CASE REPORT

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Squamous cell carcinoma developed on chronic venous leg ulcer

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Abstract

Chronic venous leg ulcers (VLU), especially long-lasting non-healing ulcers, are among the risk factors for squamous cell carcinoma (SCC). Malignant transformation of a VLU is a rare finding and the relative risk of carcinomatous transformation is quite low (about 5.8). SCC arising in the context of a VLU has a particularly aggressive behavior. A 76-year-old male patient with no relevant medical familial history, with chronic venous insufficiency CEAP C6 for 10 years [recurrent leg ulcers with favorable outcome (healing) after specific local and systemic treatment], showing for about three years one ulcerated lesion located on the anterior upper third of the right calf non-responsive to specific treatment, which subsequently increased their size and merged. Biopsy sample was taken. Histopathology showed epidermal acanthosis, papillomatosis, intense parakeratosis, pseudoepitheliomatous hyperplasia, dysplasia and moderately differentiated squamous cell carcinoma with areas of acantholysis. Immunohistochemistry (Ki67, EMA, cytokeratin 34βE12 and p63) was performed and all types of immunostaining were moderately to intense positive. Above-knee leg amputation and specific oncologic treatment were proposed as possible curative solutions but the patient refused. Ten months after diagnosis and discharge form the Department of Dermatology, the patient died. Patients with chronic venous leg ulcers and clinically suspicious lesions should be evaluated for malignant transformation of the venous lesion. When diagnosed, malignancy complicating a chronic venous leg ulcer requires a resolute treatment as it may be fatal.

Keywords: venous leg ulcer, malignant transformation, squamous cell carcinoma.

Introduction

It is well known that malignant lesions can arise on burn scars, chronic ulcers, wounds, sinuses and fistulae of variable origin [1]. Malignant lesions associated with chronic ulcers may result either from malignant transformation, usually toward well-differentiated squamous cell carcinoma (SCC), of a chronically inflamed ulcerated lesion, or may appear *de novo* and mimic the appearance of a chronic ulcer. Basal cell carcinoma (BCC) can arise but usually SCC is more frequent [2].

Chronic venous leg ulcers (VLU) are among the risk factors for SCC. This association has been described in case reports and retrospective studies especially for long-lasting non-healing ulcers. These lesions have a particularly aggressive behavior with high rates of metastases in regional lymph nodes, low five years survival rates and tendency to recurrence after treatment. Lesions located in the lower limbs seem to have a more aggressive behavior as compared to other anatomic sites in terms of metastasis, recurrence and survival rates [2, 3].

Malignant transformation of a VLU is a rare finding and the relative risk of carcinomatous transformation is quite low. The relative risk of VLU malignant transformation was retrospectively estimated to be 5.8% by matching Swedish registries of patients with chronic leg ulcers and SCC registries [4]. Still, accurate data regarding its prevalence are still lacking.

Malignant change in VLU is directly related to their duration. Some authors mention that ulcer could have existed for at least three years to evoke a diagnosis of malignancy as opposed ulcerated tumor. Chronic ulcers may require biopsy at regular intervals mainly those that do not heal after appropriate treatment [5].

Malignant lesion developed on a chronic ulcer was first described by Jean-Nicholas Marjolin in 1928, being also known as a Marjolin ulcer. Its clinical presentation can vary from an innocuously appearing lesion to overtly exophytic growth.

We present a case of a spinocellular carcinoma developed on a varicose ulcer, atypically localized in the upper third of the right leg calf, which made the diagnosing difficult.

Case report

A 76-year-old male patient, who denied alcohol consumption or smoking, and without any relevant medical family history, was admitted to the Department of Dermatology within the Emergency County Hospital of Craiova, Romania, in January 2014, presenting an ulcerated lesion located on the anterior upper third of the right calf for

about three years one. The patient's medical history revealed that, 34 years ago, he suffered an open wound injury at right calf level for which skin grafting was performed. About two years after surgery, the patient started to manifest progressive skin signs of chronic venous insufficiency consisting of dermatitis, fibrosclerosis at right calf level, and, in the last 10 years, recurrent leg ulcers with favorable outcome (healing) after specific local and systemic treatment. The current episode started about three years ago, through the emergence of three ulcerated lesions, non-responsive to specific treatment, which subsequently increased their size and merged, located on the right calf anterior side, under the knee.

The general clinical examination of the patient revealed no significant pathological changes. The local examination revealed a purple-erythematous plaque, which surrounded the entire right calf. Under the knee, this plaque presented a fungating lesion, with elevated fibrous edges, with a 10/7 cm diameter. This fungating lesion presented three round ulcers with diameters between 1 and 3 cm, covered with a necrotic deposit and with scleral edges (Figures 1 and 2).

The laboratory tests showed no changes, except for a moderate increase of erythrocyte sedimentation rate (30/50 mm). Chest X-ray showed left thoracic pachypleuritis, with left diaphragm traction. Abdominal pelvic ultrasound showed no major changes. Right calf profile X-ray showed cortical thickening in the upper third of tibia. Contrast magnetic resonance imaging showed a heterogenous skin lesion, with heterogeneous gadolinium capture and tumoral-like infiltration of the dermal fat tissue and popliteal muscle mass.

There was then taken the decision to collect biopsy sample. The lesion biopsy was performed under local anesthesia with 1% Lidocaine. The histopathological Hematoxylin–Eosin (HE) staining showed epidermal acanthosis, papillomatosis, intense parakeratosis, pseudoepitheliomatous hyperplasia, dysplasia and moderately differentiated squamous cell carcinoma with areas of acantholysis (Figures 3 and 4). The histopathological aspect revealed a squamous cell carcinoma. In order to confirm squamous cell carcinoma diagnosis, there was performed the immunohistochemical analysis using Ki67 (MKI67), epithelial membrane antigen (EMA), cytokeratin 34βE12 and p63 immunostaining. All four types of immunostaining performed were moderately to intense positive, showing pseudoepitheliomatous hyperplasia and squamous cell carcinoma (Figures 5–9). During the admission period, the patient received systemic treatment with antibiotics, local treatment with antiseptics, wound debridement, perilesional antiseptics and topical corticosteroids, in order to prevent ulcer infection (Figure 10). At discharge, the diagnosis was squamous cell carcinoma stage II – T3N0MX. There was proposed upper knee leg amputation, as a possible curative therapeutic solution. The patient refused and he was referred to the Department of Oncology for specific oncologic treatment, but he also refused this treatment. Ten months after the diagnosis and discharge from the Department of Dermatology, the patient died.

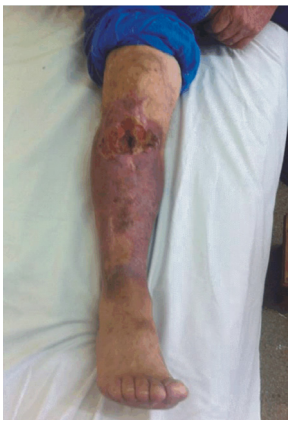

Figure 1 – ***Purple erythematous plaque, which surrounds the entire right calf. Below the knee – fungating lesion, with elevated fibrous edges showing three round ulcers with diameters between 1 and 3 cm, covered with necrotic deposit and with scleral edges.***

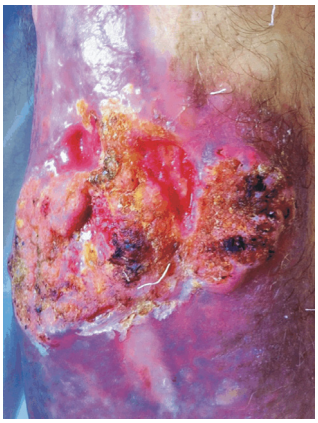

Figure 2 – ***Fungating lesion, with elevated fibrous edges, showings three round ulcers with diameters between 1 and 3 cm, covered with necrotic deposit and with scleral edges (before biopsy and wound debridement).***

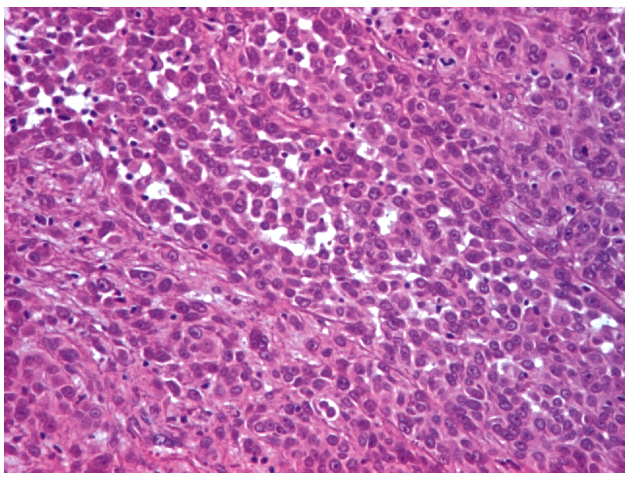

Figure 3 – ***Acantholytic squamous cell carcinoma. HE staining, ×100.***

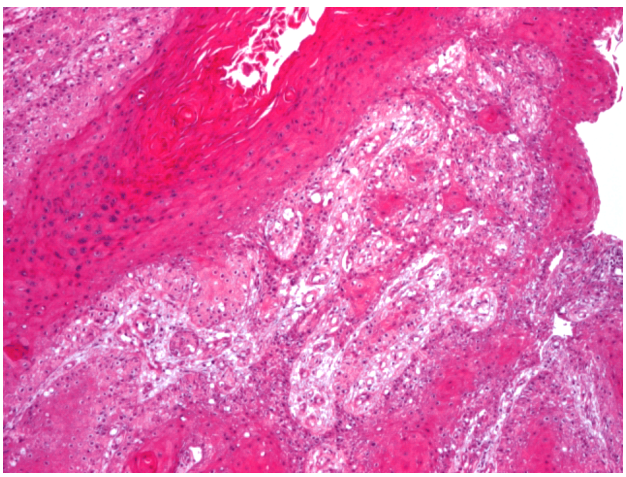

Figure 4 – ***Pseudoepitheliomatous hyperplasia. HE staining, ×100.***

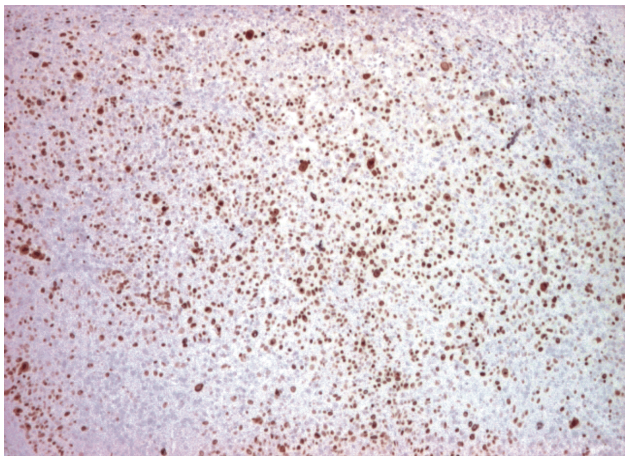

Figure 5 – ***Squamous cell carcinoma. Ki67 immunostaining, ×100.***

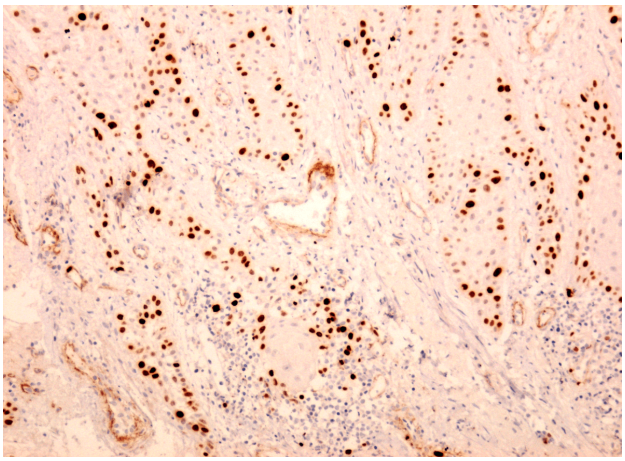

Figure 6 – ***Pseudoepitheliomatous hyperplasia. Ki67 immunostaining, ×100.***

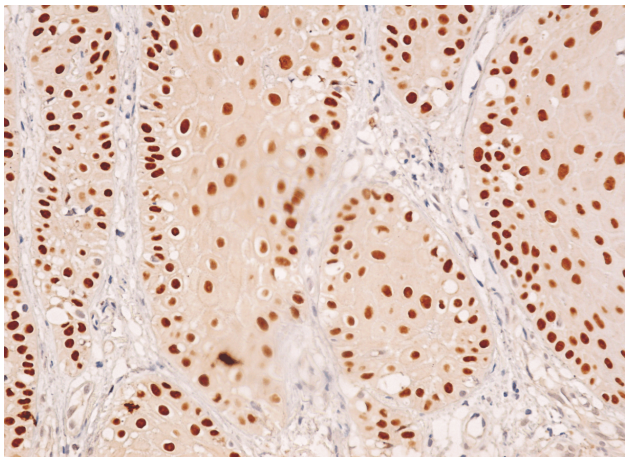

Figure 7 – ***Pseudoepitheliomatous hyperplasia. p63 immunostaining, ×200.***

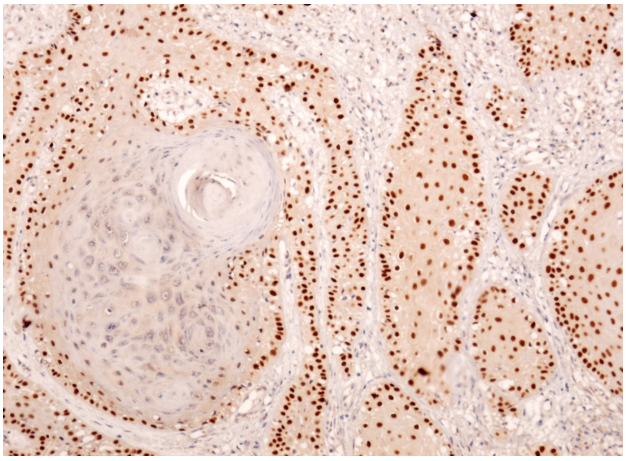

Figure 8 – ***Squamous cell carcinoma. p63 immunostaining, ×100.***

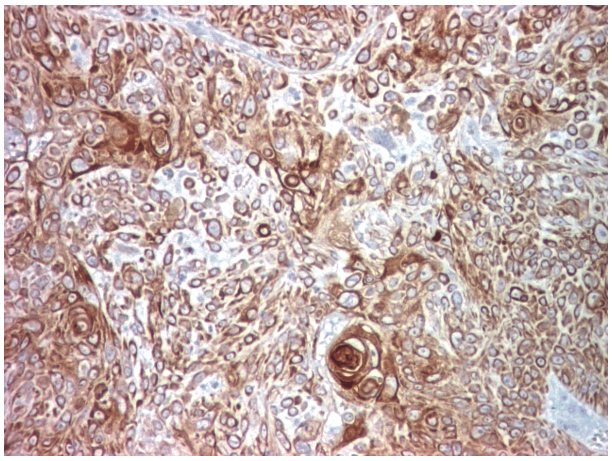

Figure 9 – ***Squamous cell carcinoma. Cytokeratin 34βE12 immunostaining, ×400.***

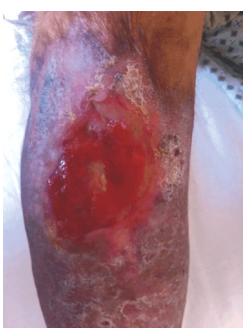

Figure 10 – ***Clinical appearance after biopsy and wound debridement.***

Discussion

Squamous cell carcinoma is a complication of chronic VLU, although the absolute risk is very small. The incidence of malignant transformation is low, resulting in a delay in diagnosis and increased morbidity and mortality in these patients.

The most important research in the field belongs to Baldursson *et al.* They estimated an incidence of SCC developed on VLU of about 0.34% matching the data on 1170 patients with VLU with corresponding data from the *Swedish Cancer Registry*. They also found that the relative risk of SCC in VLUs is around 5.80 by matching 10 913 patients with the diagnosis VLU from the *Swedish Inpatient Registry* with registrations of SCC of the lower limb recorded by the *Swedish Cancer Registry* [3]. Four years later, studying 25 patients with VLUs and SCC (11 well differentiated, 10 moderately and four poorly) regarding tumor degree of differentiation, survival rates and case evolution, they concludes that poorly differentiated tumors and some moderately differentiated may be fatal within one year [6]. Using immunohistochemistry technique, Baldursson *et al.* performed the first systematic approach examining the expression of p53, p21, Ki67 and bcl-2 proteins in chronic VLUs with and without SCC. They analyzed 69 samples (41 samples from 33 patients without SCC and 28 samples from 21 patients with SCC) and made the following findings: in the cancer group,

only 50% of the samples showed p53 staining; in the SCC samples, p53 staining was present especially towards the margins of the cell clusters; intense p53 staining was observed in six samples and 16 samples showed Ki67 expression in most of the basal cells [7].

Combemale *et al.* [8] performed a retrospective study in France, which included 80 CLUs patients (mean age 75 years) complicated with 85 histologically proven carcinomas (83 SCC, 2 BCC). Eighty-two percent of SCC were very well or well differentiated and 18% were moderately of poorly differentiated. Mortality rate was higher when visceral metastases or lymph node invasion were present. The author reported an overall death rate of 32% [8].

Senet *et al.* performed a prospective cross-sectional study in order to determine the frequency of skin cancers associated with CLUs of vascular origin failing to heal despite three months or more of appropriate treatment [9]. The study included 144 patients with 154 leg ulcers. At the time of inclusion, biopsies were taken from the most clinically suspicious areas. Throughout the follow-up period (12 months), ulcer biopsies were taken in a systematic manner, according to the investigator's decision. At the end of follow-up, the investigator confirmed or refuted the final diagnosis (CLU or cancer) and cancer outcomes. After the first set of biopsies, the results were as follows: 15 patients (16 CLUs) with cancer – nine SCCs, five BCCs, and two non-epithelial skin cancers (one melanoma and one leiomyosarcoma), 30 patients with pseudoepitheliomatous hyperplasia (32 lesions) and 99 patients with chronic ulcerations (106 lesions) – one patient being diagnosed with SCC at the end of follow-up period. Of the nine SCCs (eight patients), five were well differentiated, three were moderately differentiated, and one was verrucous type, with pseudoepitheliomatous hyperplasia. At one year of follow-up, of the eight patients with nine SCCs, four were in complete remission: three underwent surgical excision and one had surgical excision and radiotherapy. Of the other four patients, one treated with radiotherapy died of carbon monoxide poisoning before the end of the study, one received chemotherapy and radiotherapy and was still being treated at one year of follow-up, and two were not treated because of other comorbidities and older age. The overall skin cancer frequency in the CLUs was 10.4% [8].

Our patient respects the pattern of onset, histological type and unfavorable evolution of malignancy developed on chronic venous leg ulcer [9]. He is an elderly patient with venous insufficiency stage CEAP C6 [10] with chronic venous leg ulcer which initially responded favorably to specific treatment and subsequently expressed reluctance to specific therapy applied for a period exceeding three years. As in most cases, malignant transformation of venous ulcer was towards moderately differentiated squamous cell carcinoma. The decision to collect biopsy was made taking into consideration a set of criteria such as poor evolution (reluctance to heal and worsen) of the lesion despite correct standard treatment and clinical appearance highly suspicious for malignancy (multiple coalescing ulcers with fungating appearance and rolled scleral margins).

Considering clinical and histopathology findings (malignancy onset in a site of prior injury, tumor diameter greater than 2 cm, moderately differentiation) this lesion was considered a high grade SCC [2]. Intense and chaotic distribution of p63 staining can be considered as an unfavorable prognosis element, because it is associated with high mitotic activity at cellular level [11]. There was proposed upper knee leg amputation, as a possible curative therapeutic solution. The patient refused and he was referred to the Department of Oncology for specific oncologic treatment, but he also refused this treatment.

In the last 20 years, various studies have shown that chronic inflammatory processes provide favorable conditions for the onset and development of some malignant lesions [12–16]. In our patient, venous system failure prolonged calf ulceration and provided the optimal environment for the onset of chronic inflammation. The immune system cells, especially macrophages, granulocytes, lymphocytes and mastocytes, present in a chronic inflammation area, create a local mutagenic microenvironment, through the synthesis and release of reactive oxygen and nitrites species [17, 18]. These molecules have a beneficial effect by destroying local bacteria, but when the inflammatory process lasts for too long, they cause cellular DNA mutations or genetic changes, thus favoring the emergence of cancer cells [19]. Other synthesized molecules by the inflammatory cells, involved in carcinogenesis, are the following: tumoral necrosis factor alpha (TNF-α) and the macrophage migration inhibitory factor, which exacerbates DNA deterioration [20, 21].

In our patient, the lesion had a more than three years progression without any appropriate treatment. Besides the prolonged progress, the patient's old age or UV exposure might be other factors in favoring the malignant transformation of leg calf ulcer.

Patients with chronic venous leg ulcers, mainly those with long-standing evolution, must be closely monitored and checked periodically.

Various studies have shown that chronic ulcers represent a high risk for developing squamous cell carcinomas, especially in persons with immunodeficiency [22, 23].

Clinically suspicious lesions, those that do not heal despite a correct therapeutic management or even worsen with treatment, those which, in evolution, change their clinical appearance (rolled margins, multiple coalescing ulcers, nodular changes and regional lymphadenopathy) should be promptly biopsied and the sample must be submitted to immunohistochemical examination, as well. When diagnosed, squamous cell carcinoma complicating a chronic venous leg ulcer merits a thoughtful and complete investigation, including the differentiation degree and staging. Resolute treatment is indicated as poorly differentiated tumors and some moderately differentiated tumors may be fatal. It is not yet clear whether it would be necessary or favorable to biopsy long-standing ulcer at regular time intervals. One of the reasons, which stand in favor of this recommendation, is the fact that malignant transformation of a chronic venous leg ulcer is definitely linked to its duration.

Conclusions

The presence of ulceration in the upper third of the calf indicates an atypical localization of the varicose ulcer and could have drawn the attention upon other

potential skin lesions. The diagnosis was delayed due to late presentation to the doctor. The histopathological and immunohistochemical examinations have clarified the lesion diagnosis.

Conflict of interests

The authors declare that they have no conflict of interests.

Author contribution

All authors equally contributed in the present study.

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