Epidermal Tumors Arising on Donor Sites From Autologous Skin Grafts: A Systematic Review

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PRACTICE **POINTS**

- Donor site cutaneous squamous cell carcinoma (CSCC) and keratoacanthoma (KA) can be postoperative complications of autologous skin grafting.
- Surgical excision of donor site CSCC and KA typically is curative.

Common complications of skin grafting used to cover cutaneous defects include bleeding, infection, pain, and graft failure. Epidermal tumor development on graft donor sites in the postoperative period has been reported. We performed a systematic search of the literature for cases of epidermal tumors arising on skin graft donor sites in patients undergoing autologous skin graft surgery. Our results included the demographic and clinical characteristics of these cases. We also provide a discussion on the nature of these lesions.

Skin grafting is a surgical technique used to cover skin defects resulting from the removal of skin tumors, ulcers, or burn injuries.[1-3] Complications can occur at both donor and recipient sites and may include bleeding, hematoma/seroma formation, postoperative pain, infection, scarring, paresthesia, skin pigmentation, graft contracture, and graft failure.[1,2,4,5] The development of epidermal tumors is not commonly reported among the complications of skin grafting; however, cases of epidermal tumor development on skin graft donor sites during the postoperative period have been reported.[6-12]

We performed a systematic review of the literature for cases of epidermal tumor development on skin graft donor sites in patients undergoing autologous skin graft surgery. We present the clinical characteristics of these cases and discuss the nature of these tumors.

Methods

Search Strategy and Study Selection—A literature search was conducted by 2 independent researchers (Z.P. and V.P.) for articles published before December 2022 in the following databases: MEDLINE/PubMed, Web of Science, Scopus, Cochrane Library, OpenGrey, Google Scholar, and WorldCat. Search terms included all possible combinations of the following: *keratoacanthoma, molluscum sebaceum, basal cell carcinoma, squamous cell carcinoma, acanthoma, wart, Merkel cell carcinoma, verruca, Bowen disease, keratosis, skin cancer, cutaneous cancer, skin neoplasia, cutaneous neoplasia,* and *skin tumor.* The literature search terms were selected based on the World Health Organization classification of skin tumors.[13] Manual bibliography checks were performed on all eligible search results for possible relevant studies. Discrepancies were resolved through discussion and, if needed, mediation by a third researcher (N.C.). To be included, a study had to report a case(s) of epidermal tumor(s) that was confirmed by histopathology and arose on a graft donor site in a patient receiving autologous skin grafts for any reason. No language, geographic, or report date restrictions were set.

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The authors report no conflict of interest.

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Cutis. 2024 August;114(2):E6-E12. doi:10.12788/cutis.1079

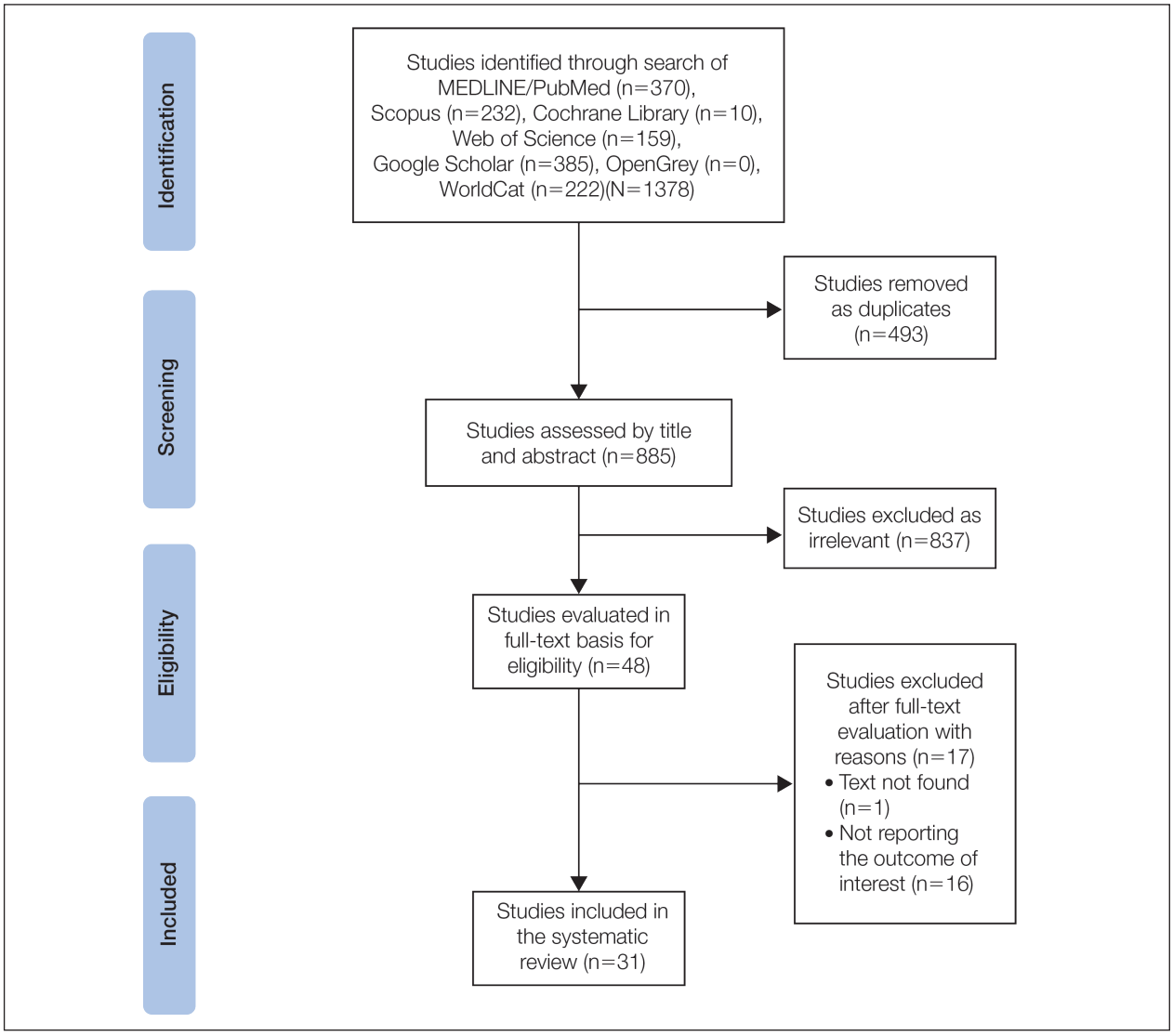
Data Extraction, Quality Assessment, and Statistical Analysis—We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[14] Two independent researchers (Z.P. and V.P.) retrieved the data from the included studies. We have used the terms *case* and *patient* interchangeably, and 1 month was measured as 4 weeks for simplicity. Disagreements were resolved by discussion and mediation by a third researcher (N.C.). The quality of the included studies was assessed by 2 researchers (M.P. and V.P.) using the tool proposed by Murad et al.[15]

We used descriptive statistical analysis to analyze clinical characteristics of the included cases. We performed separate descriptive analyses based on the most frequently reported types of epidermal tumors and compared the differences between different groups using the Mann-Whitney *U* test, $\chi 2$ test, and Fisher exact test. The level of significance was set at $P<.05$. All statistical analyses were conducted using SPSS (version 29).

Results

Literature Search and Characteristics of Included Studies—The initial literature search identified 1378 studies, which were screened based on title and abstract. After removing duplicate and irrelevant studies and evaluating the full text of eligible studies, 31 studies (4 case series and 27 case reports) were included in the systematic review (Figure).[6-12,16-39] Quality assessment of the included studies is presented in Table 1.

Clinical Characteristics of Included Patients—Our systematic review included 36 patients with a mean age of 63 years and a male to female ratio of 2:1. The 2 most



Flowchart for a systematic review and meta-analysis using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria for articles published before December 2022.

TABLE 1. Quality Assessment of Included Studies[a]

Reference (year)	Selection	Ascertainment	Causality	Reporting
McCormick and Miotke[11] (2023)	Low	Low	High	Low
Marous and Brady[32] (2021)	Low	Low	High	Low
Thomas et al[7] (2021)	Low	Low	Low	Low
Noori et al[9] (2018)				
Case 1	Low	Low	Low	Low
Case 2	Low	Low	High	Low
Case 3	Low	Low	Low	Low
de Moraes et al[16] (2017)	Low	Low	Low	Low
Ibrahim and Moisidis[26] (2017)	Low	Low	High	Low
Aloraifi et al[29] (2017)	Low	Low	High	Low
Nagase et al[17] (2016)	Low	Low	Low	Low
Lee et al[23] (2016)	Low	Low	Low	Low
Herard et al[25] (2016)	Low	Low	High	Low
Imbernón-Moya et al[22] (2015)	Low	Low	Low	Low
Kearney et al[27] (2015)	Low	Low	High	Low
Clark et al[28] (2015)				
Case 1	Low	Low	High	Low
Case 2	Low	Low	High	Low
Morritt and Khandwala[10] (2013)	Low	Low	Low	Low
Davis and Butler[39] (2012)	Low	Low	High	Low
Wright et al[6] (2012)	Low	Low	High	Low
Ponnuvelu et al[8] (2011)				
Case 1	Low	Low	High	Low
Case 2	Low	Low	High	Low
Hussain et al[37] (2011)	Low	Low	Low	Low
May and Patil[21] (2010)	Low	Low	Low	Low
Haik et al[12] (2008)	Low	Low	Moderate	Low
Griffiths[31] (2004)				
Case 1	Low	Low	High	Low
Case 2	Low	Low	High	Low

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TABLE 1. (continued)

Reference (year)	Selection	Ascertainment	Causality	Reporting
Tamir et al[35] (1999)	Low	Low	Low	Low
Taylor et al[18] (1998)	Low	Low	Low	Low
Hamilton et al[36] (1997)	Low	Low	High	Low
Abadi and Zurowski[30] (1994)	Low	Low	High	Low
de Delas et al[19] (1989)	Low	Low	High	Low
Neilson et al[20] (1988)	Low	Low	Low	Low
Hammond et al[24] (1987)	Low	Low	Moderate	Low
Wulsin[38] (1958)	Low	Low	High	Low
Dibden and Fowler[33] (1955)	Low	Low	High	Low
Jeremiah[34] (1948)	Low	Low	Low	Low

[a]The quality of the studies was evaluated across the following domains using the Murad quality assessment tool, with each domain classified into 1 of 3 quality levels (low, medium, or high): selection assesses the appropriateness of the study sample and selection process; ascertainment evaluates the methods used to ascertain or measure outcomes or exposures; causality examines the strength of evidence for causal relationships between variables; and reporting considers the clarity, completeness, and accuracy of the reported findings.[15]

common causes for skin grafting were burn wounds and surgical excision of skin tumors. Most grafts were harvested from the thighs. The development of a solitary lesion on the donor area was reported in two-thirds of the patients, while more than 1 lesion developed in the remaining one-third of patients. The median time to tumor development was 6.5 weeks. In most cases, a split-thickness skin graft was used.

Cutaneous squamous cell carcinomas (CSCCs) were found in 23 patients, with well-differentiated CSCCs in 19 of these cases. Additionally, keratoacanthomas (KAs) were found in 10 patients. The majority of patients underwent surgical excision of the tumor. The median follow-up time was 12 months, during which recurrences were noted in a small percentage of cases. Clinical characteristics of included patients are presented in Table 2.

Comparison of Variables Between CSCC and KA Groups—The most common diagnoses among the included patients were CSCC and KA. There were no significant differences between the groups in clinical variables, including age, sex, reason for grafting, time to occurrence, and rate of recurrence (Table 3).

Comment

Reasons for Tumor Development on Skin Graft Donor Sites—The etiology behind epidermal tumor development on graft donor sites is unclear. According to one theory, iatrogenic contamination of the donor site during the removal of a primary epidermal tumor could be responsible. However, contemporary surgical procedures dictate the use of different sets of instruments for separate surgical sites. Moreover, this theory cannot explain the occurrence of epidermal tumors on donor sites in patients who have undergone skin grafting for the repair of burn wounds.[37]

Another theory suggests that hematogenous and/or lymphatic spread can occur from the site of the primary epidermal tumor to the donor site, which has increased vascularization.[16,37] However, this theory also fails to provide an explanation for the development of epidermal tumors in patients who receive skin grafts for burn wounds.

A third theory states that the microenvironment of the donor site is key to tumor development. The donor site undergoes acute inflammation due to the trauma from harvesting the skin graft. According to this theory, acute inflammation could promote neoplastic growth and thus explain the development of epidermal tumors on the donor site.[8,26] However, the relationship between acute inflammation and carcinogenesis remains unclear. What is known to date is that the development of CSCC has been documented primarily in chronically inflamed tissues, whereas the development of KA—a variant of CSCC with distinctive and more benign clinical characteristics—can be expected in the setting of acute trauma-related inflammation.[13,40,41]

Based on our systematic review, we propose that well-differentiated CSCC on graft donor sites might actually be misdiagnosed KA, given that the histopathologic

TABLE 2. Clinical Characteristics of Included Patients (N=36)

Variable	Cases identified
Mean age (SD),[a] y	63 (16.9)
Sex[b]	32 (100)
Male	21 (67)
Female	11 (33)
Reason for skin grafting	32 (100)
Removal of skin tumors	22 (69)
Burn wounds	8 (25)
Other reasons	2 (6)
Donor site, n (%)	32 (100)
Thigh	28 (88)
Leg	2 (6)
Arm	1 (3)
Preauricular area	1 (3)
Median time to tumor development (IQR),[c] wk	6.5 (4-12)
Type of skin graft, n (%)	36 (100)
Split-thickness skin graft	33 (92)
Full-thickness skin graft	3 (8)

Variable	Cases identified
Histologic type, n (%)	36 (100)
CSCC	23 (64)
KA	10 (28)
BCC	1 (3)
MCC	1 (3)
KASP	1 (3)
Treatment, n (%)	29 (100)
Surgical excision	20 (69)
Pharmacologic	1 (3)
Radiotherapy	3 (10)
Combination	3 (10)
No treatment/ spontaneous involution	2 (7)
Median follow-up time (IQR),[d] mo	12 (6-19.5)
Recurrence, n (%)	22 (100)
Tumor recurred	2 (9)
No tumor recurrence	20 (91)

Abbreviations: BCC, basal cell carcinoma; CSCC, cutaneous squamous cell carcinoma; KA, keratoacanthoma; KASP, keratoacanthomatous atypical squamous proliferation; MCC, Merkel cell carcinoma.

[a]Age was reported for 33 patients.

[b]Sex was reported for 32 patients.

[c]Time to tumor development was reported for 29 patients.

[d]Follow-up time was reported for 20 patients.

differential diagnosis between CSCC and KA is extremely challenging.[42] This hypothesis could explain the development of well-differentiated CSCC and KA on graft donor sites.

Conclusion

Development of CSCC and KA on graft donor sites can be listed among the postoperative complications of autologous skin grafting. Patients and physicians should be aware of this potential complication, and donor sites should be monitored for the occurrence of epidermal tumors.

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TABLE 3. Comparison of Clinical Variables Between Patients Diagnosed With CSCC and Patients Diagnosed With KA

Variable	KA group (n=10)	CSCC group (n=23)	*P* value
Median age (IQR), y	71 (59.25-76.5)	58.5 (48.25-71.5)	.27
Males, n (%)	3 (30)	18 (78)	.07
Reason for skin grafting, n (%)			
Burn wounds	2 (20)	6 (26)	
Surgical excision of skin tumors	8 (80)	13 (57)	1
Median time to lesion occurrence (IQR), wk	6 (3.75-9)	7.5 (4.5-12)	.63
Recurrence, n (%)	1 (10)	1 (4)	.4

Abbreviations: CSCC, cutaneous squamous cell carcinoma; KA, keratoacanthoma.

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