Frequency of Malignant Neoplasms in 257 Chronic Leg Ulcers

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BACKGROUND Chronic leg ulcers are one of the most common medical conditions and are a substantial source of morbidity.

OBJECTIVES To investigate the prevalence of skin cancer mimicking leg ulcers.

PATIENTS AND METHODS This observational study included all patients with a clinical diagnosis of chronic leg ulcers (CLU) admitted to the Wound Care Unit, Division of Dermatology, University of Bologna, between March 2008 and February 2011. Patients' general health was assessed, and skin biopsy and vascular Doppler of the lower limbs were performed.

RESULTS Two hundred fifty-seven patients ages 45 to 98 with CLU were included. Skin biopsies were performed in all patients. Pathologic results showed that 10 patients had ulcerative lesions of neoplastic origin. Surgical excision was performed in all patients with neoplasms. After at least 1 year of follow-up, no recurrences were observed.

DISCUSSION AND CONCLUSION Our findings highlight the important role of systematic biopsies in diagnosing ulcerated tumors of the lower legs and indicate a high prevalence of large ulcerated basal cell carcinomas.

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Chronic leg ulcers (CLU), one of the most common medical conditions, are a substantial source of morbidity and can be difficult to treat. Between 1.5 and 3 per 1,000 people have active leg ulcers. Prevalence increases with age to approximately 20 per 1,000 in people age 80 and older.[1] Intractable ulcers are often due to patients' general health problems, such as diabetes mellitus, arterial and venous vasculopathy, eczema, vasculitis, cutaneous polyarteritis nodosa, rheumatoid arthritis, and hyperuricemia. The precancerous potential of CLU has been theorized in several reports, hence other authors have considered the association with skin cancer to be coincidental.[2,3]

Two hundred fifty-seven consecutive patients with CLU were enrolled. Doppler ultrasound of the lower limbs and histologic examination were performed to investigate the origin of CLU and the frequency of neoplastic lesions.

Patients and Methods

The study population consisted of consecutive ambulatory or hospitalized patients referred to the Wound Care Unit of the Department of Dermatology, University of Bologna, between March 2008 and February 2011. Each patient had at least one CLU, lasting from several months (≥ 6) to years clinically diagnosed or previously treated by other physicians as being related to vascular disease.

All patients who agreed to participate in the study underwent a general health assessment with

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laboratory investigation (full blood cell count, biochemistry profile, immunoglobulin levels, protein electrophoresis, and C-reactive protein) and hemodynamic evaluation of the lower limbs, with arterial and venous Doppler ultrasound.

For each patient, the ulcerated lesion was evaluated with a swab for bacteriologic culture analysis and two biopsies using a 3-mm punch, one on the bed and the other on the border of the ulcer. The specimens were transported in a 10% formalin solution to the pathologic laboratory of our Dermatologic Division.

Data were collected in accordance with good clinical practice guidelines to ensure accuracy and integrity.

Results

Two hundred fifty-seven Caucasian patients ages 45 to 98 (mean age 81; 170 male, 87 female) were included in the study. A histologically proved malignant tumor was diagnosed in 10 patients: nine with a nodular ulcerated basal cell carcinoma (BCC) and one with an ulcerated porocarcinoma. Patients with a histologic diagnosis other than a vascular ulcer or skin cancer of the lower leg were not included in this series (e.g., inflammatory condition such as vasculitis, pyoderma gangrenosum, external causes such as radiation).

Patient characteristics are reported in Table 1. We did not observe any sex predominance (5 male, 5 female). Mean duration of leg ulcers before a diagnosis of ulcerated skin cancer was made varied from 6 months to 10 years (mean duration 3.3 years). Most BCC were larger than 5 cm^2 and, according to the American Joint Committee on Cancer classification, fell in the group of giant BCC.[4] Clinically, neoplastic ulcers appeared as large lesions with granulation tissue in the center surrounded by raised borders, often showing abundant bleeding and scarce or no response to different medical treatments (Figures 1 and 2).

Doppler vascular examination of the lower limbs of these patients revealed concomitant chronic vascular insufficiency in only three cases. The pathology of BCC was similar in all patients with aspects of ulcerative micronodular, morpheaform BCC. Aggregations of basaloid cells, bizarre in shape and separated by surrounding altered stroma, were present in the dermis and the upper part of the subcutaneous fat (Figure 3). In the deep dermis and adipose tissue, basal cell strands were smaller and more bizarre in shape with prominent fibroplasia and morpheaform features.

Histopathology of porocarcinoma showed aggregations of atypical poroid keratinocytes mostly in contiguity with the epidermis. The atypical cells had large, hyperchromatic irregularly shaped nuclei and frequent mitosis. Ductal structures were often present (Figure 4).

All patients diagnosed with malignancies underwent surgical excision of the neoplasms. Repair was made using split-thickness skin grafts. Patients were followed-up regularly, every 3 to 6 months, in our Dermato-Oncological Unit. No recurrences of tumors were observed over a period ranging from 12 to 24 months.

Discussion

We report here 10 clinical cases of ulcerated skin cancers misdiagnosed as CLU. They represented approximately 4% (10/276) of the total patients of our series. Some authors have considered CLU to be a precancerous condition, but others have found the association between CLU and malignant skin cancer to be merely coincidental.[2,3,5,6]

Basal cell carcinoma is the most common cutaneous malignancy and mainly occurs on sun-exposed and sun-damaged skin. In 80% of cases, BCC are located on head and neck, with only 8% found on the lower extremities.[6]

TABLE 1. Data of Patients Presenting Malignant Neoplastic Skin Tumours and Their Clinical Presentation

Nr	Age/sex at Diagnosis	Comorbidities	Doppler Ultrasound Results	Site	Dimensions	Years from Onset	Histologic Results
1	88/F	Diabetes mellitus, chronic microcityc anemia, hepatitis C	Venous insufficiency	Internal malleolus right leg	5 cm^2	1	BCC
2	96/F	Hypertension	No signs of arterial/venous insufficiency	External malleolus left leg, pretibial right leg	27 cm^2/ 25 cm^2	5	BCC
3	86/F	Hypertension	No signs of arterial/venous insufficiency	Calf right leg	20 cm^2	5	BCC
4	80/M	Diabetes mellitus type II	No signs of arterial/venous insufficiency	Pretibial left leg	4 cm^2	2	BCC
5	94/F	Non-Hodgkin's lymphoma in remission	No signs of arterial/venous insufficiency	Pretibial left and right leg	50 cm^2/ 4 cm^2	2	BCC
6	85/M	Hypertension	No signs of arterial/venous insufficiency	Calf right leg	6 cm^2	2	BCC
7	87/M	Hypertension	No signs of arterial/venous insufficiency	Pretibial left leg	5 cm^2	3	BCC
8	85/F	Diabetes mellitus, chronic ulcer left leg	Chronic venous insufficiency	Pretibial left leg	3 cm^2	10	BCC
9	45/M	None	Arterial insufficiency	Right leg	49 cm^2	2	BCC
10	68/M	Chronic venous insufficiency, porocarcinoma Porocarcinoma	No signs of arterial/venous insufficiency	Pretibial right leg	3 cm^2	1	

BCC, basal cell carcinoma.

In a study by Aloi and colleagues, nodular and superficial BCC were the most common patterns. These authors did not observe morpheaform BCC, although prominent fibrosis was present in some cases of BCC associated with severe stasis changes. Stasis changes were found only in 25% of the cases, suggesting that they did not represent a predisposing factor for the development of BCC on the leg.[6]

There are contradictory data on the frequency and type of malignancies observed in leg ulcers. The prevalence of BCC or squamous cell carcinoma (SCC) differs in various series.[7–19]

In 1996, Yang and colleagues found a frequency of 2.2% of malignancies on leg ulcers, and BCC were predominant (75% of cases).[7]

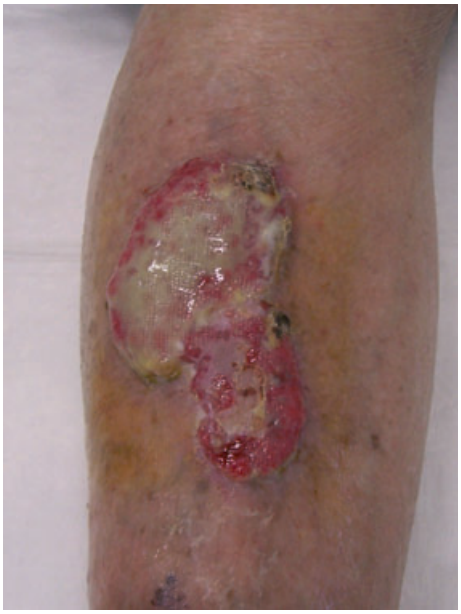

Figure 1. Basal cell carcinoma of the anterior aspect of the right leg presenting as a leg ulcer: clinical presentation.

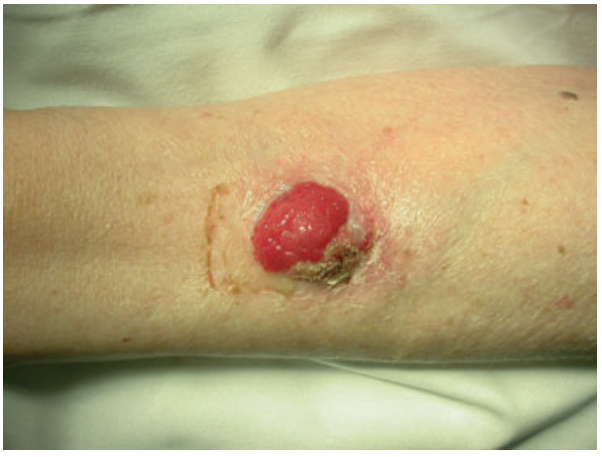

Figure 2. Porocarcinoma misdiagnosed as a chronic leg ulcer: clinical presentation.

Several cases of BCC in patients with severe chronic venous insufficiency have been reported.[5–12,20] In our series, only three of 10 patients had a chronic vascular insufficiency. Vascular insufficiency may be considered as a casual event, but the possibility of its role in an alteration of local immunity or an overexpression of protooncogenes Cfos, H-ras, and p-53 has been suggested.[12]

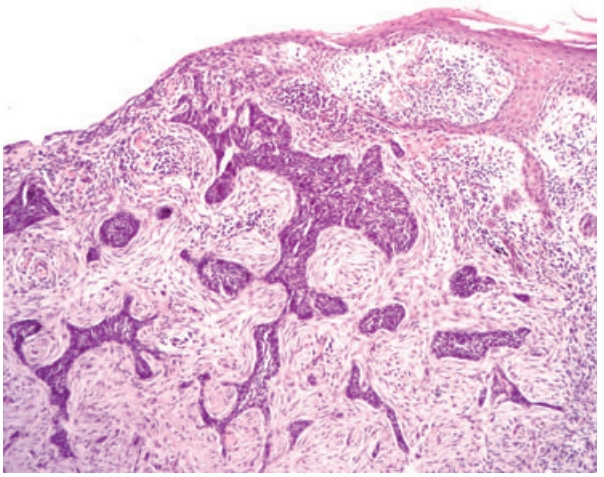

Figure 3. Histopathologic aspects of basal cell carcinoma: aggregations of basaloid cells. descending in the dermis (H&E original magnification × 25).

We did not have sufficient data to determine whether the cancer had preceded the vascular insufficiency or vice-versa. None of the lesions had previously undergone a biopsy.

The presence of large ulcerated leg lesions in the absence of vascular insufficiency (arterial, venous, and microcirculatory), as observed in the majority of our cases (7 patients), might be considered to be a clue to the diagnosis of ulcerated malignant leg neoplasms. Another clinical clue was the nonresponse to medical treatments (ranging from 6 weeks to 3 months).

Morphologic features that suggested the possibility of an ulcerated tumor were exuberant and translucent granulation tissue and raised margins of the ulcers' border. Although the number of reported misdiagnosed cases is increasing, no standardized guidelines regarding when to perform a biopsy on leg ulcers have been established. Senet and colleagues reported on a multicenter French study in which two biopsies were performed in 144 patients, and the frequency of skin cancer in their patients was 10.4% of CLU.

Squamous cell carcinoma (9) were more frequent than BCC (5) in their series.[18] Another recent study by Tang and colleagues reported a frequency of

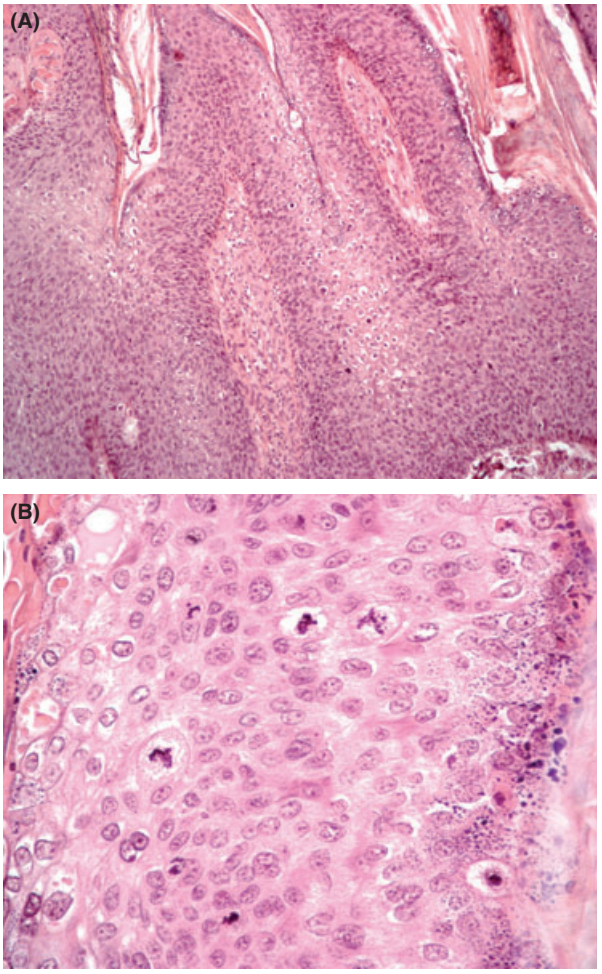

Figure 4. Nests of atypical poroid cells showing a significant degree of atypia, dyskeratotic keratinocytes, and mitotic activity (H&E (A) × 20; (B) × 40).

29.7% of atypical diagnoses in patients clinically suspected or misdiagnosed as having CLU. Among the "atypical ulcers" they included also patients with inflammatory conditions and external causes that were excluded from the present study.[19] The overall frequency of malignancies in their series was 23% of CLU.

In conclusion, we recommend two biopsy specimens from the border and the bed of the ulcers to exclude malignancies, although other authors have proposed perform multiple (up to 5) biopsies on several points of the ulcers.[13] We believe it is important to perform biopsies in the most clinically suspicious areas, such as from the excessive granulation tissue area on the bed of the ulcer and on the border of the ulcer.[18] Clinicians should always suspect that ulcers may hide something underneath, especially with nonhealing ulcers that do not respond properly to medical treatments.

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