A case presentation and brief review

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Summary

Patients with xeroderma pigmentosum (XP) frequently develop skin cancers early in life, including cutaneous squamous cell carcinoma (cSCC). The median age of death is 32 years and 60% of XP patients die before the age of 20 years. cSCC in patients with XP exhibits an exceptionally high mutation burden, suggesting a favorable response to immune checkpoint inhibitors (ICIs). We present the case of a 7-year-old boy with XP and a large facial cSCC complicated by cervical lymph node metastases. Following a tumor board recommendation, systemic immunotherapy with cemiplimab was initiated. Following therapy, the tumors rapidly and completely regressed. To date, only 10 XP patients worldwide have been reported to receive ICIs for inoperable and/or advanced cSCC, with all cases demonstrating tumor regression under ICI treatment. Among these, three were pediatric cases with XP-C (one 7-year-old and two 6-year-old children), one of whom had sarcomatoid cSCC. Incidence and nature of adverse events in XP patients were comparable to those observed in the general population. In line with the previously reported ICI-treated XP children, the present case confirms that anti-PD-1 inhibitors are highly effective in children with XP and advanced cSCC.

KEYWORDS

cemiplimab, childhood, DNA repair defects, genodermatoses, geno-photodermatoses, keratoacanthoma, nivolumab, pembrolizumab

INTRODUCTION

Xeroderma pigmentosum (XP) is a rare, inherited, autosomal recessive geno-photodermatosis characterized by a defect in the DNA repair pathway, leading to extreme sensitivity to ultraviolet (UV) radiation. XP patients are at high risk for severe sunburns, skin dryness, progressive pigmentary abnormalities, premature photoaging, and a dramatically increased incidence of malignant skin tumors in UV-exposed areas such as the face, neck, and head.[1–3] The risk of skin cancer is up to 10,000 times higher in XP patients compared to the general population for non-melanoma skin cancers (NMSC), such as basal cell carcinoma and cutaneous squamous cell carcinoma (cSCC); the

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incidence of melanoma is reported to be 2,000 times higher. Other skin tumors, such as keratoacanthoma, sebaceous cell carcinoma, fibrosarcoma, and angiosarcoma, also occur with increased frequency. XP patients who develop skin cancers tend to experience more aggressive malignancies, with a higher risk of metastasis and cancer-related death. The median age of death in XP patients is 32 years, with 60% of deaths occurring before the age of 20.[4–6] Studies indicate that XP skin cancers have a 3.6-fold higher mutation burden than sporadic skin cancers. This is particularly pronounced in XP subgroups with deficiencies in global genome nucleotide excision repair (NER), such as XP-C and XP-E, as well as in those lacking functional translesion synthesis polymerase η, as seen in XP-V. The mean tumor mutational burden (TMB) for single-base substitutions in specific XP subgroups can reach up to 350 mutations per megabase. The predominant mutation type in XP-associated tumors is the C>T transition, particularly at dipyrimidine sites, which are characteristic targets of UV-induced damage. Each XP group exhibits distinct mutational signatures, reflecting variations in their DNA repair capabilities and exposure histories. Thus, cSCC of XP patients should be highly susceptible to therapy by immune checkpoint inhibitors. While cemiplimab and other ICIs have shown excellent outcomes in terms of progression-free survival and overall survival in immunocompetent patients with advanced cSCC,[7–23] the effectiveness of ICIs in XP patients, particularly pediatric cases, is less well established. Here, we report a complete response to cemiplimab therapy in a boy with advanced cSCC and underlying xeroderma pigmentosum (XP), accompanied by a brief review of the relevant literature in this context.

CASE PRESENTATION

In November 2023, we treated a 7-year-old boy from Afghanistan with XP, type C. He had two siblings, also suffering from XP, both residing at *Friedensdorf*, a non-profit organization located in Oberhausen and Dinslaken, Germany (Figure 1a). The boy presented with a very large tumor covering three-quarters of his lips and severely affecting his left cheek, along with two sizable tumors on both sides of his temples (Figure 1b). In the 6 weeks between the time the photograph was taken and his admission to our hospital, the tumor had grown significantly. Despite being 7 years old, the boy's height (105 cm) and weight (15 kg) were unusually low for his age (50. percentile [median] 122 cm and 50. percentile 23 kg). His general condition was poor, and laboratory tests revealed severe iron deficiency anemia, with a hemoglobin level of 6.3 g/dl. He also exhibited tachycardia (heart rate: 120 bpm) and hypotension (blood pressure: 70/40 mmHg). Initial treatment included iron supplementation and nicotinamide (200 mg twice daily).

While neurological examinations and cranial magnetic resonance imaging did not reveal pathological findings, the boy suffered from photophobia, and his left eye showed signs of conjunctival injection and corneal opacification, along with ectropion. Visual impairment was noted in both eyes, with vision reduced to 80% in the left eye and 20% in the right eye. However, no tumors were detected in his eyes.

Punch biopsies taken from the left side of his face confirmed typical features of XP, as well as both high-grade and low-grade cSCC, classified as G1. The tumor proportion score and combined positive score for PD-L1 expression were 20% and 30%, respectively. Hematoxylin-eosin, PD-1, and PD-L1 staining images of the lesions are shown in Figure 2.

Our interdisciplinary tumor board did not recommend surgical treatment or radiotherapy, opting instead for ICI-based immunotherapy with cemiplimab. Two weeks later, cemiplimab therapy was initiated at a dose of 3 mg/kg body weight (totaling 45 mg), administered intravenously over 30 minutes for the first cycle. Following this treatment, the boy developed intermittent fever, with peaks reaching 40.2°C, requiring antipyretic treatment, including paracetamol suppositories and calf compresses. He also experienced persistently high respiratory rates, low blood pressure (averaging 80/40 mmHg), and a heart rate consistently above 120 bpm. Blood tests showed no improvement in anemia and continued signs of infection, with an initial CRP of 1.0 mg/dl (0.5mg/dl) and a leukocyte count of 26.61/nl (4.5–13.5/nl). However, the intermittent fever subsided after 2 days.

Within a week, we observed a dramatic reduction in tumor size, and the boy became more active, engaging in play and socializing with his peers (Figure 1c). Subsequent cemiplimab infusions were administered every 2 weeks, with weekly follow-ups and blood tests. After the third cycle, complete resolution of the tumors was observed (Figure 1d), along with increased appetite and weight gain. This led us to adjust the cemiplimab dose from 48 mg to 51 mg, and later to 54 mg, every other week. Remarkably, all previously abnormal blood test results normalized. Although there was complete clearance of the cSCC affecting his lips and temple areas, new keratoacanthomas developed on the left cheek, rapidly growing to a diameter of 3 cm and a height of 1.2 cm within days. However, these lesions regressed within a month. Ultrasound revealed complete regression of lymph node metastases after 8-month cemiplimab therapy (17th cycle). Overall, our patient experienced a favorable outcome, with no significant side effects, noticeable weight gain, normalization of blood parameters, and increased social interaction with his peer group.

DISCUSSION

The incidence of XP varies geographically, with an estimated global incidence of 1 in 250,000 live births. Higher

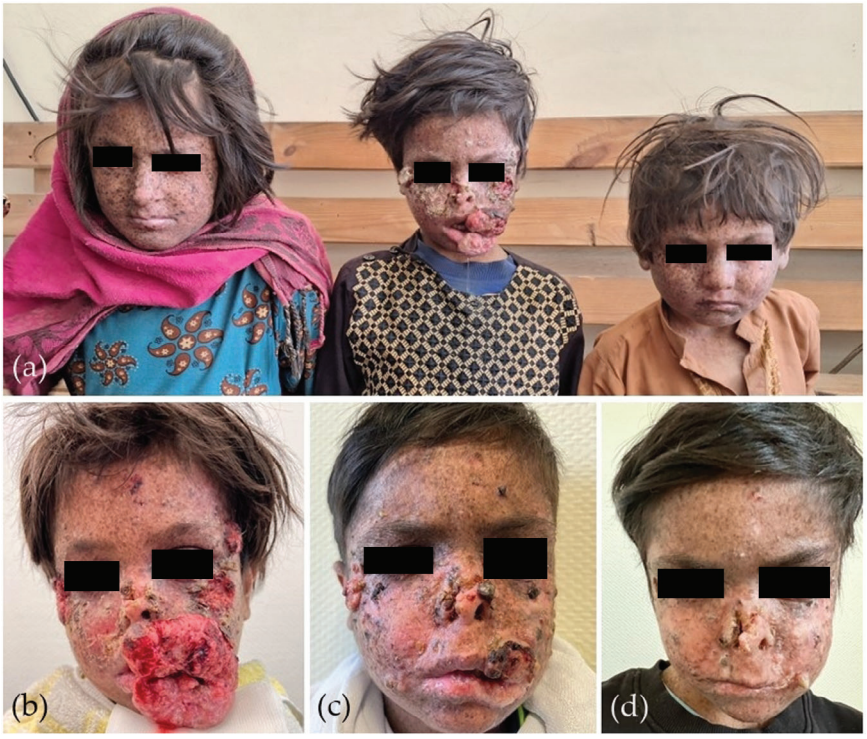

FIGURE 1 (a) Showing three siblings from Afghanistan suffering from xeroderma pigmentosum. (b) The 7-year-old boy in the middle had a large disfiguring cutaneous squamous cell carcinoma on the left side of his lips and cheek, along with two sizable tumors on both sides of his temples. (c) After one cycle of cemiplimab dramatic regression of the aforementioned tumors, (d) and after three cycles complete response to cemiplimab.

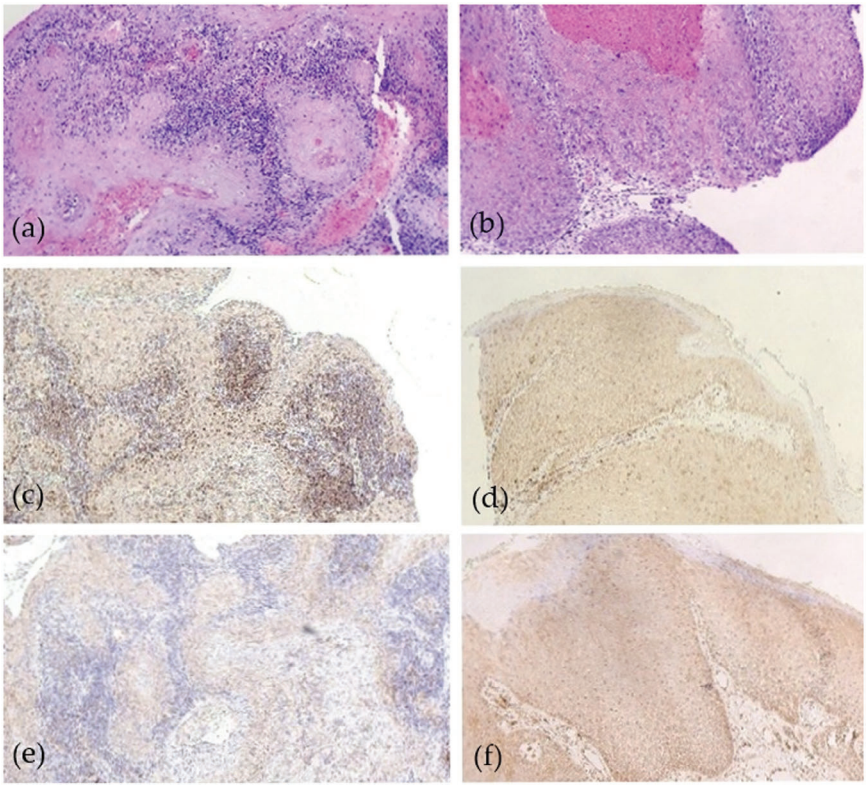

FIGURE 2 (a) Showing hematoxylin-eosin stains (x 200) of a low-grade cutaneous squamous cell carcinoma (cSCC) of the left check of a boy suffering from xeroderma pigmentosum. (b) Histology of a keratoacanthoma of the left cheek newly developing under cemiplimab therapy is also shown. PD-1 and PD-L1 expression observed (c, e) in the cSCC was higher than that (d, f) in the KA, respectively.

rates are observed in regions where consanguinity is common, such as the Middle East and Japan. In Western Europe, the incidence is estimated at 2.3 per million, while in the USA, it is as low as 1 per million. XP is caused by a defect in the DNA repair pathway, specifically in NER, which is critical for removing UV-induced DNA damage. NER involves eight key proteins (XP-A to XP-G, and XP-V), each playing a role in different stages of the repair process.[1–4] In addition to the characteristic cutaneous manifestations, XP patients often experience neurological and ophthalmic degeneration.

Approximately 20%–30% of patients develop severe neurodegenerative symptoms, particularly those with defects in transcription-coupled repair (XP-A, -B, -D, -F, -G). These symptoms may include intellectual decline, hearing loss, abnormal speech, peripheral neuropathy, and loss of motor skills. However, our patient did not exhibit any neurological abnormalities. Ocular involvement occurs in about 90% of XP patients, with UV damage primarily affecting the eyelids, conjunctiva, and cornea. Common symptoms, as observed in our case, include cataracts, conjunctivitis, blepharitis, ectropion, and corneal scarring.[1–4] Notably, under cemiplimab therapy, we observed improvements in corneal opacity and ectropion.

The primary management of XP involves strict UV protection and early detection of skin cancers, which typically necessitates surgical intervention. However, the combination of impaired DNA repair mechanisms, high mutational burden, early onset of skin lesions, inadequate photoprotection, and potentially aggressive tumor biology contributes to the development of advanced cSCC in XP. Moreover, certain XP subtypes, such as XP-C, are associated with particularly aggressive forms of skin cancer.[23] ICI, particularly anti-PD-1 inhibitors, have shown excellent efficacy in tumors with a high TMB, such as cSCC. Defects in DNA repair mechanisms in XP patients, particularly in the nucleotide excision repair pathway, result in increased accumulation of UV-induced DNA damage. This leads to a significantly higher TMB in skin cancers among XP patients compared to sporadic skin cancers, with notable variations between different XP subgroups. For instance, XP-E exhibits the highest mean tumor mutational burden (TMB) at 350 mutations/Mb, followed by XP-V with 248 mutations/Mb, and XP-C with a mean TMB of 162 mutations/Mb – still exceeding the average TMB of 130 mutations/Mb typically observed in sporadic skin cancers.[24]

Although C>T substitutions at pyrimidine dimers are the predominant UV-induced mutations across all XP subtypes, specific defects in DNA repair mechanisms result in variations both mutation distribution and burden among the XP groups. Notably, differences in the enrichment of C>T mutations in specific sequence contexts have been identified, such as TCA in XP-E, TCW in XP-C, and NCY in XP-D (where W = A or T; N = A, C, G, or T; Y = C or T). These variations may influence the formation of tumor-specific antigens.[25] Thus, the immunogenicity of mutations may vary among different XP subgroups, influenced by their specific genetic defects and the consequent impact on DNA repair mechanisms. XP-C and XP-E, with impaired global genome nucleotide excision repair (GG-NER), exhibit the highest TMB among XP patients.

XP-V: Characterized by a deficiency in translesion synthesis polymerase η, XP-V also shows a high TMB. The mutation profile in this group may be distinct, as the involvement of error-prone polymerases during replication of UV-damaged DNA leads to unique mutation patterns.

XP-A and XP-D: These subtypes, with deficiencies in both GG-NER and transcription-coupled NER (TC-NER), display a more uniform distribution of mutations across the genome. This distribution could result in a mutation spectrum that differs in its immunogenic potential compared to other XP forms.

XP groups with proficient TC-NER (e.g., XP-C and XP-E): In these subgroups, mutations tend to accumulate preferentially in the untranscribed strand of genes. This strand-specific mutation bias may lead to the generation of immunogenic mutations in actively transcribed genes, potentially increasing the likelihood of neoantigen formation.

These differences may explain potentially different responses to ICI among the group of XP patients and patients with sporadic cSCC. Moreover, as shown in Figure 2, PD-1 and PD-L1 expression is relatively high in NMSC of XP patients, further suggesting that ICIs could be a very effective treatment approach for XP patients with advanced cSCC.[9] Immunohistochemistry of PD-L1/PD-1 skin tumors of XP patients has rarely been reported.[10]

To the best of our knowledge, Hauschild et al.[11] reported the first case of an XP patient treated with ICI for melanoma and NMSC in 2017. According to recent studies by Fernandez et al.[12] and case reports by Boziou et al.[13] and Rubatto et al.,[14] a total of ten XP patients worldwide have been treated with ICIs for inoperable and/or advanced cSCC. All patients responded positively to ICIs.[12–14] Among these, three were pediatric cases with XP type C (one 7-year-old and two 6-year-old children),[15–17] one of whom had sarcomatoid cSCC.[15] Clinical details of pediatric XP cases treated with ICI are summarized in Table 1. XP patients experienced adverse events at similar rates and types as compared to the general population, suggesting that ICI-based immunotherapy is well-tolerated in both adult and pediatric XP patients.[12–17] Consistent with these reports, we observed a rapid resolution of cSCC on the face following the first cycle of cemiplimab. Following the initiation of ICI, our patient developed a high fever without any signs of infection. We believe that tumor lysis syndrome (TLS) was an unlikely cause of this possible adverse event of ICI, as the tumor burden was not substantial enough, and laboratory findings did not support TLS. A more likely explanation for the fever episodes observed in our patient is grade 1 cytokine release syndrome (CRS), characterized by fever with or without accompanying constitutional symptoms. CRS is usually observed in sepsis, COVID-19, and in chimeric antigen receptor T-cell therapy. However, it has infrequently described in the treatment with ICI as well.[25,26] Moreover, our patient developed keratoacanthomas, including a rapidly growing nodule near the left eye. These keratoacanthomas continued to erupt and resolve throughout the course of therapy. Eruptive keratoacanthomas and SCCs have been documented as rare cutaneous adverse events during anti-PD-1 therapy, particularly in photodamaged areas, and typically resolve with conventional treatments such as intralesional corticos-

TABLE 1 Children with xeroderma pigmentosum reported in the world literature with advanced cutaneous squamous cell carcinoma (cSCC) treated with immune checkpoint inhibitors (ICIs).

Patient	Tumor treated with ICI	ICI-pretreatment	ICI	Adverse events	Response to treatment	New skin cancers under ICI
6-year-old girl[15]	Sarcomatoid cSCC of the scalp	5-fluorouracil and cisplatin, surgery	Nivolumab 3 mg/kg BW, 16 cycles in total*	None	Complete remission	cSCC, 2 melanomas
6-year-old boy[16]	Metastatic cSCC of the nose and regional lymph nodes	5- fluorouracil and cisplatin, surgery	Nivolumab, first pass with 6 cycles, second pass with 16 cycles*	None	Complete remission	No
7-year-old girl[17]	Metastatic cSCC of the left lower eyelid, right conjunctiva and cornea, right parotid lymph nodes and bone, leptomeningeal	None	Pembrolizumab 2 mg/kg BW, 9 cycles in total	None	Remission, except for cornea lesions finally treated with topical 5-fluorouracil	No
7-year-old boy (present case)	Huge cSCC of the face with lymph nodes metastases of the neck	None	Cemiplimab initial 3 mg/kg BW, 24 cycles in total, therapy still ongoing	Intermittent fever over two days**	Complete remission	Keratoacanthomas

Abbr.: ICI, immune checkpoint inhibitor; cSCC, cutaneous squamous cell carcinoma; BW, body weight
*Periods of combination with radiotherapy and/or mono-chemotherapy;
**questionable if ICI-related

teroids, 5-fluorouracil, or cryotherapy. Immunoactivation of cSCCs and keratoacanthomas during anti-PD-1 therapy may induce inflammatory responses and aberrant keratinocyte proliferation in predisposed individuals. Similar PD-L1 expression and dense cytotoxic T-cell infiltrates may explain this immune-mediated mechanism. We hypothesize that due to the altered DNA repair pathway in XP patients, the likelihood of developing new skin cancer lesions during ICI therapy is higher compared to non-XP patients receiving similar treatment.[18–20] In conclusion, this case report and accompanying mini-review suggest that anti-PD-1 inhibitors could be highly effective and safe for children with XP and advanced cSCC.

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CONFLICT OF INTEREST STATEMENT

T.G. has received speaker and/or advisory board honoraria from BMS, Sanofi/Regeneron, MSD, Novartis Pharma, Roche, AbbVie, Almirall, Janssen, Lilly, Pfizer, Pierre Fabre, and Merck-Serono, outside the submitted work. J.C.B. receives speaker bureau honoraria from Amgen, MerckSerono, Pfizer, Sanofi, and Sun Pharma and is a paid consultant/advisory board member/DSMB member for Almirall, Boehringer Ingelheim, ICON, Pfizer, and Sanofi/Regeneron. His group also receives research grants from Merck Serono/IQVIA, Regeneron, and Alcedis. The other authors declare no conflicts of interest.

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