

Managing squamous cell carcinoma in recessive dystrophic epidermolysis bullosa with electrochemotherapy

Eletroquimioterapia em carcinoma espinocelular na epidermólise bolhosa distrófica recessiva

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Abstract

Epidermolysis bullosa (EB) represents a group of congenital disorders caused by mutations in skin structural proteins. Squamous cell carcinoma (SCC) is one major complication and the leading cause of death of several subtypes of EB. We report a case of a 38-year-old female patient with recessive dystrophic EB that underwent electrochemotherapy (ECT) for treatment of cutaneous SCC in the right foot. Two sessions were performed, in which the intravenous administration of bleomycin was followed by the local application of electric pulses. We verified a partial response in 8th week of follow up and a complete response in the 24th week.

ECT is a local treatment for cutaneous and subcutaneous tumors, mainly as palliative care for metastases. Studies have shown its effectiveness in primary tumors that are unresectable due to size and location, and it has been proposed as a new treatment modality for SCCs in EB with high overall response.

Keywords: Recessive dystrophic *epidermolysis bullosa*. Squamous cell carcinoma. Electrochemotherapy.

Resumo

A epidermólise bolhosa (EB) representa um grupo de doenças congénitas causadas por mutações em genes que codificam proteínas estruturais da pele. O carcinoma espinocelular (CEC) é uma das suas complicações mais temidas, sendo a principal causa de morte nalguns subtipos de EB. Apresenta-se o caso de uma doente de 38 anos com EB distrófica recessiva, que foi submetida a eletroquimioterapia (EQT) para o tratamento de um CEC no pé direito. Foram realizadas duas sessões de tratamento, com administração endovenosa de bleomicina seguida da aplicação de pulsos elétricos. Verificou-se uma resposta parcial às 8 semanas de follow-up e resposta completa às 24 semanas.

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Received: 25-10-2021

Accepted: 10-02-2022

DOI: 10.24875/PJD.M22000023

Available online: 02-08-2022

Port J Dermatol and Venereol. 2022;80(2):165-168

www.portuguesejournalofdermatology.com

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A EQT é um tratamento local para tumores cutâneos e subcutâneos, primeiramente como modalidade paliativa em metástases. Estudos demonstram a sua eficácia no tratamento de tumores cutâneos primários irresssecáveis, pelas suas dimensões ou localização, tendo sido proposta como modalidade terapêutica nos CECs na EB, com boa resposta global.

Palavras-chave: Epidermólise bolhosa distrófica recessiva. Carcinoma espinocelular. Eletroquimioterapia.

Introduction

Epidermolysis Bullosa (EB) represents a group of rare congenital disorders caused by genetic variants in skin structural proteins, resulting in disruption of the dermal-epidermal junction. It is a clinically and genetically heterogeneous disorder characterized by skin fragility, with a propensity to impaired wound healing and blister formation. Based upon the ultrastructural levels of skin cleavage, EB is classified into four major types: simplex, junctional, dystrophic, and Kindler Syndrome. Recessive dystrophic EB (RDEB) results from a mutation in the COL7A1 gene that encodes the alpha-1 chain of type VII collagen^{1,2}.

Squamous cell carcinoma (SCC) is one of the most feared complications and the leading cause of death of several subtypes of EB. The risk is higher for RDEB, especially in the generalized severe form³. To date, surgery is the first-line treatment for EB-associated SCC (EB-SCC), however, these tumors show an aggressive course, with high rates of recurrence even following complete excision^{4,5}. Systemic chemotherapy and radiotherapy are only recommended as palliative modalities since their side effects may outweigh the benefits in these fragile patients^{6,7}. Despite all treatments available, there is a high morbidity and mortality associated to EB-SCCs, with significantly reduced life expectancy.

Electrochemotherapy (ECT) is a local treatment for cutaneous and subcutaneous tumors. The first ECT clinical trial was performed in 1991 in Villejuif, France, on head and neck cutaneous metastatic SCCs⁸. The European Standard Operating Procedures of ECT (ESOPE) project, which established the guidelines for a safe application of ECT in clinical practice was published in 2006⁹. Even though ECT is mainly applied as palliative care for metastases, it may also be used for primary tumors that are unresectable due to size and location^{10,11}. ECT has been proposed as a new treatment modality for EB-SCCs, due to its effectiveness and favorable safety profile^{4,12,13}.

Case Report

We report the case of a 38-year-old female patient with RDEB who presented with a cutaneous SCC in

the dorsum of the right foot (Fig. 1). The lesion had been growing for the past 4 months, and was successfully treated with ECT, obviating the need for further treatments. The inclusion criteria and technical procedures followed the ESOPE⁹. Patient underwent an ECT session using the ePORE Gx device (Pes Med, Italy) in which bleomycin was administered intravenously at a dose of 15 000 UI/m² for 2 minutes, followed by electric pulses 8 minutes later. The lesion was examined and measured at follow-up appointments to evaluate the response to treatment and efficacy was assessed according to the Response Evaluation Criteria in Solid Tumours¹⁴. We reported stable disease 8 weeks after the first treatment, so we proposed a second session, which the patient consented. The second ECT session was performed 9 weeks after the first one, using the Cliniporator 1 device (IGEA, Italy). At 8 weeks of follow-up, we reported a partial response (Fig. 2a), with a complete response and skin healing of the treated area at 24 weeks of follow-up (Fig. 2b). ECT was well tolerated, with only mild adverse effects reported, which included muscle contractions during each pulse and local pain, erythema, and ulceration in the follow-up period. After the first three postoperative months, in which the patient was evaluated every two weeks, a quarterly follow-up was performed in the first year and every four months thereafter. At 64 weeks of follow-up, the patient is still free of recurrence.

Discussion

A major complication of EB is the development of multiple cutaneous SCCs, which generally develop in early adulthood and tend to arise at sites of chronic non-healing wounds or hyperkeratotic lesions. These tumors may be difficult to identify clinically since they frequently resemble areas of nonmalignant EB ulceration and wounds, so it is essential to maintain a straight clinical follow-up and have a low suspicion threshold to perform biopsy^{3,15}. They represent the leading cause of death in EB at or after mid-adolescence, with death from cutaneous SCC occurring within 5 years of the diagnosis of the first SCC in most patients. The cumulative risk of at least one SCC in patients with generalized severe



Figure 1. Clinical presentation. An erosive tumor, 3 × 4 cm in size, localized in the dorsum of the right foot.



Figure 2. Clinical response to treatment. **A:** a partial response was reported at 8 weeks of follow-up, with superficial ulceration at the site of the SCC. **B:** at 24 weeks of follow-up, a complete response was reported, with no clinically evident disease.

form of RDEB is 7.5%, 68%, and 90% by ages 30, 35, and 55 respectively. In contrast, the risk of these tumors is <25% by age 45 years in other forms of RDEB¹⁶.

The first line treatment for cutaneous EB-SCCs is surgery however these lesions tend to recur locally as their borders are usually indistinct⁴. Radiotherapy and conventional chemotherapy have been reserved as palliative modalities for advanced or locally recurrent SCC so other treatment options should be considered^{6,7}. ECT combines the administration of a low dose of a chemotherapeutic agent, such as cisplatin or bleomycin, and the local application of short intense electric pulses. The electric fields transiently permeabilize the cell membrane, allowing the entrance of the drug into the

neoplastic cells, enhancing its effectiveness and reducing its side effects. Only transient and mild adverse effects are usually reported^{8,10}, as in the present case. Although it has no impact in the systemic progression of the disease, it has been proposed as a treatment modality for EB-SCC with high overall response.

In this case, we verified a complete response of a cutaneous SCC after two well tolerated sessions of ECT. This report aims to reinforce the potential of ECT as a viable approach for SCCs in patient with EB, without the high risk of functional impairment after surgical excision and no contraindications related to the disease.

What does this study add

We aim to reinforce the potential of electrochemotherapy as a viable approach for squamous cell carcinoma in patients with epidermolysis bullosa, without the high risk of functional impairment after surgical excision.

Prizes and previous presentations

This case has been presented as a clinical case on “Reunião de Primavera da Sociedade Portuguesa de Dermatologia e Venereologia”, Aveiro, 9–10th July 2021 and as an e-poster on “EADV 30th congress,” Virtual, 29th September–2nd October 2021.

Funding

The authors received no financial support for the authorship or publication of this article.

Conflicts of interest

None to declare.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this investigation.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data and that all the patients included in the study have received sufficient information and have given their informed consent in writing to participate in that study.

Right to privacy and informed consent. The authors have obtained the informed consent of the patients and/or subjects mentioned in the article. The author for correspondence is in possession of this document.

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