Dermatology Practical & Conceptual

Can Cemiplimab Become a Life-Changer in Xeroderma Pigmentosum?

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Introduction

Xeroderma Pigmentosum (XP) is a rare inherited autosomal recessive disease, resulting in defective repair of the ultraviolet radiation induced DNA damage. Prognosis of xeroderma pigmentosum (XP) is unfavorable, with most patients dying from metastatic skin cancer before the age of 30.

Management is extremely challenging and includes strict avoidance of sun exposure, close monitoring and early therapeutic interventions. Cemiplimab is an anti-programmed cell death 1 (PD-1) antibody, approved for advanced nonmelanoma Skin Cancers (NMSCs) and tested also for melanoma. Taking into account the spectrum of malignancies appearing in the context of XP, anti-PD-1 antibodies may represent the ideal treatment choice [1-8].

Case Presentation

A 29-year-old female with XP was referred to our onco-dermatology, multidisciplinary unit for management. The patient had undergone numerous surgical excisions in the past. Upon clinical examination, apart from extensive freckling and numerous actinic keratoses, we identified two atypical melanocytic lesions compatible with melanoma and multiple basal (BCC) and squamous cell carcinomas (SCC) (Figure 1). CT scan of chest, upper/lower abdomen and brain MRI were unremarkable.

We decided to proceed with an "en-bloc" resection of the skin of the forehead, due to the extreme cancer burden, plus resection of the second atypical melanocytic lesion of the lower face. Histologic examination of the forehead skin

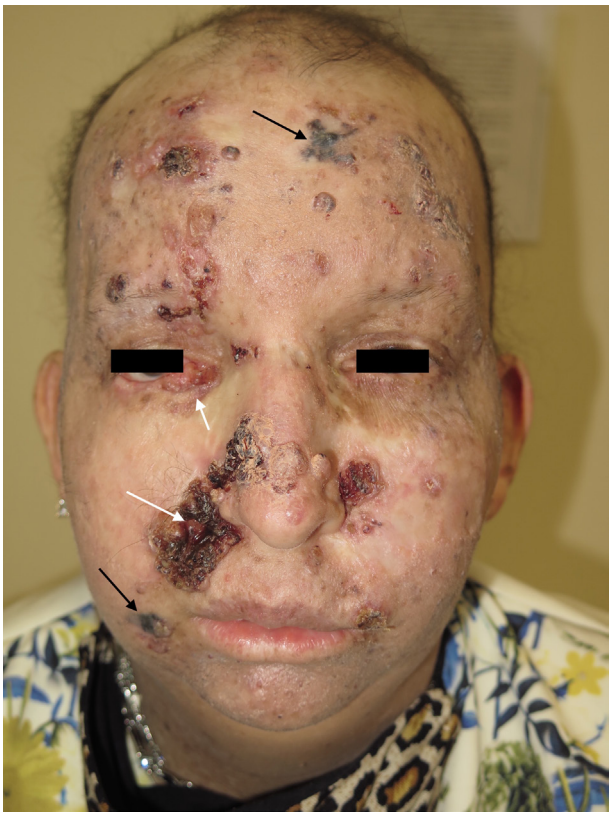

Figure 1. Extreme photodamage, with multiple freckles, two melanomas (arrows) and numerous Nonmelanoma Skin Cancers on the face, including two advanced squamous cell carcinoma, one at the right lower eyelid and one at the right nasolabial fold.

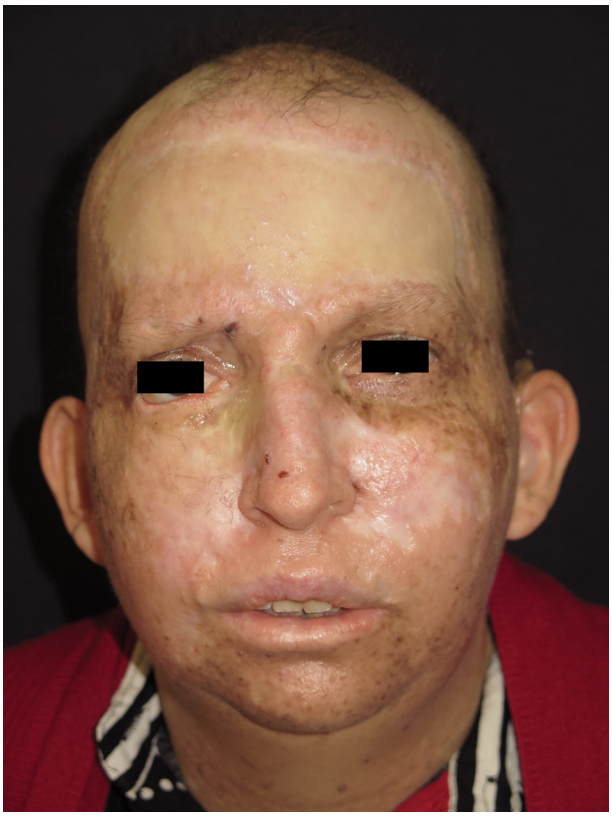

Figure 2. The patient after 1.5 year of cemiplimab initiation. We observe complete clinical response, not only of the unresectable squamous cell carcinoma (SCC) of the right lower eyelid, but also of the non-resected SCC involving the right nasolabial fold, as well as of the multiple smaller Nonmelanoma Skin Cancers of the facial skin.

showed a fully regressed melanoma, two SCCs and nine BCCs. The second melanocytic lesion was diagnosed as tumoral melanosis. Breslow thickness could not be defined due to full regression.

A combination of photodynamic therapy(PDT), sequentially to 5% imiquimod cream, plus 10mg of daily oral acitretin, as a prophylactic modality, were used. However, the locally advanced SCC of the eyelid that invaded the conjunctiva posed a serious therapeutic dilemma, since its surgical removal would inevitably lead to eye loss. Considering the limitations of the surgery, the concomitant presence of a second large SCC involving the right nasolabial fold and the overall NMSCs burden in the cancerized areas, we decided to set the patient under treatment with cemiplimab.

After 1.5 year of systemic treatment with cemiplimab, there is a remarkable response (Figure 2), with excellent tolerance and the treatment is still ongoing.

Conclusions

XP is an ideal model for studying effectiveness of immune checkpoint inhibitors (ICIs) on skin malignancies, especially when i0074 comes to the treatment of advanced SCCs and BCCs, coexisting with melanoma. Carrying out a literature review, we retrieved eight individuals with XP treated with ICIs, with only one of them receiving cemiplimab (Table 1). Overall, as in our patient, individuals receiving ICIs demonstrated a constant response of locally advanced and metastatic tumors of both origins, epithelial and melanocytic. Tolerability and safety were satisfactory as in our patient.

The particularity of the current case is the concomitant presence of unresectable NMSCs and two melanomas, which is a common scenario in the context of XP. ICIs, due to their dual therapeutic effect on both, epithelial and melanocytic skin cancers, may open a new therapeutic horizon, changing the so far unfavorable fate of XP patients.

Table 1. Outcomes of use of immune checkpoint inhibitors in xeroderma pigmentosum patients

References	Age/ Sex	Tumor (ICIs target)	Site	ICI used	Outcome of target tumor	Outcome of coexisting tumors	ICI derived AEs	Additional treatment
Rubatto et al [1]	19/F	Nonoperable, metastatic SCC	Right orbital and nasal cavity with lymph node metastasis	Cemiplimab 350 mg every 3 weeks	Partial response	Regression of NMSCs, AK	Diarrhea	Radiotherapy
Ameri et al [2]	18/F	Nonoperable SCC	Limbus of right eye	Pembrolizumab 2 mg/ kg every 3 weeks	Complete response	No response of facial BCCs	-	-
Ameri, et al [2]	19/M	Nonoperable SCC	Right orbital and nasal cavity	Pembrolizumab 2 mg/ kg every 3 weeks	Partial response	-	-	-
Ameri et al [2]	20/F	i)Metastatic Melanoma ii) Nonoperable SCC	i) MUP ii) Maxillary sinus	i)Ipilimumab 10mg/ kg every 3 weeks ii) Pembrolizumab 140mg/month	i)Notable response ii) Notable response till radiographic progression	-	-	-
Hauschild et al [3].[3]	51/M	Metastatic Melanoma	Left cheek with multiple pulmonary, lymph node and right infraorbital metastases	Pembrolizumab 2 mg/ kg every 3 weeks	90% regression of the largest lungmetastasis. Complete regression of the others.	Regression of almost all NMSCs, AK	Reddish swelling of the right orbita, inflammatory rash in sun-damaged skin, mild itching	-
Deinlein et al [4]	48/F	Metastatic SCC	Left tight with abdominal, inguinal and left supraclavicular lymph node metastases	Pembrolizumab 2 mg/ kg every 3 weeks	Significant regression of all metastases	No improvement on solar lentigines	-	Metastatic supraclavicular lymphadenectomy
Chambon et al [5]	6/F	i)Sarcomatoid carcinoma ii)SCC	Scalp with bone lytic lesions, vascular, meningeal contact and superior sagittal sinus involvement	i) Nivolumab 3mg/kg every 2 weeks ii) Nivolumab monthly & Cetuximab 250 mg/ m2/week, 3 weeks out of 4	65% Regression of the Sarcomatoid carcinoma. No response to SCC	Appearance of two invasive Melanomas on the scalp. Multiple cutaneous, lip, tongue tumors	-	Chemotherapy (5FU, Cisplatin), surgery

Table1 continues

Table 1. Outcomes of use of immune checkpoint inhibitors in xeroderma pigmentosum patients *(continued)*

References	Age/ Sex	Tumor (ICIs target)	Site	ICI used	Outcome of target tumor	Outcome of coexisting tumors	ICI derived AEs	Additional treatment
Salomon et al [6]	17/M	Metastatic Melanoma	Scalp with liver and pulmonary metastases	Pembrolizumab 2 mg/ kg every 3 weeks	Partial response of all metastases, long lasting disease stabilization	Regression of NMSCs, AK	Vitiligoid depigmentation on sun-exposed areas	-
Steineck et al [7][7]	7/F	Metastatic SCC	Right side of the face spreading to the right sphenoid bone, the cavernous sinus, the right carotid artery, the surrounding tissues, the lymph nodes & the leptomeningeal	Pembrolizumab 2 mg/ kg every 3 weeks	Reduction of tumor size, resolution of leptomeningeal spread, long lasting disease stabilization	Response of most of the oculocutaneous lesions. Mild progression of a right corneal SCC	-	-
Momen et al [8]	32/M	Cutaneous angiosarcoma	Left eyebrow with metastatic pulmonary, pericardial, mediastinal, pleural, submandibular, hepatic & bone disease	Pembrolizumab 200 mg/kg every 3 weeks	Complete response of the pulmonary & bone metastases, almost complete response of the cardiac & pericardial disease, regression of the hepatic, submandibular & pleural lesions	-	-	Radiotherapy

AEs = adverse events; AK = actinic keratoses; BCC = basal cell carcinoma; F = female; ICI = immune checkpoint inhibitor; M = male; MUP = melanoma of unknown primary; NMSCs = non-melanoma skin cancers; SCC = squamous cell carcinoma.

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