International Journal of Dermatology

Updates from medicine

Surgical management and oncological follow-up of cutaneous squamous cell carcinomas arising in epidermolysis bullosa patients

Alessia Paganelli[1,2], MD, Erminia Giordano[1], MD, Chiara Fiorentini[1], MD, Barbara Ferrari[1], MD, Camilla Reggiani[1,2], MD, Federico Garbarino[1,2], MD and Cristina Magnoni[1], MD, PhD

[1]Section of Dermatology, Modena University Hospital, Modena, Italy, [2]PhD Course in Clinical and Experimental Medicine, University of Modena and Reggio Emilia, Modena, Italy

Correspondence
Alessia Paganelli, MD
Modena University Hospital
Via del Pozzo 71, 41124 Modena (MO) - Italy.
E-mail: alessia.paganelli@gmail.com

Conflict of interest: None.

Funding source: None.

doi: 10.1111/ijd.16157

Abstract

Background Hereditary epidermolysis bullosa (EB) is a rare genodermatosis characterized by skin fragility and blistering of the skin and mucous membranes in reaction to minimal traumas. The development of cutaneous squamous cell carcinomas (cSCCs) is one of the most common medical complications in junctional and dystrophic forms of the disease. Complete surgical excision of cutaneous tumors represents the gold standard of treatment. However, not only recognition of cSCCs can be challenging in the affected skin but also wound closure after surgical excision poses a great therapeutic challenge in EB patients. The aim of our study was to analyze the postoperative outcomes of such patients in order to have a better knowledge of the main critical issues in their surgical management and oncological follow-up.

Methods We retrospectively identified a cohort of five EB patients treated at Modena University Hospital. Collected data included patient age and sex, date of cSCC diagnosis, relapses/recurrences, site of the neoplasm, number of surgical interventions, use of dermal substitutes, and postoperative infections.

Results A total of 26 cSCCs were detected in our cohort. Forty-one surgical interventions were necessary to achieve excision of cSCCs with clear margins, varying from 1 to 4 surgical sessions per cSCC. Dermal substitutes were used in most cases but carried a higher infectious risk.

Conclusions EB patients tend to develop numerous cSCCs that often relapse even after complete excision with clear margins. These results stress the importance of early cSCC diagnosis and strict postsurgical follow-up.

Introduction

Hereditary epidermolysis bullosa (EB) is a rare genodermatosis characterized by skin fragility and blistering.[1,2] EB is divided into four major types based on the mutated genes involved: EB simplex (EBS), junctional EB (JEB), dystrophic EB (DEB), and Kindler EB (KEB).[3] One of the most common complications is the development of non-Melanoma Skin Cancers (NMSCs), with cutaneous squamous cell carcinoma (cSCC) being particularly common in JEB and DEB patients.[4–6]

Early diagnosis of cSCCs is crucial and, for this reason, EB patients undergo periodic skin check-ups.[7,8] Surgical excision is the standard of care but can be complicated by both the difficulties in identifying the tumor margins and the impairment in the wound-healing process.[8–10] Skin substitutes—acellular dermal matrices in particular—are often used as postsurgical healing strategies to quicken the healing process and reduce scarring tissue.[11–13] These tumors impact patients' life in terms of both overall and disease-free survival: in fact, cSCCs tend to relapse easily and reduce patient life expectancy.[14,15]

The most recent guidelines for diagnosis and treatment of cSCCs in EB patients are based on expert consensus, but more data need to be collected in this setting.[16]

Materials and methods

A monocentric, retrospective analysis was performed on EB patients treated at the Dermatological Clinic of the Modena University Hospital. We included patients affected by EB with histologically diagnosed cSCCs and treated with surgical excision at our clinic, from inception to the present.

We collected the following clinical data for each subject: age and sex, date of cSCC diagnoses, number of cSCCs, relapses, site of the neoplasm, number of surgical interventions needed

for radical excision, use of dermal substitutes, and infections in the postoperative period.

Statistical analysis was performed with the STATA program, version 14 (StataCorp LP 4905 Lakeway Drive College Station, Texas 77,845 USA). Numerical data were expressed as mean and standard deviation or median and range as appropriate. Qualitative data were expressed as frequency and percentage. The chi-square test (Fisher's exact test) was used to examine the relation between qualitative variables. Survival analysis was done using the Kaplan–Meier method, and a comparison between two survival curves was done using the log-rank test. A P value of <0.05 was considered significant.

Results

In total, 26 cSCCs were detected in a cohort of five EB patients (three affected by DEB, two by JEB).

EB diagnosis was established with immunofluorescence mapping (IFM) and gene sequencing through new generation sequencing (NGS). All patients affected by DEB had mutations in the *COL7A1* gene. On the contrary, of the two subjects with JEB, one had *LAMB3* mutation while the *LAMC2* gene was mutated in the other patient.

All the cSCCs were located on limbs and extremities. Interestingly, while DEB patients developed nearly exclusively on lower limbs and feet, superior limbs and hands were the most common site of onset for cutaneous malignancies in the JEB group (Fig. 1).

The mean age at the first cSCC diagnosis was 34.74 years (range 27.5–40.4). Kaplan–Meier curve (Fig. 2) shows that no cSCCs were detected during the first two decades of life, while two patients were diagnosed with cSCC in their 20s, two in their 30s, and only one patient after the age of 40.

Three patients experienced at least one recurrence, despite complete excision of the neoplasm. Potentially, differences among patients could be linked to the different lengths of follow-up.

Ten cSCCs considered in the present study were recurrences, with six neoplasms being responsible for such results and some of them relapsing more than once. Relapse rates for cSCCs in our cohort of EB patients was 40% (Fig. 3). The mean recurrence time was 2.7 years (range 8.2–90.9 months).

The mean time free from disease after the first diagnosis, regardless of cSCCs being relapses or primary tumors, was nearly 1 year (11.88 months, range 0.49–51.98 months).

All the cSCCs diagnosed in the cohort of EB patients have been treated with surgical excision. A total of 41 surgical interventions were performed, varying from one to four surgical sessions per cSCC (mean 1.6).

As shown in Table 1, only 15 of the surgical procedures turned out to be radical at the first attempt (57.7%). More than one surgery was performed to achieve complete surgical removal of the tumor in nine cases. In two cases, no other interventions have been performed to date.

As for the surgical healing techniques, 10 cases were healed by secondary intention, while dermal substitutes were used in 31 cases (see Table 2). Of them, 24 were MatriDerm (58.54% of the cases), five Integra (12.2% of the cases), and two Hyalomatrix (4.87% of the cases). Interestingly, in the postoperative period, infections of the wound area occurred in eight cases (19.5%), all after dermal substitute positioning.

No significant differences between DEB and JEB patients were found in terms of clinical outcomes, postsurgical healing, infection, and relapse rates.

Discussion and conclusions

cSCCs are one of the most significant complications in the life of EB patients, especially in DEB and JEB forms.[17,18]

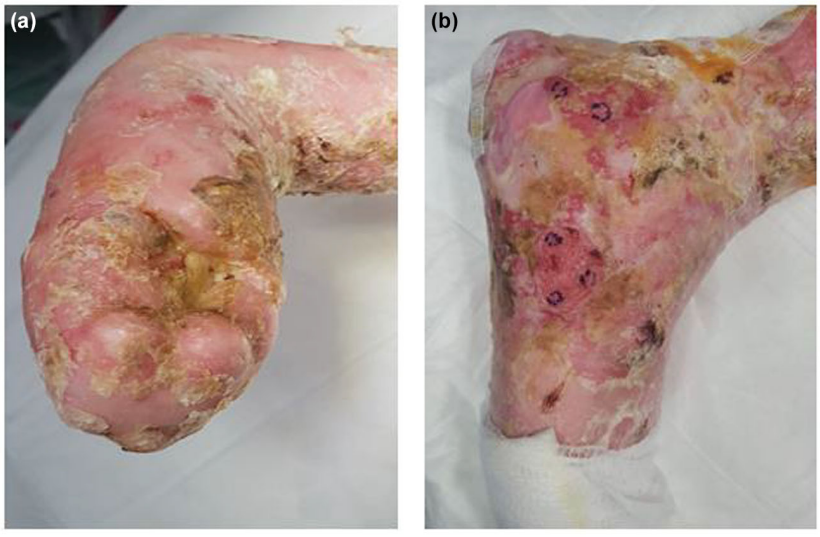

Figure 1 Clinical pictures of cSCCs in DEB (Panel a) and JEB (Panel b) patients

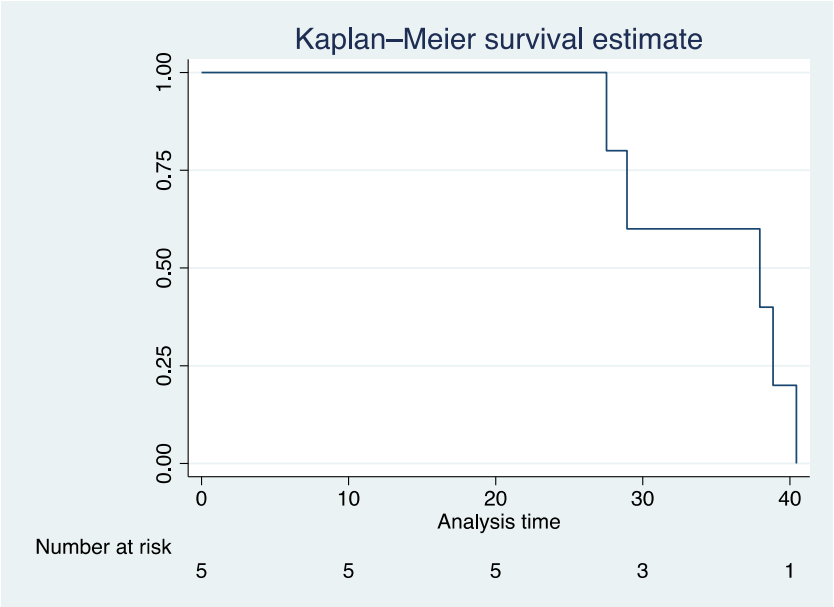

Figure 2 Kaplan–Meier curve of first cSCC diagnosis. The *y*-axis reports the total of EB patients. Patient age is represented on the *x*-axis

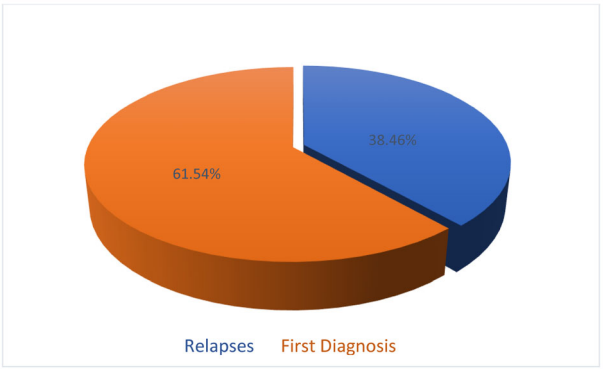

Figure 3 cSCCs in EB patients: primary tumors and recurrences

Table 1 Number of surgical interventions performed with relative percentages of successful radical excision

No. performed interventions per cSCC	Radical excision		
	No	Yes	Total surgeries
1	11	15	26
	26.83%	36.58%	63.41%
2	4	5	9
	9.75%	12.2%	21.95%
3	4	0	4
	9.75%		9.75%
4	0	2	2
		4.88%	4.88%
Total	19	22	41
	46.34%	53.66%	100%

Table 2 Wound closure strategies after cSCC surgical excision

Wound closure	Number of surgeries	Percentage
Healing by secondary intention	10	24.39%
MatriDerm	24	58.54%
Integra	5	12.2%
Hyalomatrix	2	4.87%
Total	41	100%

Interestingly, cSCCs in EB are usually well differentiated but at the same time very aggressive: various surgical interventions are sometimes needed before achieving clear margins, and frequent relapses are developed over time.

The young age of the first cSCC diagnosis in our cohort (34.7 years) is in line with other data present in the literature: in a review by H. Montaudié et al., the median age of onset of cSCC in EB-affected subjects was 36 years (range 27–48 years).[4] These findings confirm the very young age of onset of cSCCs compared with non-EB patients that are more likely to develop NMSCs in response to cumulative sun exposure. The early development of cSCCs in EB patients is presumably due to the chronic inflammatory milieu of the skin, linked to continuous blistering and rehealing, which carries an intrinsic risk of developing NMSCs.[17,19]

Surgical radicality is central to our study. As already underlined, tumor margin identification is very difficult in a setting of chronic wounds and scars, such as in EB-affected skin, and this gives the reason for the relatively low rates of complete excisions. In the Spanish casuistry, positive margin rates were even higher than in our experience (73.9% vs. 46.83% of cases).[5]

On the contrary, recurrence rates were consistent with the data reported by Castelo and coauthors (47.8%). However, the Spanish group described a median time to the first recurrence as 23.4 months, shorter than the one found in our center (32.5).[5] Probably such discrepancy could be better explained by differences in clear-margin excision rates.

Wound closure in these patients is obviously complicated by their disease and by the wound's dimension.[8] Healing by secondary intention is not only always achievable in larger wounds but also carries the risk of developing scars and adhesions that can worsen the patient quality of life.[7] The use of a skin graft is often not feasible due to the lack of disease-spared areas.[20] Nowadays, the use of dermal substitutes is the preferred wound closure strategy to quicken the healing process and reduce scar tissue formation.[11] The importance of limiting infections in these patients is crucial to improve both the clinical outcomes and the patient quality of life.[1,19] Despite the occurrence of several cases of infection, the presence of the dermal matrix did not seem to affect the response to antibiotic therapy, which was effective in 100% of cases.

The main limits of the present work are the retrospective and observational nature of data analysis and the small size of our cohort. Since EB is a rare disease, randomized trials or studies with high numbers of enrolled subjects are currently missing.

From our experience, the best approach for NMSCs in EB patients is still based on early diagnosis and removal and regular follow-up after surgery. In particular, our data suggest that an annual skin check-up should be performed from the age of 20 and should be shortened at least to every 6 months in case of previous cSCCs. However, more data are still needed in this setting, and multicentric studies among EB referral centers in different countries could lead to the development of more solid algorithms for EB surgical and oncological follow-up.

Acknowledgment

Open Access Funding provided by Universita degli Studi di Modena e Reggio Emilia within the CRUI-CARE Agreement.

References

1 Bardhan A, Bruckner-Tuderman L, Chapple ILC, *et al*. Epidermolysis bullosa. *Nat Rev Dis Primers* 2020; **6**: 78.
2 El Hachem M, Giancristoforo S, Diociaiuti A. Inherited epidermolysis bullosa. *G Ital Dermatol Venereol* 2014; **149**: 651–662.
3 Has C, Bauer JW, Bodemer C, *et al*. Consensus reclassification of inherited epidermolysis bullosa and other disorders with skin fragility. *Br J Dermatol* 2020; **183**: 614–627.
4 Montaudié H, Chiaverini C, Sbidian E, *et al*. Inherited epidermolysis bullosa and squamous cell carcinoma: a systematic review of 117 cases. *Orphanet J Rare Dis* 2016; **11**: 117.
5 Castelo B, Viñal D, Maseda R, *et al*. Epidemiology and natural history of cutaneous squamous cell carcinoma in recessive dystrophic epidermolysis bullosa patients: 20 years' experience of a reference centre in Spain. *Clin Transl Oncol* 2019; **21**: 1573–1577.
6 Yuen WY, Jonkman MF. Risk of squamous cell carcinoma in junctional epidermolysis bullosa, non-Herlitz type: report of 7 cases and a review of the literature. *J Am Acad Dermatol* 2011; **65**: 780–789.
7 Kim M, Li M, Intong-Wheeler LRA, *et al*. Epidemiology and outcome of squamous cell carcinoma in epidermolysis bullosa in Australia and New Zealand. *Acta Derm Venereol* 2018; **98**: 70–76.
8 Venugopal SS, Murrell DF. Treatment of skin cancers in epidermolysis bullosa. *Dermatol Clin* 2010;**28**:283–7, ix–x.
9 Kallini JR, Hamed N, Khachemoune A. Squamous cell carcinoma of the skin: epidemiology, classification, management, and novel trends. *Int J Dermatol* 2015; **54**: 130–140.
10 Waldman A, Schmults C. Cutaneous squamous cell carcinoma. *Hematol Oncol Clin North Am* 2019; **33**: 1–12.
11 Paganelli A, Reggiani C, Fiorentini C, *et al*. Surgical management of squamous cell carcinoma arising in patients affected by epidermolysis bullosa: a comparative study. *Int Wound J* 2020; **17**: 519–521.
12 Abboud L, Leclerc-Mercier S, Bodemer C, *et al*. Hand surgery in recessive dystrophic epidermolysis bullosa: our experience with dermal substitutes. *J Plast Reconstr Aesthet Surg* 2021; **S1748-6815**(21): 00315–00316.
13 Sibbald RG, Zuker R, Coutts P, *et al*. Using a dermal skin substitute in the treatment of chronic wounds secondary to recessive dystrophic epidermolysis bullosa: a case series. *Ostomy Wound Manage* 2005; **51**: 22–46.
14 Mallipeddi R. Epidermolysis bullosa and cancer. *Clin Exp Dermatol* 2002; **27**: 616–623.
15 Mallipeddi R, Keane FM, McGrath JA, *et al*. Increased risk of squamous cell carcinoma in junctional epidermolysis bullosa. *J Eur Acad Dermatol Venereol* 2004; **18**: 521–526.
16 Mellerio JE, Robertson SJ, Bernardis C, *et al*. Management of cutaneous squamous cell carcinoma in patients with epidermolysis bullosa: best clinical practice guidelines. *Br J Dermatol* 2016; **174**: 56–67.
17 Condorelli AG, Dellambra E, Logli E, *et al*. Epidermolysis bullosa-associated squamous cell carcinoma: from pathogenesis to therapeutic perspectives. *Int J Mol Sci* 2019; **20** (22): 5707.
18 Kim M, Murrell DF. Update on the pathogenesis of squamous cell carcinoma development in recessive dystrophic epidermolysis bullosa. *Eur J Dermatol* 2015; **25**: 30–32.
19 Koga H, Prost-Squarcioni C, Iwata H, *et al*. Epidermolysis bullosa acquisita: the 2019 update. *Front Med (Lausanne)* 2018; **5**: 362.
20 Yamada M, Hatta N, Sogo K, *et al*. Management of squamous cell carcinoma in a patient with recessive-type epidermolysis bullosa dystrophica. *Dermatol Surg* 2004; **30**: 1424–1429.