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Dichotomic response patterns to PD-1 blockade with cemiplimab in a patient with multiple squamous cell carcinomas

Dear Editor,

Cutaneous squamous cell carcinoma (cSCC) accounts for 20–50% of all skin malignancies. Most cSCCs are successfully treated with surgery resulting in cure in about 90% of cases. Locally advanced and metastatic cSCC (lacSCC and mcSCC) are defined as not amenable to surgery or radiotherapy or in which curative resection would result in unacceptable complications or morbidity.[1] The anti-programmed cell death protein 1 (PD-1) antibody cemiplimab is the first-line treatment for lacSCC and mcSCC with reported long-term durable response and improved survival.[2] However, it must be admitted that knowledge on the diversity of patterns of response in the realm of keratinocyte skin cancers is an evolving science.[3,4] Moreover, little is currently known about the efficacy of immunotherapy in patients with multiple cSCC. Herein, we report a patient with multiple cSCCs, who developed new keratinocyte cancers despite achieving good response of a lacSCC to cemiplimab.

An 84-year-old woman presented with a large, ulcerated plaques localized on a skin graft of the right leg (Figure 1a). Co-morbidities included a history of more than 20 cSCCs, ischaemic heart disease, stroke and chronic renal failure. Histopathology showing a recurrent, poorly differentiated cSCC with extensive ulceration, and massive infiltration of the dermo-hypodermic layers. The patient was presented at the multidisciplinary tumour board and considered candidate for systemic therapy with cemiplimab 350 mg, administered intravenously every 3 weeks. After the first 3 cycles, an evident clinical response associated by a significant pain reduction (Figure 1b) was noted. Between the 4th and 5th cycle, the patient developed a rapidly growing nodule of 12 mm in diameter on the right clavicle (Figure 1c,d). Immediate excision was performed, and histopathology demonstrated an invasive poorly differentiated basosquamous carcinoma with perineural and lymphovascular invasion. The tumour was treated by wide surgical excision and adjuvant radiotherapy with good response. Treatment with cemiplimab was continued, but at time of the 8th cycle the patient presented again a newly developing tumour on her left forearm, for which surgery and subsequent histopathology revealed a well-differentiated cSCC. Tumour staging with ultrasound was unremarkable but at latest follow-up at cycle 9th revealed two suspicious inguinal lymph nodes in the right groin for which short-term follow-up was scheduled due to the absence of significant changes regarding the management and treatment.

During their lifetime, over 50% of patients with SCC will develop subsequent keratinocyte tumours and this has been largely linked to the so-called cancerization field. This in turn leads to diffuse DNA damage resulting in a high mutational burden and subsequently high levels of tumour neoantigens expression.[5] Immune checkpoint inhibitors (ICI) have been shown to be particularly effective in tumours with elevated mutational burden; in fact, ICI with cemiplimab has demonstrated clinical benefit in up to 50% of patients.[6]

However, as seen also in other malignancies,[7] ICI may show different patterns including dichotomous response: some patients experience rapid and durable tumour regression while others achieve minimal or no appreciable benefit.

Interestingly, Siegel et al.[8] recently described a case with dichotomous response to cemiplimab in an immunosuppressed patient, with a mcSCC. While host factors such as immunosuppression in the case reported by Siegel et al.[8] may reasonably explain the escape mechanism of the secondary cSCCs in their patient, different genetic burden may better explain the new developing cSCCs in our, immune competent, patient.

The observation by Siegel et al.[8] and our case provide fertile ground for future research targeting to acquire (1) more data on long-term efficacy and patterns of response to ICI in patients with multiple keratinocyte skin cancers (2) host, molecular or clinical predictive factors that could identify patients with grater possibility to respond to immunotherapy (3) how to improve response in case of dichotomic response within one patient.

AUTHOR CONTRIBUTIONS

All authors have significantly contributed to this work and approved the final version of the submitted paper. Iris Zalaudek, Dahlia Fedele and Nicola di Meo defined the design and intellectual content of the paper. Giulia Bazzacco and Enrico Zelin searched for literature, wrote the draft, and edited the manuscript and preparing them for submission. Ludovica Toffoli and Claudio Conforti reviewed the article with consistent integrations.

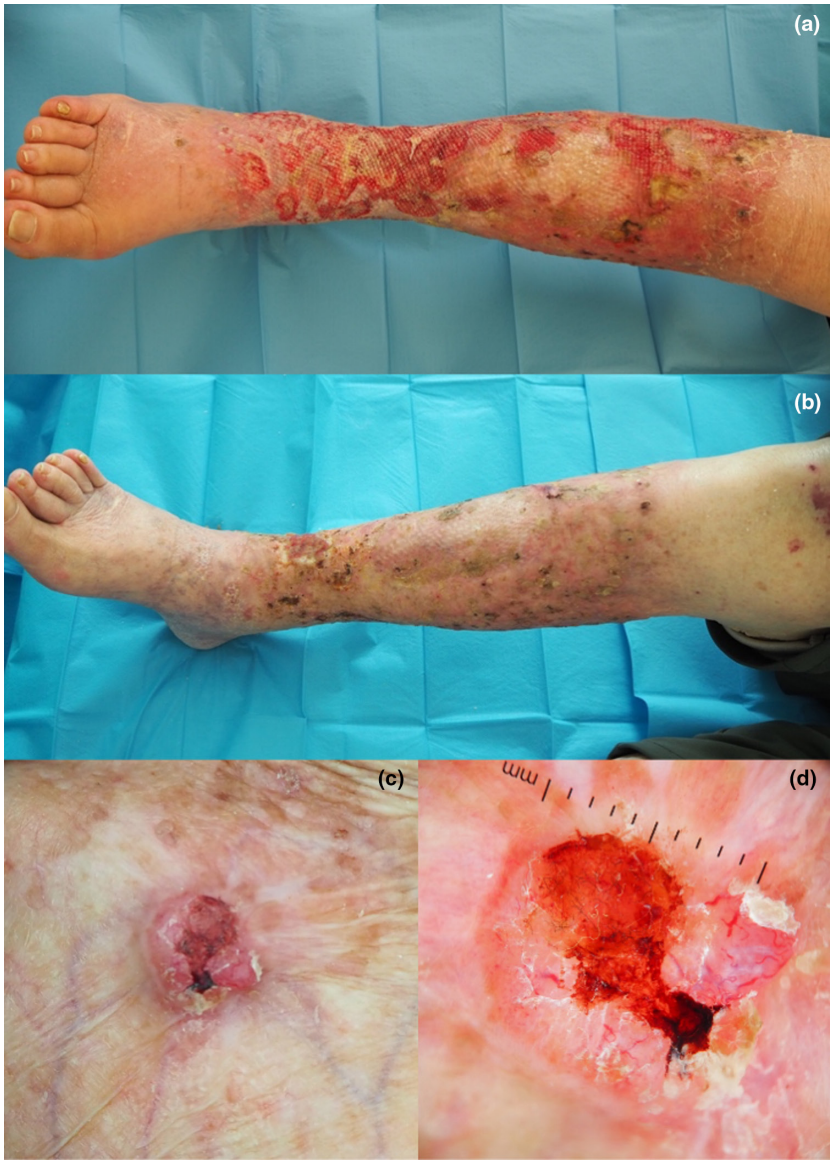

FIGURE 1 (a) Ulcerated lacSCC localized on the right pretibial region at baseline. (b) Clinical response of right pretibial cSCC after the first 3 cycles of Cemiplimab. (c, d) High-risk basosquamous carcinoma, 12 mm in diameter, localized on the right clavicle at clinical (c) and dermoscopic (d) evaluation.

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CONFLICT OF INTEREST

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript. I confirm that each co-author has completed the Conflict of Interest Form and am uploading all the completed COI forms along with my manuscript files.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

ETHICS STATEMENT

The patients in this manuscript have given written informed consent to publication of their case details.

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REFERENCES

1. Claveau J, Archambault J, Ernst DS, Giacomantonio C, Limacher JJ, Murray C, et al. Multidisciplinary management of locally advanced and metastatic cutaneous squamous cell carcinoma. Curr Oncol. 2020;27(4):e399–407. https://doi.org/10.3747/co.27.6015
2. Keeping S, Xu Y, Chen CI, Cope S, Mojebi A, Kuznik A, et al. Comparative efficacy of cemiplimab versus other systemic treatments for advanced cutaneous squamous cell carcinoma. Future Oncol. 2021;17(5):611–27. https://doi.org/10.2217/fon-2020-0823
3. Corneli P, Conforti C, Retrosi C, Vezzoni R, di Meo N, Piccolo V, et al. Pattern of response of unresectable and metastatic cutaneous squamous cell carcinoma to programmed death-1 inhibitors: A review of the literature. Dermatol Ther. 2020;33(2):e13250. https://doi.org/10.1111/dth.13250
4. Strippoli S, Fanizzi A, Quaresmini D, Nardone A, Armenio A, Figliuolo F, et al. Cemiplimab in an elderly frail population of patients with locally advanced or metastatic cutaneous squamous cell carcinoma: a single-center real-life experience from Italy. Front Oncol. 2021;11:686308. https://doi.org/10.3389/fonc.2021.686308
5. Christensen SR. Recent advances in field cancerization and management of multiple cutaneous squamous cell carcinomas. F1000Res. 2018;7:F1000 Faculty Rev-690. https://doi.org/10.12688/f1000research.12837.1
6. Hober C, Fredeau L, Pham-Ledard A, Boubaya M, Herms F, Celerier P, et al. Cemiplimab for locally advanced and metastatic cutaneous squamous-cell carcinomas: real-life experience from the French CAREPI study group. Cancers (Basel). 2021;13(14):3547. https://doi.org/10.3390/cancers13143547
7. Queirolo P, Spagnolo F. Atypical responses in patients with advanced melanoma, lung cancer, renal-cell carcinoma and other solid tumors treated with anti-PD-1 drugs: a systematic review. Cancer Treat Rev. 2017;59:71–8. https://doi.org/10.1016/j.ctrv.2017.07.002
8. Siegel JD, Bhatia A, Ko CJ, Christensen SR. Concurrent development of high-stage cutaneous squamous cell carcinoma during complete response of metastatic cutaneous squamous cell carcinoma to programmed cell death protein 1 blockade with cemiplimab. JAAD Case Rep. 2021;18:23–5. https://doi.org/10.1016/j.jdcr.2021.10.009