# Epidermolysis bullosa simplex clearance after nasopharyngeal carcinoma treatment

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## INTRODUCTION

Epidermolysis bullosa (EB) refers to a group of genetic diseases characterized by blistering in response to minor trauma. It is divided into 3 major categories based on the depth of skin blistering, as follows: 1) EB simplex (EBS), 2) junctional EB, and 3) dystrophic EB. A fourth major type was recently proposed and encompasses Kindler syndrome, since this genodermatosis shares with the other 3 major EB types the presence of mechanically fragile skin and blisters, yet, in contrast to all other EB types, typically have cleavage planes within multiple levels of the basement membrane zone.[1,2] The most recently updated classification of EB was published by Mellerio et al.[3]

EBS is most often caused by mutations within the genes encoding for keratin 5 and keratin 14, with the vast majority being autosomal dominantly transmitted.[2]

There are currently no approved therapies for any form of inherited EB. Treatments have focused on symptom relief, and the increasing understanding of the pathogenesis of EB is facilitating the development of novel evidence-based therapy approaches. Recent knowledge on disease-secondary mechanisms has led to the development and clinical testing of urgently needed symptom-relief therapies using small molecules and biologicals. For now, day-to-day management of EB focuses on the prevention of mechanical trauma, wound care, avoidance of infection, padding over bony prominences, protective bandaging, and loose-fitting clothes[1]

*Abbreviations used:*

EB: epidermolysis bullosa
EBS: epidermolysis bullosa simplex

Herein, we present the case of a 49-year-old woman with known EBS-mottled pigmentation since birth who cleared after treatment of nasopharyngeal carcinoma.

## CASE REPORT

The patient is a 49-year-old woman born of consanguineous parents with known EBS-mottled pigmentation since birth. Her 3 older siblings had blistering disease, which remained undiagnosed, and they all died before the age of 2 years.

The patient has been followed in the Dermatology Clinic at King Khalid University Hospital in Riyadh for the past 24 years. She presented with multiple blisters, which appear almost every day (Fig 1). She had received multiple treatments, including oral minocycline and doxycycline, with minimal improvement or reduction in frequency of blister formation. In October 2019, the patient was diagnosed with nasopharyngeal carcinoma, and a treatment with weekly cisplatin for 7 sessions and daily radiotherapy for 35 days was initiated on November 10. Following the second session of cisplatin, the patient reported total clearance of blisters with no recurrence since then. There was no history of alcohol drinking or smoking and no personal or family history of malignancies.

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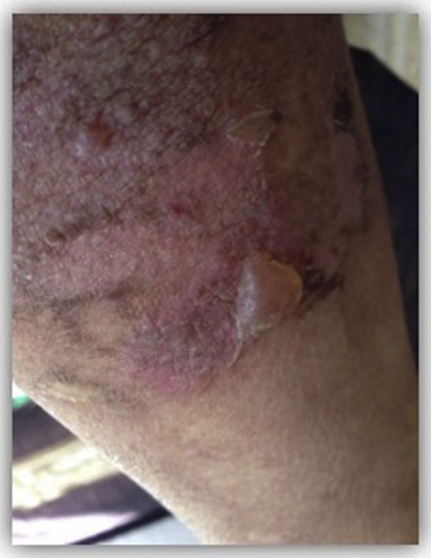

**Fig 1.** Erythematous patches with bullous eruption over the lower portion of the right limb prior to cisplatin treatment.

Two 4-mm skin punch biopsies were taken for hematoxylin-eosin and periodic acid-Schiff staining as well as for direct immunofluorescence. Photomicrography using low-power view revealed a sub-epidermal blister with scanty inflammation. Some of the basal keratinocytes were attached to the underlying basement membrane (Fig 2). Photomicrography of the dermis revealed a few scattered eosinophils and melanophages. Photomicrography using high-power view revealed a blister above the base membrane zone (Fig 3). The second skin punch biopsy for the direct immunofluorescence found no evidence of IgA, IgG, IgM, C3, and fibrinogen deposition. Physical examination revealed diffuse, brown-ashy, reticulated, pigmented patches over the trunk and extremities (Fig 4). No mucosal lesions nor Nikolsky sign were observed. There was an alopecic patch in the posterior aspect of the neck (site of radiation), but no bullae/vesicles or skin detachment/sloughing were noticed. While her finger nails were spared, her toe nails exhibited subungual hyperkeratosis. Mild palmoplantar keratoderma was also noticed. No lymph-node enlargement was observed.

A blood sample was taken for genetic analysis revealed that the patient is homozygous for KRT14: NM_000526:exon6:c, 1194delC:p.Tyr398X pathogenic variant.

The histology and genetics results confirm that our patient indeed has autosomal recessive EBS.

After reviewing the literature, we confirm that this is the first case of EBS-mottled with autosomal recessive inheritance and homozygous K14 mutations.

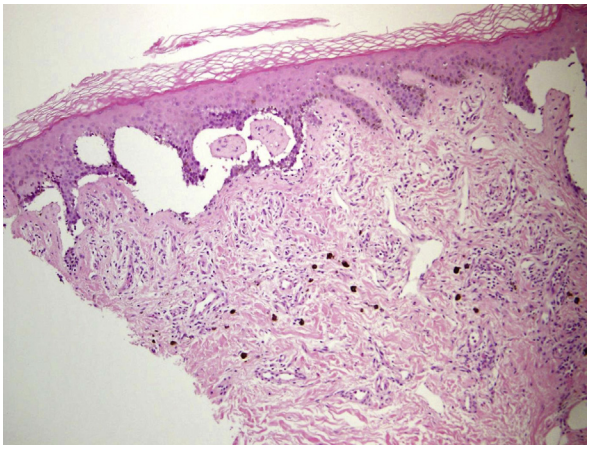

**Fig 2.** Photomicrograph (low-power view) showing a sub-epidermal blister with scanty inflammation. Some of the basal keratinocytes are attached to the underlying basement membrane. (Hematoxylin-eosin stain; original magnification, ×100.)

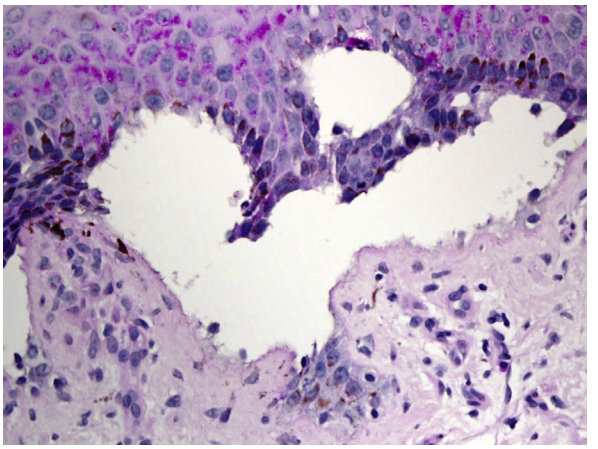

**Fig 3.** Photomicrograph (high-power view) showing a blister above the basement membrane zone. (Periodic acid-Schiff stain; original magnification, ×400.)

## DISCUSSION

Epidermolysis bullosa simplex is the most common form of EB and comprises a group of clinically and genetically diverse mechanobullous genodermatoses characterized by fragility of the skin and mucous membranes. To date, no treatment method that leads to a cure for EBS and its subtypes has been described, and so the main treatment is symptom alleviation.

Blisters and erosions of EBS with mottled pigmentation appear at birth or in early infancy after minor trauma, often on the distal extremities or acral surfaces. The erosions heal without scarring or milia,

and healed areas typically become resistant to further blistering. This may explain the rarity of blistering in adulthood. In addition, reticular hyperpigmentation appears later in infancy or early childhood and is not preceded by blister formation. The pigmentation fades with age. Adults can develop focal palmoplantar hyperkeratosis, punctate palmoplantar keratoderma, and nail dystrophy. Epidermolysis bullosa simplex-mottled pigmentation is a very rare subtype, with only 50 cases reported so far.[4]

According to the literature, there are 2 methods that can be used for the symptomatic treatment of EBS; either topicals, such as Diacerein, betulin-based oleogel, and topical sirolimus, or systemic treatment with, for example, losartan and high mobility group box protein 1-derived peptide.[5]

The present patient received cisplatin chemotherapy for the treatment of nasopharyngeal carcinoma. After the second session, the patient reported total clearance of existing blisters with no recurrence since then. In contrast to previous studies, where patients with EBS showed aggravation of their symptoms after receiving radiotherapy of $\geq 45$ gray (Gy) with the development of blisters, erosions, moist desquamation, and delayed skin healing,[6,7] our patient continued to show clinical remission, even after receiving a total of 70 Gy of radiotherapy.

In the present case, genetic analysis confirmed that she has a homozygous PTC mutation in the keratin 14 gene, and we thought of a PTC readthrough property to be more likely the mechanism of action of cisplatin, while other authors think that this is unlikely. Another factor playing an important role in the pathogenesis of EBS and its phenotype is the inflammation. The clearance of blistering during and after the course of chemotherapy could be explained by the possibility that cisplatin is acting as an anti-inflammatory agent. Cisplatin is an antineoplastic medication targeting DNA damage and causing cellular apoptosis; however, it was recently shown that it has an immunomodulatory effect. The importance of inflammation in EBS and a key role for the TH17 cytokine in its pathogenesis was published by Castela et al[8] and the role of inflammation in EBS by Jemma Mellerio.[9]

The third possible mechanism underlying the clearance of blistering, while the patient was on cisplatin, is the reversal of the mutation by restoring the wild-type phenotype to cells already carrying a phenotype-altering forward mutation.

To our knowledge, this is the first case report on the clearance of EBS following treatment with cisplatin. Genetic studies will be carried out to evaluate whether there was a reversal of the relevant mutation in our patient. We believe that our study would encourage further studies to evaluate the role of cisplatin in such a difficult disease. We cannot recommend cisplatin as a treatment for EBS until other similar cases have been reported.

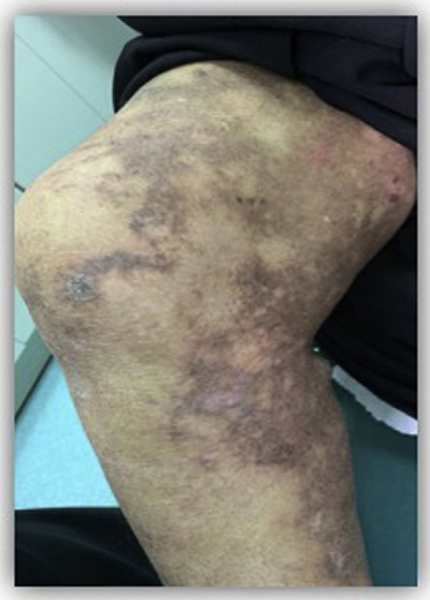

**Fig 4.** Diffuse, brown-ashy, reticulated, pigmented patches over the lower portion of the right limb with no blisters or sloughing after cisplatin treatment.

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**Conflicts of interest**

None declared.

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