Rapid response of metastatic cutaneous squamous cell carcinoma to pembrolizumab in a patient with xeroderma pigmentosum: Case report and review of the literature

Teresa Deinlein [a], Sigurd F. Lax [b], Thomas Schwarz [c], Roberta Giuffrida [a], Karin Schmid-Zalaudek [d], Iris Zalaudek [a,*]

[a] *Department of Dermatology, Medical University of Graz, Graz, Austria*
[b] *Department of Pathology, Hospital Graz South-West, Graz, Austria*
[c] *Department of Radiology, Medical University of Graz, Graz, Austria*
[d] *Department of Physiology, Medical University of Graz, Graz, Austria*

Dear Editor,

A 48-year old patient with known xeroderma pigmentosum was referred to our skin cancer unit because of the recent development of histopathologically verified squamous cell carcinoma (SCC) lymph node metastasis on her left supraclavicular region. A whole body PET-CT showed additional abdominal and inguinal lymph node metastases. Her medical history included, in addition to several minimal surgeries of early forms of keratinocyte skin cancer, a poorly differentiated cutaneous SCC (cSCC) with invasion into the lymphatic vessels on her left tight, which was treated with wide surgical excision 5 years before. Moreover, she suffered from an incipient renal insufficiency not requiring current treatment.

On whole body examination, multiple pigmented freckles and actinic keratoses but no other forms of skin cancer were detected. The supracervical lymph node metastasis presented as indurated, infiltrating plaque, while the other lymph node regions were unremarkable on palpation.

Based on these findings, a diagnosis of stage IV cSCC was made and she was presented at our interdisciplinary tumour board. Because review of the radiographic images was suggestive of the risk of an upper venous congestion in the cervical region, surgical debulking of the cervical lymph node mass was recommended before systemic treatment. With regard to the latter, a decision to treat with the programmed cell death protein 1 (PD-1) antibody pembrolizumab was made. This was based on the young age of the patient, her renal comorbidities and recent evidence showing promising results of PD-1 antibodies in advanced forms of cSCC. After 2 weeks of surgery of the supraclavicular lymph node metastases, she received 2 milligram (mg) pembrolizumab per kilogram body weight in a 3-weekly intravenous infusion schedule. The treatment was well tolerated by the patient. After the third cycle, restaging by whole body PET-CT was performed showing a significant regression of all metastases (Fig. 1A and B). Based on the evident partial response, treatment with pembrolizumab was continued and is still ongoing.

The expression of PD-1, programmed death-ligand 1 (PD-L1) and epidermal growth factor receptor (EGFR)

* *Corresponding author*: Department of Dermatology, Medical University Graz, Auenbruggerplatz 8, 8036 Graz, Austria. Fax: +43 316 385 16827.
E-mail address: iris.zalaudek@gmail.com (I. Zalaudek).

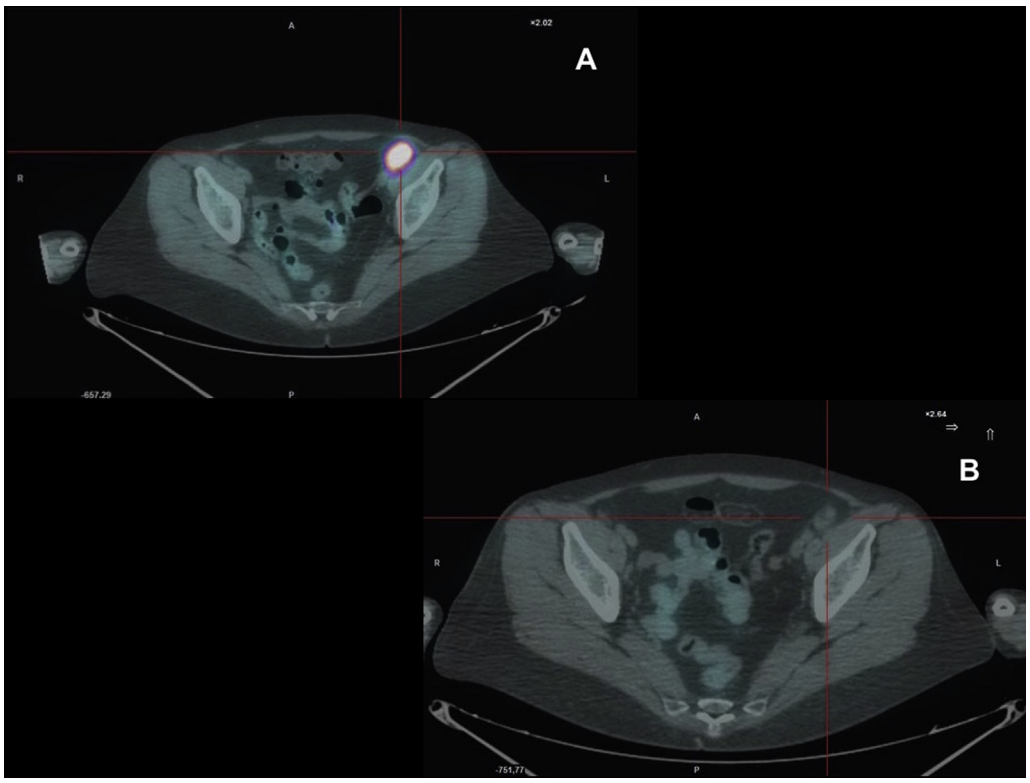

Fig. 1. **A** and **B**: Pathological lymph nodes para-aortic (A) and complete remission after three circles with pembrolizumab (B).

in the cervical lymph node metastasis was analysed by immunohistochemistry.

Serial sections of the paraffin-embedded core biopsy material were cut at 2 μm and further processed using a BenchMark™ Ultra automated stainer (Roche Ventana). For the particular primary antibodies, the following procedures were used: PD-L1 (clone 28-8; Abcam) diluted at 1:100 was incubated for 32 min and the OptiView™ DAB detection kit ultra CC1 was used for 36 min. PD-1 (clone NAT 105; Cell Marque AK) ready to use incubated for 32 min followed by the UltraView™ DAB detection kit ultra CC2 for 44 min. EGFR (clone 3C6; Roche) ready to use was incubated for 32 min after antigen retrieval by protease 1 for 8 min. For detection, the UltraView™ DAB detection kit and for counterstaining haematoxylin were used. The evaluation of immunohistochemistry was performed semiquantitatively. A weak-to-moderate immunoreactivity for PD-L1 was found in 10%–20% of the tumour cell and 20%–30% of the lymphocytes (Fig. 2B). A moderate-to-strong PD-1 immunoreactivity was present in about 20% of the lymphocytes, whereas the tumour cells were negative (Fig. 2C). About 70% of the tumour cells showed a moderate to strong EGFR immunoreactivity (Fig. 2D).

Comment:

Xeroderma pigmentosum (XP) is a rare, autosomal-recessive transmitted genodermatosis. The basic defect in XP is in the nucleotide excision repair, leading to deficient repair of ultra-violet radiation–induced DNA damages. As a consequence, patients with XP develop multiple cutaneous malignancies including non-melanoma skin cancer and melanoma already at young age [1,2]. The most important causes of mortality are due to metastatic melanoma and cSCC.

Because of the rarity of XP-associated stage IV malignancies, currently, there is no established standard of care for stage IV melanoma or cSCC.

Inhibition of the PD-1 has achieved a highly effective antitumour activity in several forms of cancers including cutaneous melanoma, Merkel cell carcinoma, and more recently, also in advanced forms of cSCC [2–8].

A review of the literature reveals up to 12 patients with advanced cSCC treated with pembrolizumab of whom 11 responded well to treatment (Table 1).

Hauschild *et al.* were the first to report the use of the PD-1 antibody pembrolizumab in a patient with XP, who suffered from metastatic melanoma [2]. They observed a notable regression of the melanoma metastases as well as disappearance of other forms of non-melanocytic skin cancer after 3 months of treatment.

To the best of our knowledge, our patient is the first report on the effectiveness of pembrolizumab in a patient with XP-associated metastatic cSCC. Similar to the observation by Hauschild *et al.*, we observed a rapid response to treatment after only three cycles of treatment. However, we did not note any significant improvement of the pre-existing cutaneous freckles in our patient. This may be explained by a possible less

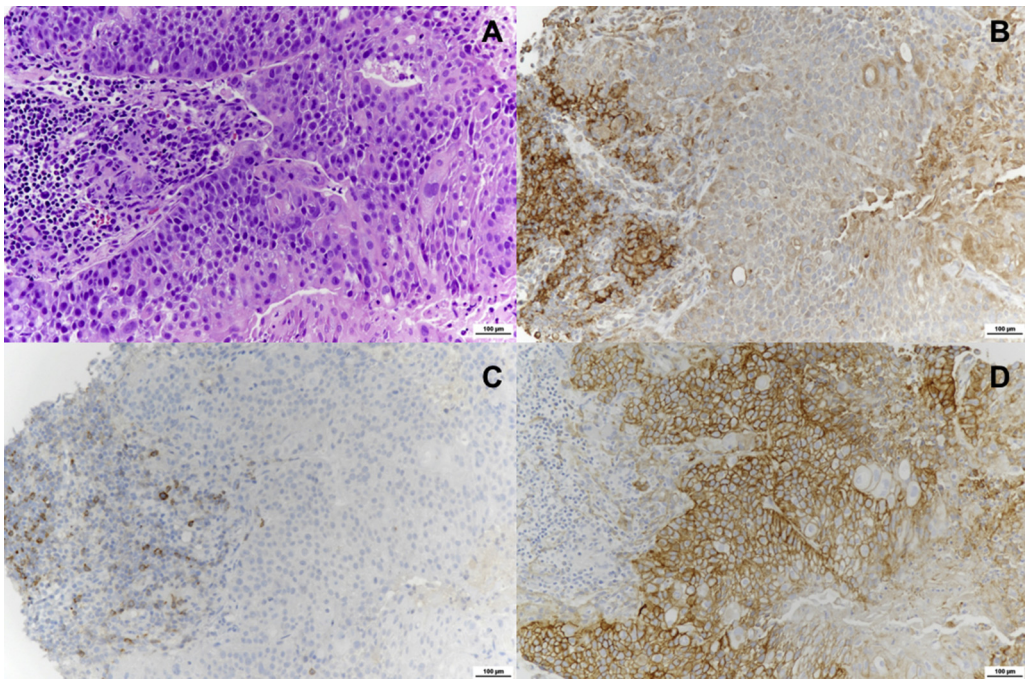

Fig. 2. **A**–**D**: Moderately differentiated non-keratinising squamous cell carcinoma surrounded by lymphocytes (biopsy of a lymph node metastasis; HE staining) (A). PD-L1 immunoreactivity is present in both tumour cells and lymphocytes (B) whereas PD-1 immunoreactivity is only found in lymphocytes (C). The majority of tumour cells show EGFR immunoreactivity (D). Abbreviations: PD-L1, programmed death-ligand 1.

Table 1
Summary of all hitherto described cases of locally advanced or metastatic squamous cell carcinoma treated with PD-1 inhibitors.

Reference	Sex	Location	Histological subtype	PD-1 inhibitor	PD-L1 immunostaining	Best overall response
Chang *et al.* 2016	Male	Right temple	Moderately to poorly differentiated	Pembrolizumab	Strongly positive in the primary tumour	Partial response
Falchook *et al.* 2016	Male	Left cheek	Not specified	REGN2810	Not specified	Complete response
Tran *et al.* 2017 *Patient I*	Male	Right temple	Not specified	Pembrolizumab	Tumour-infiltrating lymphocytes positive	Partial response
Tran *et al.* 2017 *Patient II*	Male	Left upper back	Not specified	Pembrolizumab	Not specified	Complete response
Tran *et al.* 2017 *Patient III*	Male	Unknown	Unknown	Nivolumab	Not specified	Partial response
Tran *et al.* 2017 *Patient IV*	Male	Left chin	Acantholytic	Pembrolizumab	Not specified	Partial response
Tran *et al.* 2017 *Patient V*	Female	Left shoulder	Moderately differentiated	Pembrolizumab	Not specified	Mixed response
Tran *et al.* 2017 *Patient VI*	Female	Left postauricular	Poorly differentiated	Pembrolizumab	Not specified	Progression
Stevenson *et al.* 2017	Male	Right superior forehead	Not specified	Pembrolizumab	Strongly positive in the primary tumour	Complete response
Hauschild *et al.* 2017	Male	Multiple; caused by xeroderma pigmentosum	Not specified	Pembrolizumab	Not specified	Partial response
Degache *et al.* 2017 *Patient I*	Male	Left temple	Intermediately differentiated	Pembrolizumab	Not specified	Partial response
Degache *et al.* 2017 *Patient II*	Male	Left cervical	Poorly differentiated	Pembrolizumab	Not specified	Partial response

immunogenic profile of initial versus advanced forms of keratinocytic skin cancer.

Notably, immunohistochemistry of the lymph node metastasis in our patient did not reveal a high expression of PD-1 or PD-L1 in the tumour, but was mainly detectable in the infiltrating lymphocytes. In contrast, the tumour showed high expression of EGFR.

Although Stevenson [4] proved increased PD-1 and PD-L2 expressions in high-risk cSCC and concluded that both proteins might function as predictors of response to treatment, there is considerable discussion about the role of PD-1 expression as a predictive factor in melanoma, as both tumours with high and low expressions respond well to treatment. Our case is in line

with the current observations made in melanoma and contradicts the assumption that PD-1 expression may be predictive for treatment response in cSCC. Similarly, current data also do not support any predictive value of EGFR expression for response to the EGFR inhibitor cetuximab in cSCC [5].

In conclusion, the current literature along with our case suggests that the PD-1 inhibitor pembrolizumab represents a promising therapy for locally advanced or metastatic cSCC with or without association with XP. However, there is the need for prospective clinical trials with sufficient long-term follow up to better define the role of PD-1 inhibitors in the systemic treatment of cSCC.

Conflict of interest statement

None declared.

Financial disclosure

None to declare.

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