Dermatology Practical & Conceptual

Eruptive Non-melanoma Skin Cancers/Squamous Atypia Following Skin Surgery. Report of Two New Cases, Concise Review of the Literature With Special Emphasis on Treatment Options

Marco Adriano Chessa[1,2], Valentino Marino Picciola[3], Federica Filippi[1,2], Annalisa Patrizi[1,2], Cosimo Misciali[1,2], Bianca Maria Piraccini[1,2], Ignazio Stanganelli[4], Francesco Savoia[4]

1 IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy

2 Dermatology Unit, Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Bologna, Italy

3 University of Bologna, School of Medicine and Surgery, Bologna, Italy

4 Skin Cancer Unit, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy

Key words: Eruptive non-melanoma skin cancers, keratoacanthomas after cutaneous surgery, keratoacanthomas AND split-thickness skin graft, cutaneous squamous cell carcinomas AND split-thickness skin graft

Citation: Chessa MA, Marino Picciola V, Filippi F, et al. Eruptive non-melanoma skin cancers/squamous atypia following skin surgery. Report of two new cases, concise review of the literature with special emphasis on treatment options. *Dermatol Pract Concept.* 2022;12(4):e2022193. DOI: https://doi.org/10.5826/dpc.1204a193

Accepted: March 7, 2022; **Published:** October 2022

Funding: None.

Competing interests: None.

Authorship: All authors have contributed significantly to this publication.

Corresponding author: Federica Filippi, MD, Dermatology, Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Via Massarenti, 1 – 40138 Bologna, Italy Tel: +39051-2144849; Fax +39-0512144867; E-mail: federicafilippi8@gmail.com

ABSTRACT

Introduction: Eruptive cutaneous squamous cell carcinomas (ESCC), eruptive squamous atypia (ESA) and eruptive keratoacanthomas (EKA) are different terms used to describe the occurrence of multiple cutaneous squamous neoplasms after skin surgery, laser treatment, traumas, such as tattoos, and local or systemic medical treatments.

ESCC have been reported to arise at the sites of skin surgery, including the area affected by the primary tumor and split thickness skin graft (STSG) donor and recipient sites.

Objectives: The aim of this study is to report 2 additional cases of ESCC after skin surgery and make a critical revision of the literature, analyzing the clinical, histological features and outcomes of ESCC after cutaneous surgery.

Methods: Up to August 2021, according to our systematic review of the literature, we have collected 19 published articles and a total of 34 patients, including our 2 cases.

Results: The results of this review highlight five red flags that clinicians should consider: (i) lower and upper limbs represent the cutaneous site with the highest risk, representing 83,78% of the cases in the

literature; (ii) the median time to onset of ESCC is approximately 6 weeks; (iii) primary cutaneous squamous cell carcinomas were completely excised with free margins on histologic examination in the totality of the cases of the literature, and therefore ESCC should not be considered recurrences; (iv) any surgical technique involves a risk to promote ESCC; (v) treatment of ESCC includes medical treatment, surgery or combined surgical and medical treatment.

Conclusions: This review highlights 5 red flags which could support clinicians in the diagnosis and management of ESCC after skin surgery.

Introduction

Eruptive cutaneous squamous cell carcinomas (ESCC), eruptive squamous atypia (ESA) and eruptive keratoacanthomas (EKA) are different terms used to describe the occurrence of multiple cutaneous squamous neoplasms occurring after skin surgery, laser treatment, traumas, such as tattoos, local or systemic medical therapies. In this paper, we decided to use only the term ESCC.

ESCC have been reported to arise at the sites of skin surgery, including the area affected by the primary tumor and split thickness skin graft (STSG) donor and recipient sites [1-19]. The best therapeutic option for ESCC after surgery in our opinion is still a challenge.

Objectives

The aim of our study is to report 2 additional cases of ESCC after skin surgery and make a critical revision of the literature, analyzing the clinical, histological features and outcomes of ESCC after cutaneous surgery [18]. An overview of this rarely reported condition is provided, in order to raise awareness of this clinical entity and of the treatment options.

Methods

We identified studies indexed in PubMed from its inception to June 31, 2021. All papers reported in the present study involved human clinical studies, including case reports, case series and reviews. Search parameters included the terms "Keratoacanthomas after cutaneous surgery", "Keratoacanthomas AND STSG", "Cutaneous squamous cell carcinomas AND STSG", "Cutaneous squamous cell carcinomas after cutaneous surgery", "squamous cell carcinoma after Mohs Micrographic surgery (MMS)", "eruptive squamous cell carcinoma and surgery", "eruptive squamous atypia and surgery", "eruptive keratoacanthomas and surgery", "koebnerized cutaneous squamous cell carcinoma".

A subsequent review of the relative bibliographies aimed to identify any undetected reports. We collected sex, age, involved cutaneous area, surgical procedure, medical treatment and histopathology findings of primary cutaneous skin cancer of all the patients included in this review. Furthermore, we reported the time lapse from the primary surgery to the onset of ESCC, clinical and histological features, management, recurrences and outcome. In addition, we describe here our personal experience with two patients visited at the Skin Cancer Unit of Bologna between January 2012 and August 2021, who developed ESCC after cutaneous squamous cell carcinoma (CSCC) excision and reconstruction with STSG.

Results

Up to August 2021, according to our systematic review of the literature, we found only 19 published articles (Table 1).

A total of 34 ascertained patients, including our two cases, were included in this study, with a sex ratio F/M = 0.88, a mean age = 68.94 years (standard deviation [SD] = 13.6).

The main clinical features of the 34 patients diagnosed with ESCC after surgery are reported in Table 2.

The extremities (upper and lower limbs) were the sites most frequently involved by primary tumors, representing 83.78% of cases in our sample. The second most involved site was the head, with 13.51% of cases. Regarding our two patients, the first had a CSCC of the head and the second a cutaneous SCC of the right leg.

Histological examination of the primary skin cancer was consistent with a CSSC in 30/37 cases (81.08%), while basal cell carcinoma, actinic keratosis, malignant melanoma and lentigo maligna were detected in 7 cases (18.92%).

Different surgical techniques were used for the excision of the primary skin tumors, although classic fusiform excision, excision plus STSG, MMS and subsequent reconstruction with or without STSG were the most commonly performed procedures, in 32/37 cases (86.49%).

The main clinical features of the ESCC after skin surgery are reported in Table 3. The median time to the onset is approximately 6 weeks, and in 28/34 of the patients (82.35%) it occurred within 16 weeks from the primary surgery.

Surprisingly, ESCC occurred in the area of the skin affected by the primary tumor in 26/37 of the cases

Table 1. Eruptive non-melanoma skin cancers following skin surgery: literature review and our cases.

	Patients			First Skin Lesion				Eruptive NMSC					
Study and Year	N.	Case	Age, Sex	Area involved	Surgery procedure performed	Medical Treatment	Histopathology findings	Time Onset after SuRgery (Weeks)	Area involved	Histopathology findings	Surgical Treatment	Medical Treatment	Recurrence
Neilson et al, 1988 [1]	1		59, M	dorsum of his right ring finger (upper limbs)	Ex + STSG	None	SCCs	12	GDS	SCC	Ex	None	No
Clark et al., 2015	1		73, F	B Legs (lower limb)	Ex + STSG	None	SCCs	4	ExS + GDS	KASP	Ex + STSG	Acitretin 25 mg/d	Yes
Juhász and Marmur, 2014	1		82, F	R Shin (lower limb)	MMS + STSG	3 months of topical mupirocin + warm 2% milk compresses for loss of the graft, wound dehiscence, and persistent ulceration	KA	20	MMS site	KA	MMS	None	No
Bangash et al, 2009	5	1	81, F	L Wrist and Hand (upper limb)	MMS	None	SCC	4	MMS site	SCC	MMS	None	No
		2	63, M	L Hand (upper limb)	MMS	None	SCC	8	MMS site	SCC	MMS	None	No
		3	54, M	L occipital Ridge (head)	Ex	None	SCC	7	ExS	SCC with features of KA	MMS	None	No
		4	58, M	Left leg and R Elbow (upper and lower limb)	MMS	None	SCC; SCC	6	MMS site; MMS site	SCC; SCC	MMS	None	Yes, Yes
		5	55, F	L Hand (upper limb)	MMS + STSG	None	SCC	72	MMS site	SCC	MMS + STSG	Acitretin 10 mg/die	Yes

Table 1 continues

Table 1. Eruptive non-melanoma skin cancers following skin surgery: literature review and our cases. *(continued)*

	Patients			First Skin Lesion				Eruptive NMSC					
Study and Year	N.	Case	Age, Sex	Area involved	Surgery procedure performed	Medical Treatment	Histopathology findings	Time Onset after SuRgery (Weeks)	Area involved	Histopathology findings	Surgical Treatment	Medical Treatment	Recurrence
Hadley et al, 2009	3	1	67, M	Forearm (upper limb)	MMS	None	SCC	16	MMS site	KA	Ex	None	Yes
		2	70, F	Forearm (upper limb)	Ex	None	SCC	12	ExS	KA	MMS	None	Yes
		3	88, F	B Legs (lower limb)	S + Co + ED	None	KA	2	Treatment Site	KA	Co + ED	None	Yes
Haik et al, 2008	1		64, M	Left Big Toe (lower limb)	A + STSG	None	MM	6	GDS	SCC	Ex	None	No
Goldberg et al, 2004	6	1	72, M	L Leg and Finger (lower limb)	MMS	None	SSCs	6	MMS site	KA	MMS	None	Yes
		2	69, M	L Forearm. (upper limb)	MMS	None	SCC	4	MMS site	KA	MMS	None	No
		3	74, F	R Leg (lower limb)	MMS	Isotretinoin 40 mg/d for 30 days	SCC	3	MMS site	KA	Co + ED	Isotretinoin 40 mg/d	Yes
		4	79, M	R Forearm (upper limb)	MMS	None	LM	4	MMS site	KA	Ex	None	No
		5	71, M	R Thigh (lower limb)	MMS	None	SBCC	2	MMS site	KA	None	Isotretinoin (40 mg/d) for 1 month.	No
		6	75, M	R Forehead (head)	Co + ED	None	SCC	4	Treatment Site	KA	MMS	Isotretinoin (40 mg/d) for 1 month.	No
Hussain et al, 2010	1		52, M	R Hand (upper limb)	Ex + STSG	None	SCC	8	GDS	SCC	Ex + reconstructed with an islanded VeY advancement flap	None	No

Ponnuvelu et al, 2011	2	1	58, M	Left parietal scalp (head)	Ex + STSG	None	nodulocystic BCC	2	GDS	SCC	Ex	None	N/A
		2	88, F	left shin (lower limb)	Ex + STSG	None	KA	5	GDS	SCC	Ex + flap	None	No
Lee et al, 2017	1		95, F	R Shin (lower limb)	Ex + STSG	None	KA	20	Exs + GDS	KA	Co + ED	Imiquimod 5% cream application	Yes
Saltivig and Matzen, 2018	1		78, F	L Knee (lower limb)	Ex + STSG	None	MM	960	STSG primary excision site	Marjolin Ulcer	Ex	N/A	N/A
Kimyai-Asadi et al, 2004	1		76, M	R Hand (upper limb)	Ex	None	SCC	8	ExS	KA	Ex	None	No
Negase et al, 2016	1		78, F	Nose (head)	FTSG	None	AK	3	STSG primary excision site	KA	Ex	None	N/A
Marcus and Brady, 2021	1		39, F	L Thigh (lower limb)	MMS + STSG	None	SCC	12	GDS	SCC	MMS	None	N/A
Vergara et al, 2007	1		80, F	R Leg (lower limb)	Ex + STSG	None	KA	96	GDS	KA	Ex	None	Yes
L. Kearney et al, 2015	1		48, M	R Chest	Ex + STSG	None	MM	6	GDS	SCC	Ex	None	N/A
Morritt and Khandwala, 2012	1		82, F	L Leg (lower limb)	Ex + STSG	None	SCCs	117	ExS + GDS	SCCs	Ex	None	Yes
Gambichler 2021	2	1	49 F	Leg (lower limb)	MMS + STSG	None	SCC	3	MMS	SCC	Ex	None	Yes
		2	60 M	Back of the hand (upper limb)	MMS + STSG	None	SCC	3	MMS	SCC	Ex	None	Yes

Table 1 continues

Table 1. Eruptive non-melanoma skin cancers following skin surgery: literature review and our cases. *(continued)*

	Patients			First Skin Lesion				Eruptive NMSC					
Study and Year	N.	Case	Age, Sex	Area involved	Surgery procedure performed	Medical Treatment	Histopathology findings	Time Onset after SuRgery (Weeks)	Area involved	Histopathology findings	Surgical Treatment	Medical Treatment	Recurrence
Que et al 2019	1		62M	R and L legs (Lower limbs)	Ex	None	3 SCC	Not specified	Exs sites	Suspected eruptive squamous atypia	None	Intralesional 5-fluorouracil plus acitretin	No
Chessa et al, 2021	2	1	65,M	R occipital area of the scalp (head)	Ex + STSG	None	SCC	4	STSG primary excision site	SCC	Ex	Acitretin 25 mg/die	Yes
		2	80,F	R Leg (lower limb)	Ex + STSG	None	SCC	6	STSG primary excision site	SCC	Ex	acitretin 25 mg/daily and intralesional methotrexate 10 mg/weekly	No

AK = Actinic Keratosis; A = Amputation; B = Bilateral; CEMP = Cutaneous extramedullary plasmacytomas; Co = Courettage; ED = Electrodesiccation; Ex = Excision; ExS = Excision Site; F = Female; FTSG = Full-Thickness Skin Graft; GDS = Graft Donor Site; ; KA = Keratoacanthoma; KASP = Keratoacanthomatous atypical squamous proliferation; L= Left; N/A= data not available LM = lentigo maligna; M = Male; MM = Malignant Melanoma; MMS = Mohs Micrographic Surgery; MU = Marjolin Ulcer; N = Number of patients involved;
SCC = Squamous Cell Carcinoma; SG = Skin Graft; SGS = Skin Graft Site; Sh = Shave; STSG = Split-Thickness Skin Graft.
R= Right; SBCC = superficial basal cell carcinoma;

Table 2. Clinical findings of primary tumor in 34 patients diagnosed with eruptive squamous cell carcinomas/squamous atypia following skin surgery.

Findings	
Number of primary skin cancers excised	37
Patients with one primary skin cancer	32 (94.12%)
Patients with two primary skin cancer	2 (5.88%)
Sex	
Male	18 (52.94%)
Female	16 (47.06%)
Mean Age ± SD	68.94± 13.06 (39-95)
Cutaneous site involved	
Head and neck	5 (13.51%)
Upper limbs	12 (32.43%)
Lower limbs	19 (51.35%)
Chest	1 (2.70%)
Histopathology	
Squamous Cell Carcinoma	25 (67.56%)
Keratoacanthoma	5 (13.51%)
Melanoma	3 (8.12%)
Basal cell carcinoma	2 (5.41%)
Actinic Keratosis	1 (2.70%)
Lentigo maligna	1 (2.70%)
Treatment performed	
Excision	6 (16.22%)
Excision plus Split-Thickness Skin Graft	12 (32.43%)
Mohs Micrographic Surgery	10 (27.03%)
Mohs Micrographic Surgery plus Split-Thickness Skin Graft	5 (13.51%)
Courettage plus electrodesiccation	2 (5.41%)
Amputation plus Split-Thickness Skin Graft	1 (2.70%)
Excision plus Full-Thickness Skin Graft	1 (2.70%)

Table 3. Main features of eruptive squamous cell carcinomas/squamous atypia following skin surgery.

Features	
Number of primary skin cancers excised	37
Patients with one primary skin cancer	32 (94.12%)
Patients with two primary skin cancers	2 (5.88%)
Time onset after surgery median weeks	6 (2-960)
Cutaneous site involved by eruptive squamous cell carcinomas/squamous atypia	
Cutaneous site affected by primary tumor treated with Mohs micrographic surgery	14 (37.84%)
Cutaneous site affected by primary tumor treated with simple excision.	6 (16.22%)
Cutaneous site affected by primary tumor treated with split-thickness skin graft	4 (10.81%)
Cutaneous site affected by primary tumor treated with courettage plus electrodesiccation	2 (5.41%)
Graft donor site	8 (21.61%)
Cutaneous site affected by primary tumor treated with excision and graft donor site	3 (8.11%)
Cutaneous site affected by eruptive squamous cell carcinomas/squamous atypia	
Head and neck	3 (8.11%)
Upper limbs	10 (27,03%)

Table 3 continues

Table 3. Main features of eruptive squamous cell carcinomas/squamous atypia following skin surgery. *(continued)*

Features	
Lower limbs	11 (37.84%)
Donor site affected by eruptive squamous cell carcinomas/squamous atypia	
Lower limbs	13 (35.14%)
Histopathology of eruptive squamous cell carcinomas/squamous atypia	
Squamous cell carcinoma	18 (48.65%)
Keratoacanthoma	14 (37.84%)
Marjolin Ulcer	1 (2.70%)
Keratoacanthomatous atypical squamous proliferation	1 (2.70%)
Not performed histopathological examination	3 (8.11%)
Concordance between histological diagnosis of primary tumor and and eruptive squamous cell carcinomas/squamous atypia	
yes	17 (50.00%)
no	17 (50.00%)
Treatment performed	
Surgery without medical treatment	
Excision	13 (38.24%)
Excision plus flap	2 (5.88%)
Mohs Micrographic Surgery	10 (29.42%)
Courettage plus electrodesiccation	1 (2.94%)
Surgery associated with medical treatment	
Excision plus acitretin 25 mg/die	1 (2.94%)
Excision plus acitretin 25 mg/daily and intralesional methotrexate 10 mg/weekly	1 (2.94%)
Excision plus split-thickness skin sraft and acitretin 25 mg/die	1 (2.94%)
Mohs micrographic surgery plus split-thickness skin graft and acitretin 25 mg/die	1 (2.94%)
Mohs micrographic surgery plus isotretinoin 40 mg/die	1 (2.94%)
Courettage plus electrodesiccation plus imiquimod cream application	1 (2.94%)
Courettage plus electrodesiccation isotretinoin 40 mg/die	1 (2.94%)
Medical treatment without surgery	
Isotretinoin 40 mg/die without surgery	1 (2.94%)
Intralesional 5-fluorouracil plus acitretin	1 (2.94%)
Recurrences	
Yes	15 (40.54%)
No	17 (45.95%)
Not available	5 (13.51%)

(70.27%), the graft donor site (GDS) or both. All primary tumors in our series were completely excised, with free margins on histological examination. In our sample, cutaneous STSG was harvested from the lateral thigh in almost all patients and was therefore considered the only cutaneous donor site affected.

ESCC were histologically represented by CSCC and keratoacanthomas (KA) in 91.9% of cases while in 3 patients was not performed histopathological examination. The same histological diagnosis between the primary skin cancer and the ESCC was found in 50% of cases and eruptive KAs or CSCCs also appeared after excision of lentigo maligna or melanoma.

The surgical treatment of ESCC is extremely varied (Table 3). However, simple fusiform excision and MMS were the most used surgical techniques, comprising 62.16% of cases. Medical therapy was associated with surgery in 7/34 cases while two patients were treated with isotretinoin 40 mg/die without surgery and 1 patient was treated with intralesional 5-fluorouracil plus acitretin 20 mg daily (Table 3).

Of note, the paper from Que et al describe 30 cases of ESCC, but only one case is clearly and without doubts associated to a previous skin surgery and was added to our review [19].

The treatment was effective without recurrences in 17/37 cases; these patients were treated with surgery alone in 13 cases, combined surgical and medical treatment in 2 cases and with medical therapy in two cases. Isotretinoin 40 mg/die resulted effective alone and in combination with Mohs surgery [7]. Surgery combined with acitretin (25 mg/daily) plus intralesional methotrexate 10 mg/weekly was administered to the first our patient, favoring a complete resolution without recurrences (Figure 1).

Recurrences of ESCC were reported in 15/37 cases (10 treated with surgery alone and 5 treated with combined medical and surgical therapy). All 15 cases with recurrences were treated with a combination of surgery and medical therapy. Patients showed a complete resolution of ESCC recurrences at follow-up in 6/15 cases (40%). The following therapies proved effective on recurrences: 1 to 2 mL in intralesional administration of 50 mg/mL 5-fluorouracil (FU) [5,19]; acitretin (25 mg/day); combined intralesional 5-FU and methotrexate to reduce the toxicity of any single agent [5]; isotretinoin 40mg/die [7]; oral acitretin (20 to 25 mg/day) [10,15]; lastly our second patient was treated with surgery plus 25 mg/daily acitretin (Figure 2). In 5/34 cases data on recurrences were not available in the papers (Table 1).

Finally, 2/34 patients died, due to lung cancer in one case and CSSC metastases in 1 of our patients, who was also affected by chronic lymphatic leukemia [5].

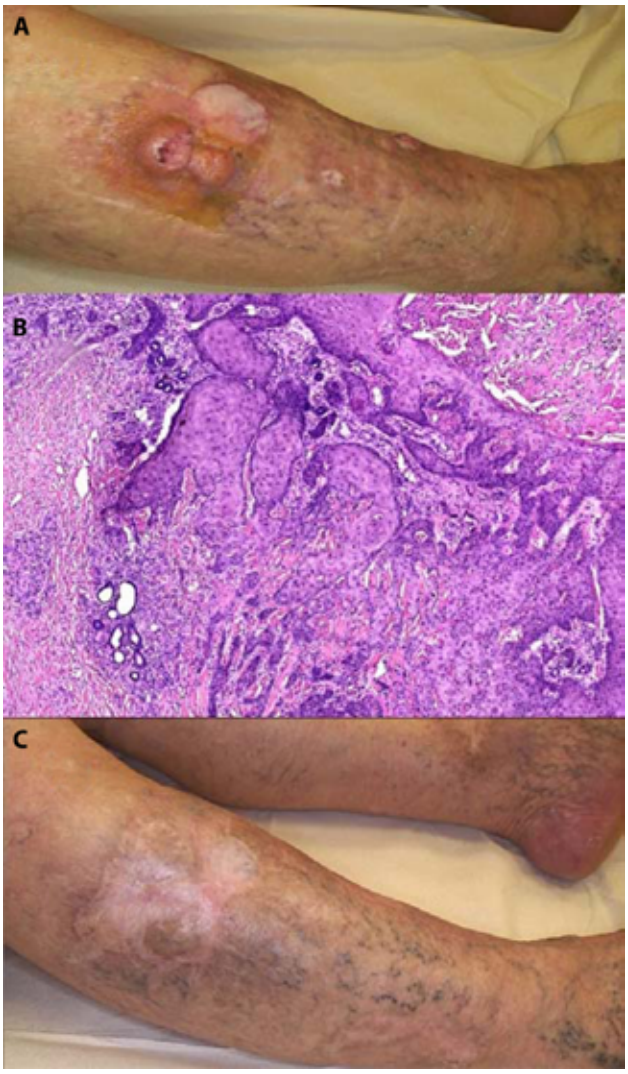

Figure 1. (A) Six weeks after local excision and repair with an STSG, 6 x 4.5 cm in diameter, of large squamous cell carcinomas of the right leg, three keratotic nodules appeared, two closes to the surgical wound and one a few centimeters far from it. (B) Histopathological examination eruptive keratotic nodules: proliferation of atypical keratinocytes extends into the reticular dermis. The nuclei are large, hyperchromatic, and pleomorphic, and the cytoplasm is eosinophilic (10 X H&E). (C) Complete healing after surgery and medical therapy with oral acitretin 25 mg/daily and intralesional methotrexate 10 mg/weekly after 8 months of treatment. No recurrences were observed at 2-year follow-up and regional lymph nodes were free from metastases.

Conclusions

The pathogenesis of ESCC is not clarified and is currently a matter of debate [18-23].

Local appearance of ESCC could be referred to residual cancer tissue following the excision of the primary tumor [21,22]. However, eruptive NMSC in skin graft donor sites have no local relation to the original tumor site, even if tumor cells could theoretically spread by direct contact (if the same needle was used to infiltrate the tumor and donor site) or systemically (via the blood or lymphatic vessels). Moreover, ESCC different from primary tumor excised, such as KAs after lentigo maligna or melanoma, have been reported [6,7,11,16].

The patient immune system must also be taken into account. Immunodeficiency induced by drugs or other diseases, such as hematologic disorders, may explain the propensity for the development of cancer, inducing a generalized 'field of cancerization' that can induce a Koebner phenomenon and the development of new cutaneous cancers in the site of surgery [17,21-23].

The presence of a chronic lymphatic leukemia may have been a predisposing factor in one of our patients for the development of ESCC soon after surgery, as well as a negative prognostic factor for the development of distant metastases, leading to exitus. Interestingly, the only patient that developed distant metastases after the development of ESCC had the primary CSSC located on the scalp, while none of the cases of ESCC reported in the Literature localized both on upper or lower extremities had a poor prognosis. This distinction can be important and to confirm this statement in the paper of Que et al reporting 30 cases of eruptive squamous atypia, without the specification if the onset was spontaneous, after surgery or other treatments o traumas, all the

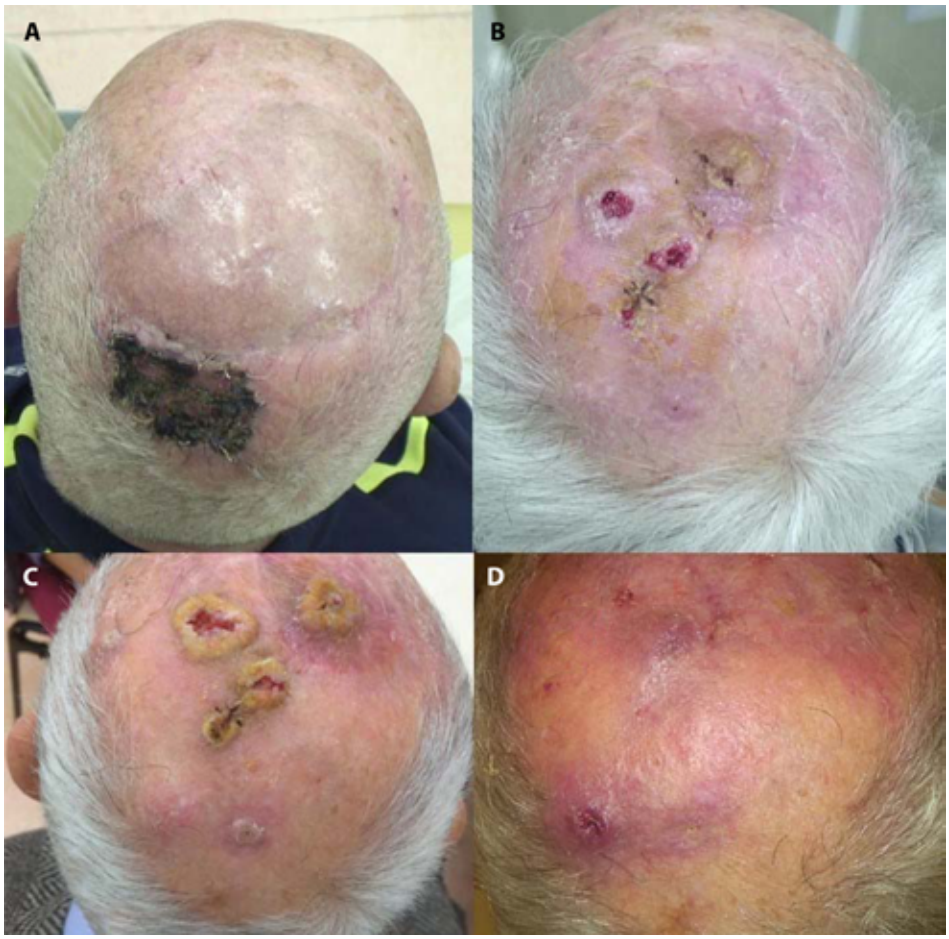

Figure 2. (A) Split thickness skin graft (STSG) on the scalp, 5 x 3.5 cm in diameter, after simple excision of ulcerated cutaneous squamous cell carcinomas (SCC) of the right occipital area of the scalp. (B) Thirty days after the removal of the stitches, on the site of the STSG, an erythematous firm papule appeared. (C) The papule quickly enlarged to form a nodule and then multiple keratoacanthoma-like lesions appeared. (D) Initial good response to surgery and acitretin 25 mg/die therapy, with only 1 residual nodule in the occipital area, which was surgically removed. Three months after the last surgery treatment, SCC metastases to the latero-cervical lymph nodes were detected both clinically and with ultrasound examination. The patient died 6 months later.

patients had a localization on upper or lower extremities or both and none developed metastases [19].

According to Nwabudike LC et al, ESCC could also be a perfect example of locus minoris resistentae as described by Ruocco [20,24]. An immunocompromised district can be defined as a regional destabilization of the neuro-immuno-cutaneous system, and surgical procedures, as well as the scars resulting from them, impair both lymph circulation and neuro-immune crosstalk in the traumatized area [24,25]. Gambichler and colleagues demonstrated in two patients affected by "koebnerized" CSCC that the wound healing processes can induce a proliferative stimulus and growth factors release, which could be able to promote the growth of pre-neoplastic keratinocytes and cancer formation, on the basis of pre-existing altered epigenetic pathways and cell cycle dysregulation [18].

The results of this review highlight five red flags that clinicians should consider in the diagnosis and management of ESCC after skin surgery. First of all, the extremities (lower and upper limbs) represent the cutaneous site with the highest risk, representing 82.35% of the cases in the literature.

The second point concerns the time of onset of ESCC, which is wide, ranging from 2 to 960 weeks. The median time to onset of ESCC is approximately 6 weeks, and in 28/34 (82.35%) of cases reported in the literature they appeared within 16 weeks from the primary cutaneous surgery.

The third point is that primary CSCC were completely excised with free margins on histologic examination in all cases of the literature, and therefore the ESCC reported were not considered recurrences. This concept has important legal implications.

The fourth point is that any surgical technique, including classic fusiform excision, excision plus STSG, MMS and subsequent reconstruction with or without STSG, involves a risk to promote ESCC, which can surprisingly affect both the area affected by the primary tumor and the graft donor site.

Large longitudinal surgery studies are necessary to evaluate the risk assessment of surgical technique and ESCC.

The fifth point is that the treatment of ESCC includes medical treatments, surgery or combined surgical and medical treatments. Que et al reported a 67% resolution rate using intralesional 5-fluorouracil for eruptive squamous atypia of the upper and lower limbs. However, 5-fluorouracil is chemotherapeutic agent that can be used only in hospital, it is off-label and much more difficult to obtain in Italy than intralesional methotrexate or oral acitretin. Moreover, Que et al have specified that it can be used only for lesions smaller than 15 mm, while over 15 mm of diameter, surgery is still considered the best choice. According to our review, ESCC recurrences are a medical challenge and have been treated combining surgical and medical treatment, with complete resolution in about one third of patients [5,7,10,15]. When using a nonsurgical treatment modality for ESCC, the concern of missing an aggressive CSSC is an important issue, that must be kept in mind, especially in sites different from the upper and lower extremities.

In conclusion, even though the pathogenesis remains unclear, this review highlights 5 red flags which could help support clinicians in the diagnosis and management of ESCC after skin surgery.

References

1. Neilson D, Emerson DJ, Dunn L. Squamous cell carcinoma of skin developing in a skin graft donor site. *Br J Plast Surg*. 1988;41(4):417-419. DOI: 10.1016/0007-1226(88)90086-0. PMID: 3293679.
2. Clark MA, Guitart J, Gerami P, Marks BR, Amin S, Yoo SS. Eruptive keratoacanthomatous atypical squamous proliferations (KASPs) arising in skin graft sites. *JAAD Case Rep*. 2015;1(5):274-276. DOI: 10.1016/j.jdcr.2015.06.009. PMID: 27051751. PMCID: PMC4809229.
3. Juhász MLW, Marmur ES. A Multiple Recurrent Keratoacanthoma of the Lower Leg After Repeated Wide-Excision and Mohs Micrographic Surgery. *Dermatol Surg*. 2018;44(7):1028-1030. DOI: 10.1097/DSS.0000000000001422. PMID: 29953419.
4. Bangash SJ, Green WH, Dolson DJ, Cognetta AB Jr. Eruptive postoperative squamous cell carcinomas exhibiting a pathergy-like reaction around surgical wound sites. *J Am Acad Dermatol*. 2009;61(5):892-897. DOI: 10.1016/j.jaad.2009.01.037. PMID: 19766351.
5. Hadley JC, Tristani-Firouzi P, Florell SF, Bowen GM, Hadley ML. Case series of multiple recurrent reactive keratoacanthomas developing at surgical margins. *Dermatol Surg*. 2009;35(12): 2019-2024. DOI: 10.1111/j.1524-4725.2009.01327.x. PMID: 19758354.
6. Haik J, Georgiou I, Farber N, Volkov A, Winkler E. Squamous cell carcinoma arising in a split-thickness skin graft donor site. *Burns*. 2008;34(6):891-893. DOI:10.1016/j.burns.2007.06.006. PMID: 17869430.
7. Goldberg LH, Silapunt S, Beyrau KK, Peterson SR, Friedman PM, Alam M. Keratoacanthoma as a postoperative complication of skin cancer excision. *J Am Acad Dermatol*. 2004;50(5):753-758. DOI: 10.1016/j.jaad.2003.11.065. PMID: 15097960.
8. Hussain A, Ekwobi C, Watson S. Metastatic implantation squamous cell carcinoma in a split-thickness skin graft donor site. *J Plast Reconstr Aesthet Surg*. 2011;64(5):690-692. DOI: 10.1016/j.bjps.2010.06.004. PMID: 20584636.
9. Ponnuvelu G, Ng MF, Connolly CM, Hogg FJ, Naasan A. Inflammation to skin malignancy, time to rethink the link: SCC in skin graft donor sites. *Surgeon*. 2011;9(3):168-169. DOI: 10.1016/j.surge.2010.08.006.
10. Lee S, Coutts I, Ryan A, Stavrakoglou A. Keratoacanthoma formation after skin grafting: A brief report and pathophysiological hypothesis. *Australas J Dermatol*. 2017;58(3):e117-e119. DOI: 10.1111/ajd.12501. PMID: 27273800.
11. Saltvig I, Matzen SH. Marjolin's ulcer in a 20 years old split thickness skin graft on the knee-A case report. *Int J Surg Case Rep*. 2018;42:102-103. DOI: 10.1016/j.ijscr.2017.11.059. PMID: 29241101. PMCID: PMC5730427.
12. Kimyai-Asadi A, Shaffer C, Levine VJ, Jih MH. Keratoacanthoma arising from an excisional surgery scar. *J Drugs Dermatol*. 2004;3(2):193-194. PMID: 15098978.
13. Nagase K, Suzuki Y, Misago N, Narisawa Y. Acute development of keratoacanthoma at a full-thickness skin graft donor site shortly after surgery. *J Dermatol*. 2016;43(10):1232-1233. DOI: 10.1111/1346-8138.13368. PMID: 27027399.
14. Marous M, Brady K. Cutaneous Squamous Cell Carcinoma Arising in a Split Thickness Skin Graft Donor Site in a Patient With Systemic Lupus Erythematosus. *Dermatol Surg*. 2021;47(8):1106-1107. DOI: 10.1097/DSS.0000000000002955. PMID: 33731573.
15. Vergara A, Isarría MJ, Domínguez JD, Gamo R, Rodríguez Peralto JL, Guerra A. Multiple and relapsing keratoacanthomas developing at the edge of the skin grafts site after surgery and after radiotherapy. *Dermatol Surg*. 2007;33(8):994-996. DOI: 10.1111/j.1524-4725.2007.33207.x.
16. L. Kearney, R.T. Dolan, N.A. Parfrey, E.J. Kelly. Squamous cell carcinoma arising in a skin graft donor site following melanoma extirpation at a distant site: A case report and review of the literature. JPRAS Open. 2015;3:35-38. DOI: 10.1016/j.jpra.2015.02.002
17. Morritt, D.G., Khandwala, A.R. The development of squamous cell carcinomas in split-thickness skin graft donor sites. *Eur J Plast Surg*. 32013;6:377–380. DOI:10.1007/s00238-012-0786-z.
18. Gambichler T, Rüddel I, Hessam S, Bechara FG, Stockfleth E, Schmitz L. Altered epigenetic pathways and cell cycle dysregulation in healthy appearing skin of patients with koebnerized squamous cell carcinomas following skin surgery. *J Eur Acad Dermatol Venereol*. 2018;32(9):1485-1491. DOI: 10.1111/jdv.14887. PMID: 29478287.
19. Que SKT, Compton LA, Schmults CD. Eruptive squamous atypia (also known as eruptive keratoacanthoma): Definition of the disease entity and successful management via intralesional 5-fluorouracil. *J Am Acad Dermatol*. 2019;81:111-122. DOI: 10.1016/j.jaad.2018.10.014. PMID: 31103317.
20. Nwabudike LC, Tatu AL. Reply to Gambichler T et al.: Altered epigenetic pathways and cell cycle dysregulation in healthy appearing skin of patients with koebnerized squamous cell carcinomas following skin surgery. *J Eur Acad Dermatol Venereol*. 2019;33(1):e3-e4. DOI: 10.1111/jdv.15084. PMID: 29797668.
21. Slaughter DP, Southwick HW, Smejkal W. "Field cancerisation" in oral stratified epithelium. Clinical implications

of multicentric origin. *Cancer.* 1953;6(5):963–968. DOI: 10.1002/1097-0142(195309)6:5<963::aid-cncr2820060515>3.0.co;2-q. PMID: 13094644.

22. Höckel M, Dornhöfer N. The hydra phenomenon of cancer: why tumors recur locally after microscopically complete resection. *Cancer Res.* 2005;65(8):2997-3002. DOI: 10.1158/0008-5472.CAN-04-3868. PMID: 15833823.
23. Vakharia PP, Nardone B, Schlosser BJ, Lee D, Serrano L, West DP. Chronic exposure to tetracyclines and subsequent diagnosis for non-melanoma skin cancer in a large Midwestern U.S. patient population. *J Eur Acad Dermatol Venereol.* 2017;31(12):e534-e536. DOI: 10.1111/jdv.14399. PMID: 28609551.
24. Ruocco V, Brunetti G, Puca RV, Ruocco E. The immunocompromised district: A unifying concept for lymphoedematous, herpes-infected and otherwise damaged sites. *J Eur Acad Dermatol Venereol.* 2009;23(12):1364-1373. DOI: 10.1111/j.1468-3083.2009.03345.x. PMID: 19548975.
25. Baroni A, Buommino E, Piccolo V, et al. Alterations of skin innate immunity in lymphedematous limbs: Correlations with opportunistic diseases. *Clin Dermatol.* 2014;32(5):592-598. doi: 10.1016/j.clindermatol.2014.04.006. PMID: 25160100.