

ONLINE FIRST

Malignancy and Chronic Leg Ulcers

The Value of Systematic Wound Biopsies: A Prospective, Multicenter, Cross-sectional Study

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Objective: To determine the frequency of skin cancers associated with chronic leg ulcers (CLUs) presumably of vascular origin and failing to heal (ie, increased wound area or depth) despite 3 months or more of appropriate treatment.

Design: Prospective cross-sectional study.

Setting: Ambulatory or hospitalized patients from 17 dermatology departments.

Patients: Between January 1, 2006, and May 31, 2008, a total of 144 patients consulted for CLUs, attributed to venous and/or peripheral arterial disease(s), increasing in wound size, that is, larger area and/or depth, despite appropriate standard treatment for at least 3 months.

Main Outcome Measures: At inclusion, at least two 6-mm punch biopsies, 1 at the wound edge and 1 in the wound bed, in the most clinically suspicious areas, were systematically performed. The primary end point was the skin cancer frequency diagnosed in at least 1 wound biopsy specimen obtained at inclusion.

Results: The 144 patients included had 154 CLUs. The overall skin cancer frequency in the CLUs was 10.4%: 9 squamous cell and 5 basal cell carcinomas, 1 melanoma, and 1 leiomyosarcoma; 56.3% had persisted for at least 3 years. Univariate analyses retained older age, abnormal excessive granulation tissue at wound edges, high clinical suspicion of cancer, and number of biopsies, but not wound area or duration, as being significantly associated with skin cancer in 1 or more biopsy specimens.

Conclusions: The combined primary ulcerated cancer or malignant transformation frequency was sufficiently high in CLUs referred to tertiary care centers to consider systematic biopsy of a wound refractory to 3 months or more of appropriate treatment.

Trial Registration: clinicaltrials.gov Identifier: NCT 00709631

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SKIN CANCERS ASSOCIATED with chronic leg ulcers (CLUs) are underrecognized^{1,2} and may result from CLU malignant transformation (Marjolin ulcer [MU]), usually toward squamous cell carcinoma (SCC), or may arise de novo and mimic the appearance of CLUs.³ The clinical appearance of CLU-associated skin cancers ranges from innocuous lesions to overtly exophytic growths. An MU occurs after a prolonged CLU duration.^{1,3,4} Thus, guidelines and experts recommend biopsying atypical CLUs for differential diagnoses⁵ or inappropriate clinical progression.^{2,6} Nevertheless, although the association between skin cancers and CLUs has been described in case reports and retrospective studies, it has never been evaluated pro-

spectively, to our knowledge. This trial was undertaken to determine the frequency of skin cancers associated with CLUs presumed to be of vascular origin and failing to heal despite at least 3 months of appropriate therapy.

METHODS

DESIGN OVERVIEW

This prospective observational trial, conducted between January 1, 2006, and May 31, 2009, including 1 year of follow-up, in 17 French medical centers, was performed in accord with the Declaration of Helsinki. The Institutional Review Board of Paris North Hospitals, Assistance Publique-Hôpitaux de Paris, and regulatory authorities approved its protocol. Informed consent was obtained before participant inclusion.

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Group Information: The names of the investigators from the Angio-Dermatology Group of the French Society of Dermatology are given at the end of this article.

SETTING AND PARTICIPANTS

The study population consisted of consecutive ambulatory or hospitalized patients, treated by or referred to the medical center for CLU management, with at least 1 CLU, lasting for 3 months or longer, diagnosed as being related to venous disease, associated or not with concomitant peripheral arterial disease, without evidence of healing (ie, increased wound area and/or depth) despite appropriate standard treatment for at least 3 months. All the patients should have been prescribed and followed standard therapy for at least 3 months, including compression therapy adapted to the ankle brachial index and dressings depending on the wound stage.⁷ Total wound duration was based on self-reporting. Wound area was estimated by measuring wound length and width.⁸ For inclusion, increased wound area during the past 3 months had to be documented in the patient's medical file. Inclusion was considered at the first consultation if the wound area(s) had increased during the past 3 months and if adequate wound care, compression, and treatment compliance were confirmed. Otherwise, patients were observed for 3 months at the medical center before enrollment in our study was considered. The exclusion criteria were ongoing systemic diseases known to be associated with pyoderma gangrenosum or necrotizing vasculitis or known to delay wound healing (eg, uncontrolled cardiac, renal, or hepatic insufficiency; hypertensive leg ulcer; calciphylaxis; foot ulcer; corticosteroid, cytotoxic drug, or immunosuppressant drug use during the preceding 3 months; and noncompliance with standard treatment).

STUDY PROCEDURES

Information was obtained during medical history taking, physical examinations, and medical record reviews. All patients who met the enrollment and exclusion criteria and who agreed to participate were assessed for their medical history and treatments and underwent a physical examination. When several CLUs were present, all that fulfilled the inclusion criteria were included. The following information was recorded: sociodemographics, concomitant illness(es), medications used, echo Doppler examination findings, total CLU duration, CLU cause (venous, with or without arterial component) and location, and 1 or more abnormal features, including exophytic and exuberant granulation tissue at the wound edge or in the wound bed, excessive bleeding, and pain. The ankle brachial index was systematically determined at inclusion if peripheral pulses were absent. The investigator noted as low or high the clinical suspicion of ulcerated skin cancer or an MU, considering physical examination findings and the patient's history.

At least two 6-mm punch biopsies, 1 at the wound edge and 1 in the wound bed, both in the most clinically suspicious areas, were systematically performed, and the specimens were transported in a 10% formalin solution to the investigator's pathology laboratory. Each investigator decided on the subsequent CLU investigations (eg, additional biopsies) and treatment, according to standard care. At 12 months of usual follow-up, the investigator confirmed (or refuted) the final diagnosis (CLU or cancer) and cancer outcomes.

Data were collected in accord with good clinical practice guidelines to ensure accuracy and integrity. During the study, a qualified monitor verified the accuracy and completeness of the recorded data at each participating center.

OUTCOMES AND MEASUREMENTS

The primary end point was the frequency of skin cancer diagnosed in at least 1 wound biopsy specimen obtained at study inclusion.

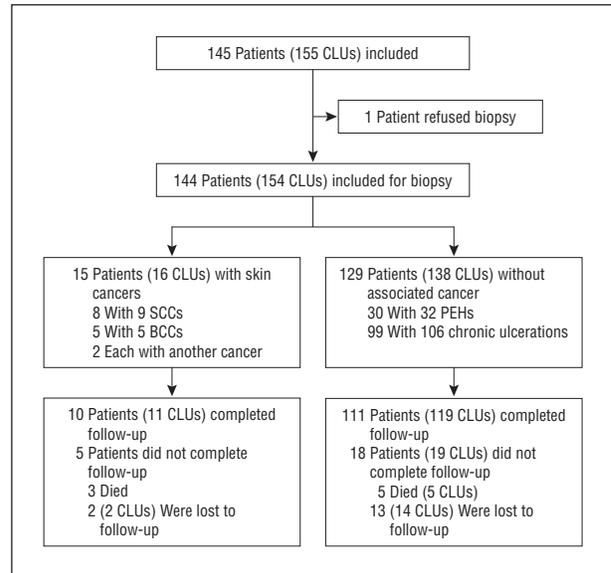


Figure. Flow diagram of patients through the trial. BCC indicates basal cell carcinoma; CLU, chronic leg ulcer; PEH, pseudoepitheliomatous hyperplasia; and SCC, squamous cell carcinoma.

STATISTICAL ANALYSES

A sample size of 150 patients was chosen to enable estimation of the skin cancer frequency with an associated 2-sided 95% CI of $\pm 3.5\%$ for a frequency of approximately 5% and of $\pm 4.8\%$ for a frequency of approximately 10%.

Possible independent predictors of cancer were first identified by univariate analysis using the *t* test or the Mann-Whitney test for continuous variables (according to their statistical distribution) or the χ^2 test for qualitative variables. Because some patients' multiple ulcers introduced a certain degree of nonindependence between the observations, logistic regression with a random effect (ie, the patient) was used to obtain a more precise estimate of the odds ratios and *P* values. Similarly, nonindependence of the observations was also considered when calculating sensitivity, specificity, and positive or negative predictive values for qualitative variables identified as being associated with skin cancers. According to the rules of Peduzzi et al,⁹ the small number of events did not allow multivariate logistic regression analysis. All the analyses were made using a commercially available software program (SAS, version 9.2; SAS Institute, Inc).

RESULTS

This study included 155 CLUs on 145 patients, but 1 patient withdrew his consent before undergoing biopsy, leaving 154 CLUs on 144 patients (**Figure**). Patients with skin cancer were significantly older than those without skin cancer (mean [SD] age, 82.2 [5.8] vs 75.2 [12.7] years; *P* = .03). No significant sex effect was found (80% of patients with skin cancers and 61% without were women, *P* = .17). The CLU characteristics are given in **Table 1**. The overall skin cancer frequency in the CLUs was 10.4%: 9 SCCs, 5 basal cell carcinomas (BCCs), and 2 nonepithelial skin cancers (1 melanoma and 1 leiomyosarcoma). Of the 9 SCCs, 5 were well differentiated, 3 were moderately differentiated, and 1 was verrucous type, with pseudoepitheliomatous hyperplasia (PEH)

Table 1. Characteristics of the 154 CLUs in This Study

Characteristic	Skin Cancer		OR (95% CI)	P Value ^a
	Absent	Present		
CLUs, No.	138	16	NA	NA
Area, mean (SD), cm ²	88.7 (104.4)	99 (195)	NA	.29
Duration, mean (SD), mo	72.2 (84.9)	67.4 (59.5)	NA	.86
Relapsing disease, No. (%)	45 (32.6)	5 (31.3)	1.06 (0.34-3.3)	.92
Located on sun-exposed areas, No. (%)	77 (55.8)	9 (56.3)	1.00 (1.00-1.00)	.65
Venous origin, No. (%)	115 (83.3)	12 (75.0)	NA	NA
Abnormal granulation tissue, No. (%)				
At the wound edge	48 (34.8)	15 (93.8)	25.05 (3.51-178.67)	.001
In the wound bed	34 (24.6)	13 (81.3)	12.76 (3.51-46.350)	<.001
Abnormal bleeding, No. (%)	13 (9.4)	4 (25.0)	3.22 (0.89-11.57)	.07
Abnormal pain, No. (%)	37 (26.8)	5 (31.3)	1.23 (0.42-3.57)	.71
High clinical suspicion, No. (%)				
CLU transformation	12 (8.7)	9 (56.3)	14.44 (4.31-48.31)	<.001
Ulcerated skin cancer	5 (3.6)	6 (37.5)	16.4 (4.18-64.3)	<.001
No. of biopsies per wound, mean (SD)	2.6 (1)	2.1 (0.9)	0.2 (0.1-0.6)	.01

Abbreviations: CLU, chronic leg ulcer; NA, not applicable; OR, odds ratio.
^aBy the Mann-Whitney test for continuous variables.

at the biopsied ulcer edge. Granulation tissues at the wound edge and in the wound bed of 13 of 16 skin cancers were abnormal, but the biopsy findings were not systematically positive at both sites. Three of 9 SCCs, all 5 BCCs, and the leiomyosarcoma were located in sun-exposed areas on the leg (anterior, external, or posterior part of the leg). None of the skin cancers was at a metastatic stage when biopsied. Histologic examination of the 154 CLUs found PEH in 32 (20.8%).

At 1 year of follow-up, of the 8 patients with 9 SCCs, 4 were in complete remission: 3 underwent surgical excision and 1 had surgical excision and radiotherapy. Of the other 4 patients, 1 treated with radiotherapy died of carbon monoxide poisoning before the end of the study, 1 received chemotherapy and radiotherapy and was still being treated at 1 year of follow-up, and 2 were not treated because of other comorbidities and older age. Of the 5 patients with BCC, 2 were in complete remission after surgical excision, 1 died of septic shock, and 2 had been lost to follow-up. The patients with melanoma and leiomyosarcoma had undergone surgical excision: 1 was in remission and the other died of pneumonia. Regarding CLUs exhibiting PEH histologic features, 1 patient died before the end of follow-up, 5 patients were lost to follow-up, and the diagnosis was unchanged for the remaining 24 patients (26 CLUs). Regarding the 106 CLUs that were neither skin cancer nor PEH, 8 patients were lost to follow-up (9 CLUs) and 4 patients, each with 1 CLU, died before the end of the study. The diagnoses for the 92 remaining CLUs (86 patients) were unchanged at 1 year, leaving only 1 CLU (1 patient) finally diagnosed with SCC after a large surgical biopsy specimen was obtained because of exophytic granulation tissue extension.

Of the 16 skin cancers associated with CLUs, the CLUs had persisted for longer than 3 years (range, 3 months to 15 years) for 56.3% of them (6 of 9 SCCs, 2 of 5 BCCs, and 1 of 2 other cancers), but, to our knowledge, none of these lesions had undergone biopsy before inclusion. Considering the clinical diagnosis at inclusion and the

wound duration, 6 of 9 SCCs and 1 of 5 BCCs were long lasting (>5 years) and were highly suspected of being CLU malignant transformation. Two BCCs and the melanoma had lasted for less than 5 years and were highly suspected of being ulcerated cancer misdiagnosed as CLU. For the other skin cancers (3 of 9 SCCs, 2 of 5 BCCs, and the leiomyosarcoma), it was impossible to definitively decide between CLU malignant transformation and ulcerated cancer misdiagnosed as CLU. Univariate analyses retained older age, abnormal excessive granulation tissue at the wound edges, high clinical suspicion of ulcerated skin cancer or an MU, and number of biopsies as being significantly associated with skin cancer in at least 1 biopsy specimen. Neither wound area ($P=.3$) nor wound duration ($P=.9$) was significantly associated with skin cancer.

Abnormal excessive granulation tissue and its location at the wound edge seemed to be highly sensitive variables for skin cancer; high clinical suspicion of CLU transformation, high clinical suspicion of ulcerated skin cancer, and abnormal bleeding seemed to be highly specific variables for skin cancers associated with CLU (**Table 2**).

COMMENT

In this prospective study, 16 of 154 nonhealing CLUs (10.4%) were associated with skin cancer. Dermatologists' patient recruitment and the setting of the study in tertiary care centers might partially explain this high rate. The fact that all the investigators were dermatologists could also explain the lesion targeting and the small number of biopsies of suspected malignant as opposed to non-malignant CLUs. The relative risk of CLU malignant transformation was retrospectively estimated to be 5.8 by matching Swedish registries of patients with CLUs and SCC registries.⁴ In Australia, which has the world's highest cancer rate, skin cancers were retrospectively associated with 2.2% of biopsied CLUs in a tertiary leg ulcer

Table 2. Sensitivity, Specificity, and Positive (PPV) and Negative (NPV) Predictive Values

Variable	OR (95% CI)			
	Sensitivity	Specificity	PPV	NPV
High clinical suspicion of				
CLU transformation	59.5 (31.8-82.3)	91.2 (85.1-95.0)	42.0 (21.7-65.4)	95.4 (90.1-98.0)
Ulcerated skin cancer	37.8 (16.7-64.9)	96.4 (91.4-98.5)	54.6 (25.3-81.0)	93.3 (87.6-96.5)
Abnormal granulation tissue				
At the wound edge	93.9 (64.9-99.2)	64.9 (55.9-72.9)	23.5 (14.1-36.4)	98.9 (92.3-99.9)
In the wound bed	81.3 (53.3-94.3)	75.9 (67.4-82.8)	27.3 (15.6-43.4)	97.2 (91.5-99.1)
Abnormal bleeding	25.0 (9.0-53.0)	90.5 (84.2-94.5)	23.4 (8.7-49.6)	91.5 (85.2-95.3)

Abbreviations: CLU, chronic leg ulcer; OR, odds ratio.

clinic; 75% of them were BCCs and 25% SCCs, that is, the same percentages as for whole-body surface, indicating that these SCCs were mostly ulcerated skin cancers misdiagnosed as CLUs.² In a retrospective review¹⁰ of 75 CLU biopsy specimens, carcinoma was detected in 13 patients when biopsies had been performed for 2 indications: CLUs that had developed suspicious carcinoma features and CLUs that had no suspicious features other than nonhealing.

Nevertheless, retrospective studies might have underestimated the risk of the skin cancer–CLU association, as biopsies preferentially target exophytic growth or irregular wound edges rather than resistance to appropriate therapy.¹ Regardless of the definition of resistance to treatment, the period of nonhealing that justifies wound biopsy is still being debated in the literature.¹⁰ Some researchers¹¹ recommend biopsying all ulcers without evidence of healing after 2 weeks of standard treatment. However, recent guidelines^{5,6} recommend biopsying after 6 weeks to 3 months of nonhealing, but how these times were determined was not specified.

The protocol to follow for these patients represents a real challenge, as CLUs affect 0.5% to 1% of the general population,¹² and the results of several studies¹³⁻¹⁵ indicated that many of them will have prolonged healing, despite best medical practices. For this study, we chose to biopsy CLUs, presumed to be of vascular origin, after at least 3 months of appropriate treatment, as it seems to be a reasonable threshold in our practice and in the literature, to evaluate the therapeutic response of long-lasting CLUs, which are preferentially referred to tertiary care centers.^{6,13}

The mean wound duration was approximately 5 years in this study, underscoring that long-lasting CLUs are resistant to standard care and are more frequently referred to tertiary care centers than are “routine” CLUs, healing in a few months.^{7,13,16} This prolonged preference time also suggests that CLU biopsy indications are probably not well known by primary care providers. One limitation to performing biopsy might reflect the physician’s fear of worsening wound outcome. However, as recently shown,¹¹ wound biopsy is a safe procedure that does not aggravate the CLU healing process, and biopsy sites heal within a few weeks.

In this study, wound duration was not associated with the skin cancer risk because systematic biopsies detected CLU malignant transformations and ulcerated car-

cinomas mimicking CLU and because included CLUs were, by definition, resistant to treatment and, thus, mainly large and long lasting. The frequency of such degeneration into an MU is debated in the literature and, for some researchers, such progression can be diagnosed only when a previous negative tissue biopsy finding is available or a wound persists for more than 3 years.⁴ All 5 BCCs identified herein were located on sun-exposed areas of the leg, and 4 of them may be ulcerated BCC mimicking CLU. Nevertheless, the absence of previous negative biopsy findings cannot rule out the possibility of their malignant transformation. With the increasing prevalence of skin cancers in developed countries, and considering that the legs are sun-exposed areas, it is likely that ulcerated skin cancers mimicking CLUs may increase in prevalence during the coming decades.

No significant association was noted between cancer and excessive bleeding, abnormal pain, or wound location, possibly because of the relatively low number of skin carcinomas identified. Increased pain, exudates, or odors may be features of CLUs that are too common to prompt wound biopsy.¹⁰ On the other hand, abnormal excessive granulation tissue at the wound edges was significantly associated with skin cancer. These results are in accord with those of a previous retrospective study¹ of 85 CLU malignant transformations, for which 96% of the biopsies had been performed because of abnormal tissue granulation or inappropriate clinical progression. Almost 21% of the included CLUs exhibited PEH, reflecting the wound’s inflammatory healing process. The question of whether long-standing PEH can undergo malignant transformation remains unanswered.¹⁷ Careful scrutiny and follow-up of these CLUs may be required, with repeated biopsies if necessary, particularly when an exophytic mass develops in the wound or clinical progression is inappropriate.²

The combined primary ulcerated cancer or malignant transformation frequency was sufficiently high in patients with CLUs referred to tertiary care centers to seek dermatologic advice and consider systematic biopsy of a wound refractory to 3 months of appropriate treatment.

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