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Good clinical response to cemiplimab in a young patient with locally advanced cutaneous squamous cell carcinoma on preexisting recessive dystrophic epidermolysis bullosa

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Abstract

Recessive dystrophic epidermolysis bullosa (RDEB) is a rare genetic skin disease caused by mutations in the type VII collagen gene (*COL7A1*; 3p21.31). Mutations in this gene lead to an alteration in function or reduced amounts of collagen VII. This alteration of collagen VII leads to skin fragility and lesions at minor injuries with difficult healing. Cutaneous squamous cell carcinoma (cSCC) is more frequent in patients with RDEB than in the general population because of chronic wound formation; it constitutes a major cause of morbidity and is often cited as a cause of death for these patients. There is little experience with the treatment of cSCC in patients with RDEB. We report the case of a 19-year-old female patient with RDBE and inoperable locally advanced cSCC of the left arm. Because of the lack of therapy options, therapy with cemiplimab was started at a dose of 350 mg administered intravenously every 3 weeks. A confirmed clinical response was observed after the second cycle of treatment with no toxicity. During follow-up, the patient had a notable clinical response with no auto-immune adverse reactions. This shows that cemiplimab has a good safety profile for cSCC in patients with RDEB and is a valuable therapy option.

Keywords: recessive dystrophic epidermolysis bullosa, squamous cell carcinoma, cemiplimab, checkpoint inhibitor, programmed death-1 inhibitor

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Introduction

Epidermolysis bullosa (EB) is a condition that occurs due to the absence of various components of the basal membrane secondary to inherited autosomal dominant or autosomal recessive genetic mutations. It is manifested by skin fragility and chronic wound formation. EB is divided into four main types: simplex EB, junctional EB, dystrophic EB, and Kindler EB, depending on the genetic mutations detected (1).

This case report refers in particular to the dystrophic form of EB, which has been associated with mutations in the *COL7A1* (3p21.31) gene, which encodes collagen type VII (2). Depending on the nature of these mutations, there can be reduced secretion or complete absence of collagen VII. The condition manifests through the formation of skin and mucosal blisters, which subsequently heal but leave behind dystrophic scars. These lesions primarily affect the limbs and may eventually lead to the development of pseudosyndactyly.

Dystrophic epidermolysis bullosa causes high morbidity and mortality among patients. The lack of specific treatment and complications that occur secondary to repeated injuries coupled with impaired healing can lead to a decrease in the quality of life of patients. Even with the observance of rigorous hygiene and prevention rules, patients may experience specific complications of the disease as well as loss of mobility of the fingers and toes, anemia, recurrent infections, and malnutrition, and they have an increased risk of developing cutaneous squamous cell carcinoma (cSCC) (3). Patients with EB have a notably higher incidence of cutaneous squamous cell carcinoma (cSCC) due to the frequent occurrence of lesions and the skin's fragility. Typically, cSCC arises in EB patients 15 to 35 years old, and it tends to progress aggressively due to limited treatment options, becoming a significant contributor to mortality in this population (3). However, in 2018, the Food and Drug Administration (FDA) approved cemiplimab, an anti-programmed death (PD)-1 monoclonal antibody, for treating metastatic or locally advanced cSCC, based on promising clinical trial results. Subsequently, in 2019, this treatment gained approval by the European Medicines Agency (EMA), marking a transformative shift in the therapeutic landscape for this condition.

Here we present the case of a 19-year-old female patient diagnosed with recessive dystrophic EB (RDEB) that sought treatment at our oncology department for locally advanced cSCC.

Case report

A 19-year-old female patient, with no significant familial history, had been diagnosed with recessive dystrophic epidermolysis bullosa (RDEB) at the age of 6 months. At the time of presentation, she exhibited significant arm damage characterized by pseudosyndactyly and stump formation. About 7 months prior, she had been referred to an oncologist due to a tumor on her left arm. Biopsy results indicated invasive, moderately differentiated (G2) keratinized squamous cell carcinoma, compounded by superinfected erosions of epidermolysis bullosa (Fig. 1). Specific antibiotic treatment based on the antibiogram had been promptly initiated.

To assess the extent of the disease, imaging investigations were conducted. CT scans did not reveal visible metastases, but both ultrasound and CT scans detected a suspicious left axillary adenopathy measuring about 3 cm (lacking a fat center and exhibiting vascularization). To obtain a precise assessment of disease extension, a biopsy of the left axillary adenopathy was performed, showing a reactive histopathological aspect. The final diagnosis

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was locally advanced cSCC of the left arm, concurrent with RDEB. It is worth noting that the patient had undergone molecular studies to analyze the COL7A1 gene, but no mutations had been detected in exons 80, 81, and 82, leading to the discontinuation of genetic investigations.

Therapeutic options had been deliberated within the oncology committee and in consultation with the patient. As an initial treatment, the patient underwent debridement of the tumor tissue on the left arm to enhance quality of life, albeit with modest results. Following treatment guidelines, amputation of the affected limb was proposed, but the patient declined this option. Given the concomitant pre-existing pathology, radiation therapy was deemed unsuitable due to the potential for adverse effects outweighing clinical benefits. Thus, the case was considered one of inoperable locally advanced cSCC with no indication for radiation therapy, and initiation of treatment with cemiplimab 350 mg intravenously every 3 weeks was decided.

During the pretherapeutic clinical examination, the patient exhibited multiple erosions on the skin, along with pseudosyndactyly and bilateral stump formation (Fig. 2). The tumor had extensively invaded the left stump and was accompanied by left axillary adenopathy, diffuse alopecia, and dental erosions. Biologically, iron-deficiency anemia resulting from recurrent bleeding secondary to bullous epidermolysis lesions was noted. Cardiological examination did not reveal any preexisting cardiac pathology.

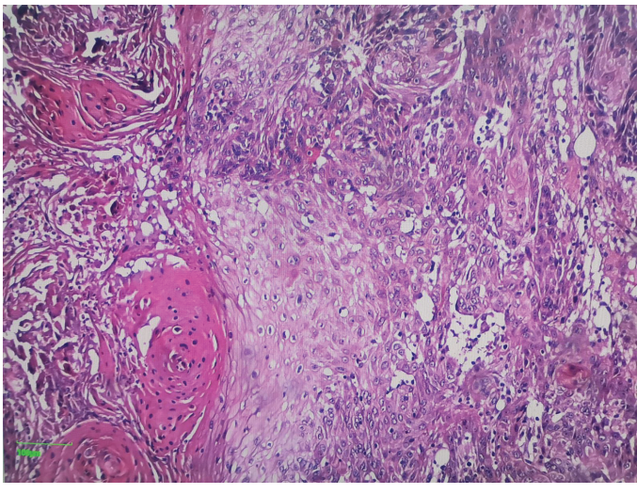

Figure 1 | Histopathological examination of invasive, moderately differentiated (G2) keratinized squamous cell carcinoma (H&E stain, 10× magnification).

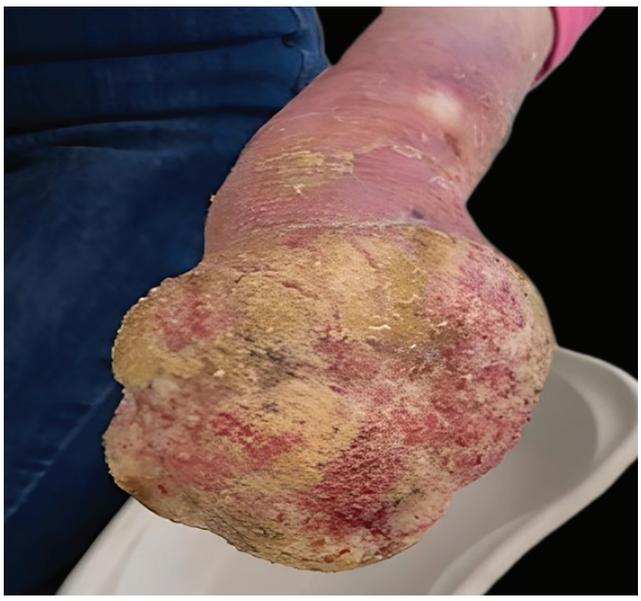

Figure 2 | Pretreatment image showing squamous cell carcinoma on the left arm stump with pseudosyndactyly.

Treatment with cemiplimab 350 mg intravenously every 3 weeks commenced with excellent immediate tolerance, and the patient did not manifest any treatment-specific toxicities. Clinical examination of the tumor formation and dressing was performed at each presentation (Fig. 3). Following the second cycle of treatment, a notable reduction in tumor volume and favorable local response were noted (Fig. 4). Improvement in appearance was evident at each examination throughout the six cycles of cemiplimab, with local examination proving to be the most suitable means of assessing treatment response (Figs. 5–9).

During treatment with cemiplimab, the patient experienced a

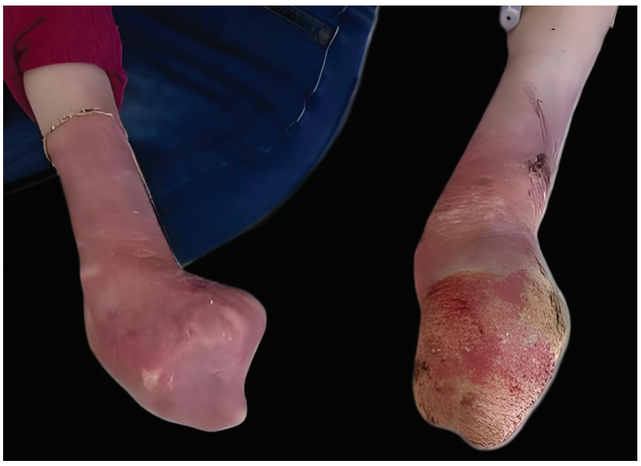

Figure 3 | Clinical response after the first cycle of cemiplimab.

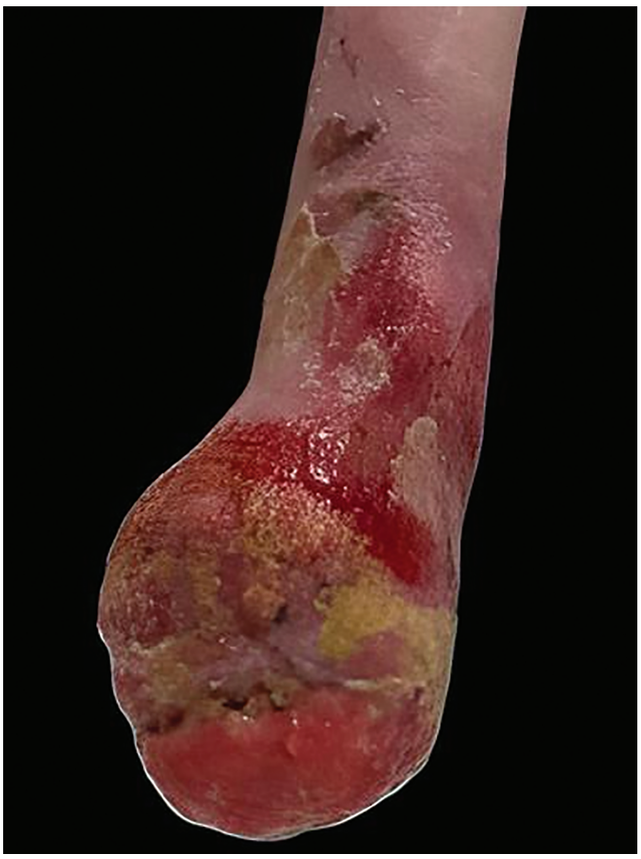

Figure 4 | Clinical response after the second cycle of cemiplimab.

slight decrease in appetite. CT scans performed every 6 months did not identify distant metastases. There was no exacerbation of RDEB or immunotherapy-specific toxicities. As of the time of writing, the patient remains on cemiplimab treatment.

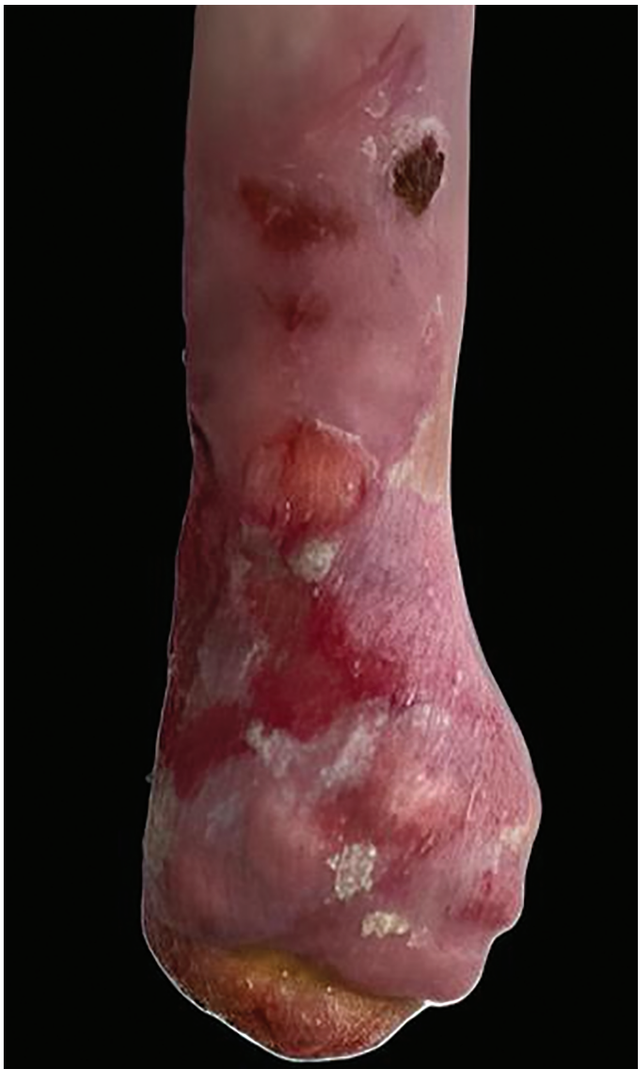

Figure 5 | Clinical response after the third cycle of cemiplimab.

Discussion

cSCC ranks second in frequency among non-melanoma skin cancers, following basal cell carcinoma (4). Various risk factors contribute to the development of this condition, including exposure to UV radiation, immunosuppression, and infection with human papilloma viruses. In the general population, severe burns or chronic skin lesions can also act as risk factors, albeit less frequently. RDEB stands as a distinct condition within the spectrum of epidermolysis bullosa and holds second position in frequency among its various subtypes. Despite its prevalence, RDEB is marked by the most severe disabilities among patients (5). It is associated with mutations in the COL7A1 gene, which encodes the production of collagen VII. The appearance of lesions in the limbs with the development of pseudosyndactyly leads to a significant decrease in the quality of life among patients. Other complications associated with RDEB include anemia, esophageal narrowing leading to progressive dysphagia, developmental delays, malnutrition, intestinal transit disorders, and deficient dentition.

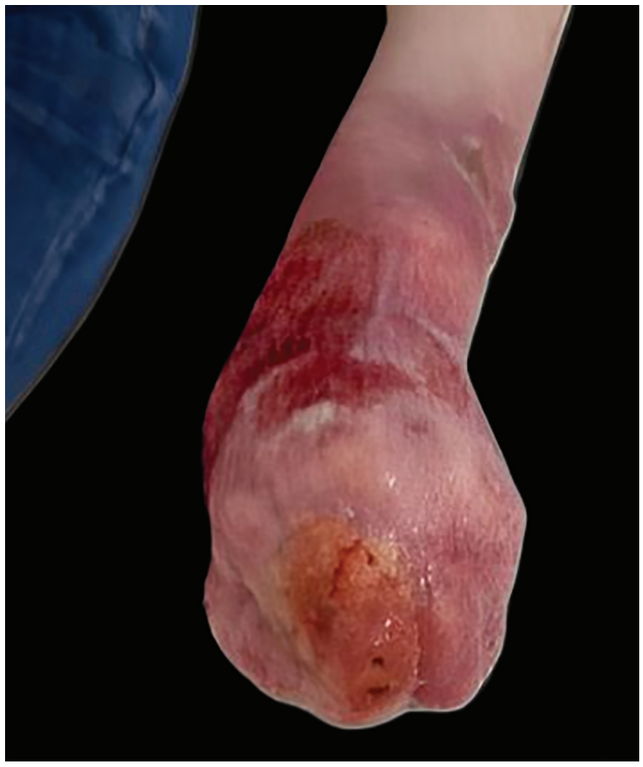

Figure 6 | Clinical response after the fourth cycle of cemiplimab.

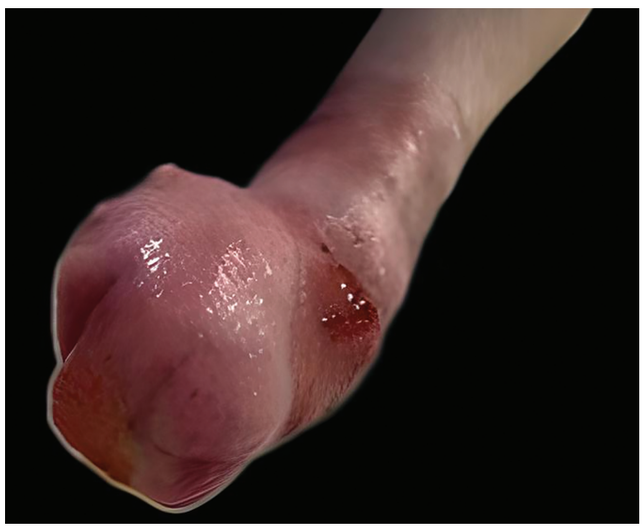

Figure 7 | Clinical response after the fifth cycle of cemiplimab.

One significant complication arises from repeated infections of the lesions secondary to RDEB, resulting in poor wound healing and an increased incidence of cSCC. In addition, the risk of developing this neoplasm escalates with the patient's age.

cSCC in patients with RDEB has a more aggressive evolution than cSCC secondary to UV exposure, being characterized by significant morbidity and representing the main cause of mortality among these patients (4).

Treatment of patients with RDEB that develop cSCC is a challenge. Local surgical treatment is not an optimal therapeutic option, relapses being frequent. Local treatments, the most studied being imiquimod, did not show an improvement in the quality of life, nor a favorable effect on the disease in the long term (1). Radiation therapy is frequently not a viable treatment choice for locally advanced cases due to the potential exacerbation of chronic

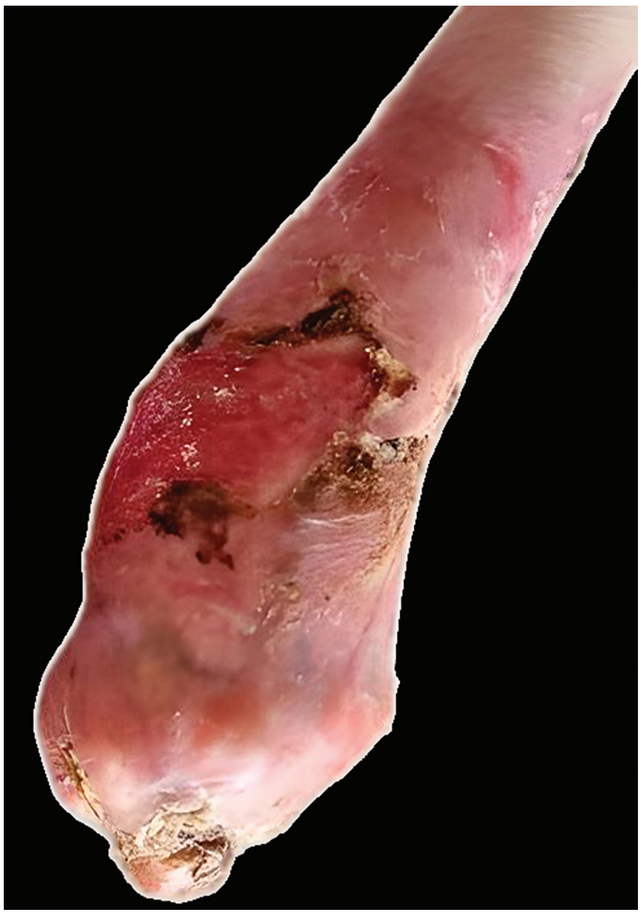

Figure 8 | Clinical response after the sixth cycle of cemiplimab.

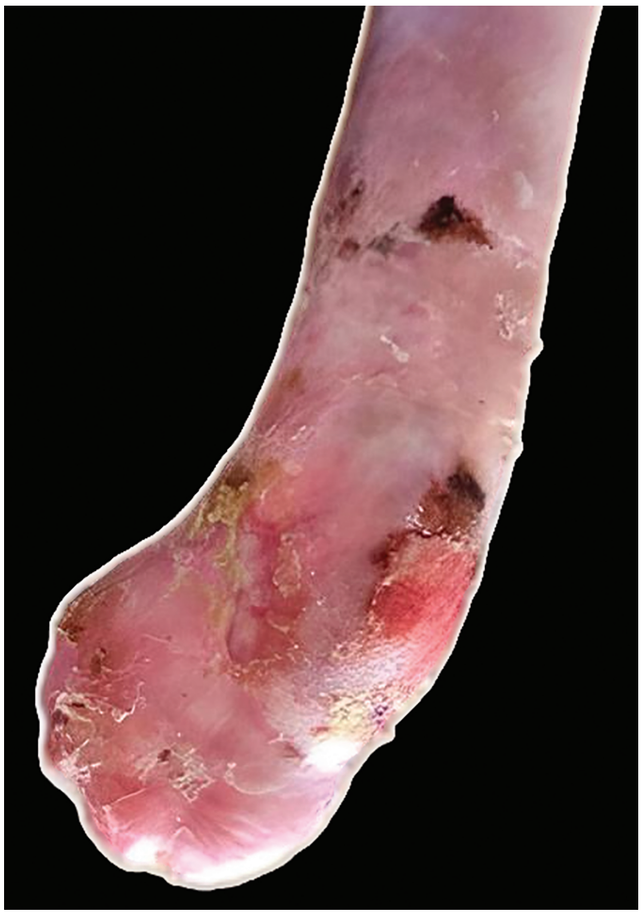

Figure 9 | Clinical response after the seventh cycle of cemiplimab.

pathology caused by its adverse effects. Until recently, chemotherapy had been regarded as the standard treatment for patients with metastatic or locally advanced inoperable cSCC. However, chemotherapy-induced immunosuppression poses a significant risk of severe and life-threatening infections in patients with EB, who often suffer from superinfected lesions. Moreover, chemotherapy-induced stomatitis and skin reactions resulting from chemotherapy extravasation can further compromise the quality of life for EB patients. As such, chemotherapy is not typically prioritized as the initial therapeutic option in these cases.

PD-1 inhibitors represent a novel class of medications designed to block PD-1 and stimulate the immune system to target tumor cells. Among these biological therapies, cemiplimab stands out as a high-affinity human IgG4 monoclonal antibody that disrupts the interaction between PD-1 and PD-ligand 1. Notably, cemiplimab is the first immunotherapy endorsed by the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) for the treatment of locally advanced and metastatic cSCC (6). Its efficacy in treating cSCC has been underscored by heightened response rates to treatment and minimal occurrence of secondary neutropenia and skin side effects (7). However, patients with EB were generally excluded from the clinical trials, with only isolated cases reported in the literature (6, 7). The dearth of data concerning this subgroup complicates the establishment of a standard treatment protocol. Some researchers have documented successful utilization of other PD-1 inhibitors for cSCC in patients with RDEB (8, 9). In addition, recent preclinical investigations have identified the JAK1/2 inhibitor ruxolitinib (10) and transforming growth factor beta receptor 1 (TGF-βR1) kinase inhibitors (11) as potential novel therapies for cSCC associated with RDEB.

Our patient presented a good response to treatment with cemiplimab, and these results were confirmed after the local examination. The lack of side effects suggests a good safety profile for patients with RDEB.

Conclusions

cSCC causes significant morbidity and mortality among patients with RDEB. Specific complications of this genetic disease may pose contraindications to the available therapeutic options for cSCC. Promising results from phase 1 and 2 studies plus the safety profile of cemiplimab treatment also highlighted in the case presented may lead to the emergence of a standard of treatment for this subgroup of patients.

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