

## INHERITED EPIDERMOLYSIS BULLOSA – ASSOCIATED CUTANEOUS SQUAMOUS CELL CARCINOMA ON THE LEG – WHEN TO AMPUTATE?

### HEREDITARNA EPIDERMOLIZA – SKVAMOZNI KARCINOM NA NOZI – KADA JE VREME ZA AMPUTACIJU?

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Case report

*Prikaz slučaja*

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#### Abstract

**Introduction.** Inherited epidermolysis bullosa comprises a heterogeneous group of genetic disorders characterized by skin fragility, resulting in blisters, erosions, and scarring of the skin and mucous membranes following minimal mechanical trauma. Patients with inherited epidermolysis bullosa are at increased risk of developing aggressive cutaneous squamous cell carcinoma, most commonly arising on the extremities. **Case Report.** We report a case of a 21-year-old female with inherited epidermolysis bullosa who presented with a progressively enlarging tumor on the right lower leg, appearing as a small crusted lesion. Physical examination revealed a firm, elevated lesion measuring approximately 10 cm in greatest diameter, covered with crusts. The patient had previously undergone two surgical excisions the same site for confirmed cutaneous squamous cell carcinoma. Radiological evaluation demonstrated no evidence of bone invasion, while ultrasonography identified a single enlarged lymph node in the right inguinal region. Partial biopsy of the lesion confirmed cutaneous squamous cell carcinoma, and lymph node biopsy revealed reactive lymphadenitis without metastatic involvement. Considering the presence of typical lesions throughout the body, the patient's inability to achieve verticalization, limited reconstructive options, and repeated recurrence of aggressive carcinoma, limb amputation was considered the most appropriate therapeutic approach. **Conclusion.** In patients with inherited epidermolysis bullosa who develop recurrent cutaneous squamous cell carcinoma, particularly after multiple local recurrences and in the absence of feasible reconstructive options, amputation may represent an unavoidable yet life-preserving treatment strategy, even in the setting of localized disease.

**Key words:** Epidermolysis Bullosa; Carcinoma, Squamous Cell; Amputation, Surgical; Recurrence

#### Introduction

Inherited epidermolysis bullosa (IEB) represents a heterogeneous group of genetic disorders characterized by skin fragility, leading to blister formation, erosions, and wounds of the skin and mucous membranes following minor mechanical trauma. IEB encompasses a wide

#### Sažetak

**Uvod.** Hereditarna epidermoliza predstavlja grupu genetskih poremećaja povezanih sa povećanom osetljivošću kože, koja dovodi do formiranja plikova, erozija i ožiljaka na koži i sluzokoži i to kao odgovor na minimalnu mehaničku traumu. Hereditarna epidermoliza je povezana sa povećanim rizikom od agresivnog kutanog skvamoznog karcinoma, koji se javlja češće na ekstremitetima. **Prikaz slučaja.** Pacijentkinja stara 21 godinu, koja boluje od hereditarne epidermolize, javila se lekaru sa tumorom na desnoj nozi. Tumor je započeo u formi male kruste koja je postepeno počela da raste tokom vremena. Fizikalnim pregledom otkrivena je lezija lokalizovana na desnoj potkoljenici, iznad nivoa kože, ovalnog oblika, 10 cm u najvećem prečniku, tvrde konzistencije, prekrivena krustama. Ranije je imala dve operacije sličnih lezija na istom mestu (Ph: kutani skvamozni karcinom). Radiološka dijagnostika nije pokazala infiltraciju kostiju, a ultrazvučno je viđen samo jedan uvećan limfni čvor u desnom ingvinumu. Parcijalna biopsija lezije potvrdila je skvamozni karcinom, a biopsija limfnog čvora reaktivni limfadenitis bez prisustva metastatskih ćelija. S obzirom na prisutnost tipičnih lezija po celom telu, nemogućnost vertikalizacije pacijentkinje, nedostatka resursa za rekonstrukciju, i prisutnog recidiva agresivnog kutanog skvamoznog karcinoma, amputacija se smatrala optimalnim rešenjem. **Zaključak.** Kod pacijenata koji boluju od hereditarne epidermolize, sa dve ili više recidiva kutanog svamoznog karcinoma i uz dodatni nedostatak lokalnih mogućnosti hirurške rekonstrukcije, bez obzira na to što se radi o lokalizovanoj bolesti, amputacija može biti nevoljno, ali neophodno rešenje.

**Ključne reči:** epidermoliza; skvamozni karcinom; amputacija; recidiv

spectrum of phenotypes, ranging from severe cutaneous and extracutaneous involvement caused by deficiencies in key adhesion proteins to mild cutaneous fragility characterized by subtle molecular defects [1]. Epidemiological data regarding the incidence and prevalence of EB vary considerably across studies worldwide, and to date, epidemiological studies on IEB have been con-

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### Abbreviations

IEB	– inherited epidermolysis bullosa
EBS	– epidermolysis bullosa simplex
JEB	– junctional epidermolysis bullosa
DEB	– dystrophic epidermolysis bullosa
KEB	– Kindler epidermolysis bullosa
BMZ	– basement membrane zone
cSCC	– cutaneous squamous cell carcinoma
LN	– lymph node

ducted in Serbia. Based on 16 years of data collection in the United States, the overall incidence and prevalence of IEB were estimated at 19.57 per 1 million live births and 11.07 per 1 million population, respectively [2].

Four major classical types of IEB are recognized: epidermolysis bullosa simplex (EBS), junctional epidermolysis bullosa (JEB), dystrophic epidermolysis bullosa (DEB), and Kindler epidermolysis bullosa (KEB). The classification of IEB is complex, as mutations within the same gene may be inherited in either an autosomal dominant or recessive manner, resulting in distinct clinical phenotypes. Conversely, similar phenotypes observed in DEB and EBS may arise from mutations in different genes, which can also be inherited in either dominant or recessive forms [3]. The diagnosis of IEB is primarily based on clinical assessment, supported by skin biopsy with histopathological analysis and genetic testing to identify disease-specific mutations. Additional diagnostic tools, including immunofluorescence mapping and transmission electron microscopy, may further assist in subtype differentiation and disease characterization.

Damages occurring within or beneath the cutaneous basement membrane zone (BMZ) lead to chronic, fibrotic, and inflamed wounds that heal with scarring. Patients afflicted by IEB are therefore at a markedly increased risk of developing one or more cutaneous squamous cell carcinomas (cSCC), particularly at sites of long-standing, non-healing wounds and scarring. These tumors may result from genetic alterations that disrupt key regulatory pathways, leading to aberrant cell growth and malignant transformation within injured skin [4]. Potential pathogenic mechanisms include upregulation of basic fibroblast growth factor, mutations in the p53 gene, and reduced activity of natural killer cells [5]. In patients with recessive DEB, these cSCC are particularly aggressive and frequently represent the leading cause of mortality within [4].

In individuals with IEB, cSCC most commonly arises within chronic, non-healing ulcers located over bony prominences. Early detection of malignant transformation is often challenging, as cSCC may closely resemble typical chronic ulceration characterized by scarring and crusting. Similar to tumors arising in burn scars, EB-associated cSCC typically originate at the margins of chronic ulcers.

Although variations in age of onset, tumor localization, and carcinogenic mechanisms exist among different IEB subtypes, IEB-associated cSCC represent a valuable clinical model for studying the interconnected mechanisms driving carcinogenesis within a fibrotic and inflammatory environment.

### Case Report

A 21-year-old patient with IEB presented with tumor on her right leg. The lesion initially appeared as a small crust and progressively enlarged over time. Physical examination revealed an oval lesion located on the right lower leg below the knee measuring approximately 10 cm in maximum diameter and elevated up to 1 cm above the skin surface. The lesion was firm in consistency, brown in color, and covered with scaly crusts. In addition to the suspicious tumor lesion, multiple areas of de-epithelialization were observed both in the perilesional region and diffusely over the patient's body. The patient had previously undergone two surgical excisions of similar lesions in the same site (Ph: cSCC). Following these earlier interventions, the case was reviewed by the Oncology Committee, which recommended close clinical follow-up with regular assessment of local and locoregional status, without adjuvant therapy, due to the patient's underlying condition. At the time of this third recurrence, radiological imaging showed no evidence of bone infiltration. Ultrasonographic examination revealed a single enlarged right inguinal lymph node (LN). Partial biopsy of the lesion confirmed cSCC, while biopsy of the lymph node did not show evidence of metastatic involvement. The case was discussed at a multidisciplinary team meeting involving a plastic surgeon, orthopedic surgeon, oncologist, and psychologist. Vacuum-assisted closure (VAC) therapy was considered; however, it was deemed contraindicated due to the extreme skin fragility associated with IEB, which carries a high risk of additional tissue damage. Taking into account the presence of typical lesions in patients with IEB throughout the body, the patient's inability to achieve verticalization, the lack of reconstructive surgical options, and the repeated recurrence of aggressive carcinoma, limb amputation was determined to be the most appropriate therapeutic option. A supracondylar amputation of the lower right leg was therefore indicated and performed (**Figure 1**). The postoperative course was uneventful, with satisfactory wound healing and no complications (**Figures 2 and 3**). Unfortunately, due to the underlying disease and pre-existing joint contractures, which had prevented ver-



Figure 1. Supracondylar amputation of the lower right leg



Figures 2 and 3. Three months postoperatively

ticalization even prior to the amputation, prosthetic fitting of the lower limb was not feasible.

### Discussion

Inherited epidermolysis bullosa (IEB) is a heterogeneous group of disorders characterized by a wide spectrum of clinical severity, diverse inheritance patterns, and numerous causative genetic mutations. The most severe forms are associated with profound morbidity, including chronic pain, recurrent infections and inflammation, limb amputations, and reduced life expectancy [6]. Individuals afflicted by IEB have a markedly increased risk of developing cSCC, particularly at sites of chronic, non-healing wounds and scarred skin.

Published data indicate that patients with IEB develop cSCC at a significantly younger age compared with the general population, with a mean age at diagnosis of approximately 36 years versus around 80 years in non-IEB individuals [7].

Prognostic factors such as poor differentiation, tumor diameter greater than 2 cm, perineural invasion, and invasion beyond the subcutaneous fat are inconsistently reported in the literature, complicating the staging process. In particular, perineural invasion and depth of invasion are rarely addressed in the literature.

The preferred treatment involves performing a wide and deep surgical excision. Mellerio et al. recommended a minimum surgical margin of 2 cm around the tumor based on clinical assessment [8]. However, accurate delineation of tumor margins is often challenging and surgical margins are frequently limited by surrounding structures. Even when clear margins are achieved, complete disease control is not guaranteed. Surgical treatment is often aggressive, especially in advanced tumors, and prolonged wound healing is common. Consequently, limb amputation is frequently required [8]. Montaudie et al. reported that amputation was necessary in approximately 25% of IEB patients diagnosed with cSCC [7]. In the present case, amputation was performed after the second recurrence. Neoadjuvant radiotherapy may theoretically reduce tumor size and minimize surgical intervention; however, its use in patients with IEB requires extreme caution. The fragile skin and impaired regenerative capacity characteristic of IEB - particularly in generalized forms - significantly increase the risk of radiation-induced toxicity, delayed wound healing, and ulcer formation. Similarly, systemic chemotherapy with cytotoxic agents such as cisplatin combined with 5-fluorouracil or doxorubicin has shown some efficacy in advanced cSCC, but its substantial toxicity limits its use in patients with IEB and is generally not recommended [9].

In selected cases, a surgically aggressive approach, including amputation, may be necessary to minimize the risk of future recurrences. A crucial question remains: after how many tumor recurrences should amputation be considered the preferred therapeutic option? The answer is highly individualized and depends on multiple factors, including tumor stage and patient functional status. Early detection of regional lymph node metastases may improve prognosis. However, in IEB patients, lymph node enlargement is frequently caused by chronic inflammation or infection, increasing the risk of false-positive findings during staging. Systemic therapies, including conventional chemotherapy and newer targeted therapies may be considered in palliative settings, with careful evaluation of potential adverse effects. Psychological support is essential for patients with IEB and their families [10]. Additionally, mirror therapy may provide benefits for amputated patients by improving motor

function, manual dexterity, fine motor skills, and range of motion when practiced consistently over time [11].

### Conclusion

In patients with inherited epidermolysis bullosa who develop recurrent cutaneous squamous cell carcinoma and face limitations related to verticalization and local reconstructive surgery, limb amputation may represent a necessary last-resort treatment. This approach is aimed to reduce the risk of further disease progression and serious complications. The complexity of inherited epidermolysis bullosa-associated cutaneous squamous cell carcinomas underscores the need for multidisciplinary approach and the ongoing need of improved therapeutic options.

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