Induced remission of metastatic squamous cell carcinoma with an immune checkpoint inhibitor in a patient with recessive dystrophic epidermolysis bullosa

Karam Khaddour
Emily S. Gorell
Farrokh Dehdashti
Jean Y. Tang
George Ansstas

Follow this and additional works at: https://digitalcommons.wustl.edu/open_access_pubs
Induced Remission of Metastatic Squamous Cell Carcinoma with an Immune Checkpoint Inhibitor in a Patient with Recessive Dystrophic Epidermolysis Bullosa

Karam Khaddoura  Emily S. Gorellb  Farrokh Dehdashtic  Jean Y. Tangb  George Ansstasa

aWashington University in Saint Louis, Division of Medical Oncology, Saint Louis, MO, USA; bStanford University School of Medicine, Department of Dermatology, Stanford, CA, USA; cWashington University in Saint Louis, Division of Nuclear Medicine, Department of Radiology, Saint Louis, MO, USA

Keywords
Recessive dystrophic epidermolysis bullosa · Squamous cell carcinoma · Immune checkpoint inhibitor · Programmed death-1 inhibitor

Abstract
Recessive dystrophic epidermolysis bullosa (RDEB) is a genodermatosis that leads to skin fragility and chronic wound formation. Patients with RDEB are at risk for cutaneous squamous cell carcinoma (SCC) which is a major cause of morbidity and mortality in these patients. No standard of care exists for the treatment of SCC in this patient population and therapy is based on anecdotal reports and expert opinion. We report a 32-year-old man with RDEB with previously localized SCC who later developed metastatic SCC. He was started on cemiplimab (an immune checkpoint inhibitor) 350 mg IV every 3 weeks. An objective radiological response was noted within 3 cycles. On 14 months follow-up, there was a durable response to treatment clinically and on imaging, without immune-related adverse events. To our knowledge, this is the first case report describing safe administration of immune checkpoint inhibitors in a patient with RDEB with objective and durable response of metastatic SCC. Larger case series and controlled clinical trials are needed to further investigate these medications in the RDEB population, given their high burden of aggressive and often lethal SCC.

© 2020 The Author(s). Published by S. Karger AG, Basel

Karam Khaddour and Emily. S Gorell contributed equally to this work.
Introduction

Recessive dystrophic epidermolysis bullosa (RDEB) is a rare genetic skin disease caused by mutations in the gene \textit{COL7A1}, leading to absent or defective type VII collagen, with skin fragility and resulting chronic wounds. These patients may develop extremely aggressive and often metastatic cutaneous squamous cell carcinoma (SCC). The risk for developing these lesions increases dramatically in the third decade; malignancy is often the cause of death \cite{1}. Surgical treatment is the mainstay for localized tumors. There is no optimal therapy for advanced or metastatic SCC in this patient population given the partial short-lived response with conventional chemotherapy and the absence of controlled trials \cite{2}.

Immune checkpoint inhibitors block receptors in the tumor microenvironment responsible for immune suppression and malignancy progression. Cemiplimab is a monoclonal antibody that blocks programmed death-1 (PD-1) receptors leading to reactivation of the immune system against tumor cells. It was approved by the Food and Drug Administration in September 2018 to treat locally advanced and metastatic cutaneous SCC \cite{3}. However, no reports currently exist in the literature describing its safety and efficacy in RDEB patients. We present a case of an RDEB patient with an objective durable response to cemiplimab therapy for metastatic SCC.

Case Presentation

A 32-year-old male presented with severe RDEB, confirmed via genetic testing (homozygous for c.8440C>T [p.R2814X] in exon 114 of \textit{COL7A1}). He had a prior history of multiple SCCs on the lower back and right hand. Initial treatments of localized SCCs included numerous surgical resections. Recurrences were treated with topical imiquimod 5%, 5-fluorouracil and calcipotriene followed by intradermal injection with 5-fluorouracil and methotrexate. However, the patient subsequently developed a large axillary lymph node and a new large fungating eroded nodule on the right forearm, positive for invasive SCC on shave biopsy.

The patient was treated several years prior with autologous keratinocyte skin grafts corrected with a retroviral vector locally to the upper back \cite{4} and intradermal injections of autologous fibroblasts corrected with a lentiviral vector to the posterior neck and foot. SCC tissue samples and serum samples were negative for presence of these viruses.

Prior to initiation of therapy, positron emission tomography/computed tomography (PET/CT) with \textit{[18}F\textit{]}fluorodeoxyglucose (FDG) revealed several foci of intense uptake along the right upper extremity including the right axilla, anterior right forearm, and dorsal and volar surfaces of the distal right forearm and hand (Fig. 1A), consistent with SCC sites. PET/CT also revealed numerous foci of mildly increased FDG uptake associated with skin thickening throughout the body, likely related to RDEB.

The patient commenced cemiplimab 350 mg IV every 3 weeks, with a single treatment of radiotherapy (total of 16 Gy) to the right axilla and forearm. Two months after initiation of cemiplimab, repeat FDG-PET/CT showed marked metabolic response at the known sites of SCC in the right upper extremity and right axillary lymph nodes (Fig. 1B). There was no significant change in the numerous foci of mildly increased FDG uptake of the skin. No cutaneous lesions were visible on exam and no lymphadenopathy was apparent. Scans every 3 months were without evidence of SCC.

The patient reported mild nausea and fatigue, but denied any other side effects, including worsening RDEB wounds. There were no immune-related adverse events reported during or after initiation of immunotherapy. At the time of this report, he continues cemiplimab dosing every 3 weeks. The response has been sustained for 14 months.
Discussion

SCC is a major cause of morbidity and mortality in RDEB patients. Median survival after SCC diagnosis is estimated at 2.4 years; over one third are estimated to develop metastatic disease [1]. SCC usually arises at chronic wounds and shows resistance and refractoriness to topical treatments as well as a pattern of recurrence after surgical resection. Chemotherapies have been described as a palliative approach in locally advanced and metastatic disease, with inconsistent outcomes [2]. Chemotherapies and targeted epidermal growth factor receptor inhibitor cetuximab have been described to be effective for metastatic SCC in RDEB patient [5]. However, these therapies typically incur a substantial risk for severe infections due to the need for indwelling vascular accesses, bone marrow suppression with neutropenia, and cutaneous side effects such as desquamation, mucositis, and severe (grade 3 to 4) acneiform reactions, which could be disastrous in patients with severe RDEB (Table 1) [2].

Cemiplimab is a monoclonal antibody that targets PD-1 receptors on immune cells leading to augmentation of anti-tumor response. In an expansion cohort phase 1 study and a phase 2 single arm cohort, it has shown durable tumor responses in patients with cutaneous metastatic SCC without observed severe skin reactions, increased risk of neutropenia, or serious infections, which has led to its approval as a monotherapy of locally advanced and
metastatic SCC [3, 8]. However, clinical trials of cemiplimab did not include RDEB patients. Given the significant risk of treatment complications associated with conventional chemotherapies and tyrosine kinase inhibitors, there is an unmet need for effective and safe therapies in metastatic SCC in patients with RDEB.

The loss of type VII collagen results in a fragile dermal-epidermal skin barrier causing development of chronically colonized and infected cutaneous wounds with multiple drug-resistant bacteria that can often lead to sepsis [9]. This risk can be exacerbated when RDEB patients are treated with chemotherapies, which suppresses the bone marrow, and with tyrosine kinase inhibitors that can cause irritation of the skin barrier due to mucositis. The use of cemiplimab does not usually require indwelling vascular access. Furthermore, there have been only mild and minimal skin adverse events associated with the use of cemiplimab without observed bone marrow suppression.

Our patient demonstrated a sustained radiological response for 14 months, with minimal side effects and no immune-related adverse effects, which is promising. However, additional larger case studies and controlled trials are needed to confirm the safety and efficacy of cemiplimab in RDEB patients with cutaneous metastatic SCC.

**Conclusion**

To our knowledge, this is the first report of outcomes of treatment with a PD-1 inhibitor in a patient with metastatic SCC and RDEB. This report is important as patients with RDEB have high risk of metastatic SCC, which is a major cause of morbidity and mortality. No standard of care exists regarding these patients; therefore, we report the safety and efficacy with durable response (14 months) in one patient. This report should be interpreted with caution, as larger studies are needed to confirm the safety and efficacy of this approach.

**Statement of Ethics**

The patient has given his written informed consent to publish his case (including publication of images).
Conflict of Interest Statement

The authors have no competing interests to declare.

Funding Sources

No sources of funding were utilized in the preparation of this report.

Author Contributions

K.K. and E.S.G. contributed equally as first authors to the conceptualization, collection of data, and production of manuscript. F.D. provided the PET imaging with commentary and reviewed the work. J.Y.T. and G.A. supervised the whole work. All authors have read and approved the manuscript.

References