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Limb Salvage With Vismodegib in a High-Risk Marjolin Ulcer-Type Basal Cell Carcinoma of the Leg

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Abstract

Marjolin ulcer classically describes squamous cell carcinoma arising in chronic wounds, whereas basal cell carcinoma (BCC) transformation within a chronic venous ulcer is rarely reported. We describe an elderly woman with chronic venous insufficiency (CEAP 6) and a two-decade medial malleolar ulcer who developed nodular adenoid and trabecular BCC within the ulcer bed, alongside a synchronous, independent contralateral nodular adenoid BCC. Given her age, comorbidities, and suspected microvascular compromise, she was a poor candidate for excision with flap reconstruction; amputation was proposed and declined. She was started on oral vismodegib as limb-sparing therapy. Imaging showed stable disease without deep invasion, followed by ulcer resolution with cicatricial change and a biopsy negative for residual tumor. The contralateral BCC responded to topical imiquimod. Adverse effects were limited to alopecia, dysgeusia, and muscle cramps. This case highlights BCC as an underrecognized cause of Marjolin ulcer and supports vismodegib as an effective, well-tolerated limb-sparing alternative to amputation.

Categories: Oncology, Dermatology
Keywords: basal cell carcinoma, chronic venous ulcer, limb-sparing therapy, marjolin ulcer, vismodegib

Introduction

Marjolin ulcer refers to malignant transformation within chronic wounds, scars, or areas of long-standing injury, most classically squamous cell carcinoma arising in burn scars or venous leg ulcers. The proposed mechanism involves persistent inflammation, impaired immune surveillance, and repeated epithelial regeneration in a hypoxic, fibrotic wound bed, promoting accumulation of oncogenic mutations over years [1]. Chronic venous ulcers are especially susceptible, with reported mean durations before diagnosis exceeding 15 years; therapy resistance despite optimal wound care is the most consistent warning sign, and diagnostic delay is linked to progression from curative excision to amputation [2].

Basal cell carcinoma (BCC) arising within chronic venous ulcers is reported far less frequently than squamous cell carcinoma: reported rates of BCC arising from venous stasis ulcers range from 1.5% to 15%, and locally BCC-type Marjolin ulcers are documented mainly as isolated case reports [2,3]. Locally advanced lower-extremity BCC poses a distinct therapeutic challenge [2]. Current European and National Comprehensive Cancer Network (NCCN) guidelines recommend surgery as the standard first-line treatment, consider radiotherapy for patients who are not surgical candidates, and reserve Hedgehog pathway inhibitors (vismodegib or sonidegib) for locally advanced BCC not amenable to curative surgery or radiotherapy after multidisciplinary tumor board discussion [4,5]. However, curative resection may not be feasible in elderly patients with significant venous or microvascular comorbidity, particularly when extensive defects would require complex reconstruction or amputation. In this setting, vismodegib, an oral Hedgehog pathway inhibitor approved for locally advanced and metastatic BCC, represents a valuable non-surgical option that may enable tumor control while preserving limb function, with toxicity that is often clinically manageable.

This report describes a locally advanced BCC arising within a chronic venous ulcer, managed with vismodegib as a limb-sparing alternative after amputation was declined, together with a synchronous contralateral BCC treated topically.

Case Presentation

A 78-year-old woman, Fitzpatrick skin type III, with a background of chronic venous insufficiency (CEAP 6), deep venous thrombosis, hypertension, dyslipidemia, diabetes mellitus, and hypothyroidism presented with two cutaneous tumors arising in the context of long-standing lower-limb venous disease. The clinical course is summarized in Table 1.

She described a chronic, non-healing ulcer over the medial malleolar region of the left leg of approximately

two decades' duration, with marked worsening over the preceding year and a half. Examination revealed an ulcer extending from the medial malleolus to the posterior distal third of the leg, measuring 8.5 × 5 cm, with a friable, exophytic, actively bleeding erythematous nodule (1.5 × 1.5 cm) at its posterior margin (Figures *1A*, *1B*). A second, distinct lesion was noted on the posterior right leg: a 2 × 2 cm erythematous-brown plaque with superficial yellow-white scale and ill-defined borders (Figure *1C*). Dermoscopy demonstrated dotted and glomerular vessels on a light brown background. Truncal varicosities and bilateral hyperpigmentation consistent with chronic venous insufficiency were also present.

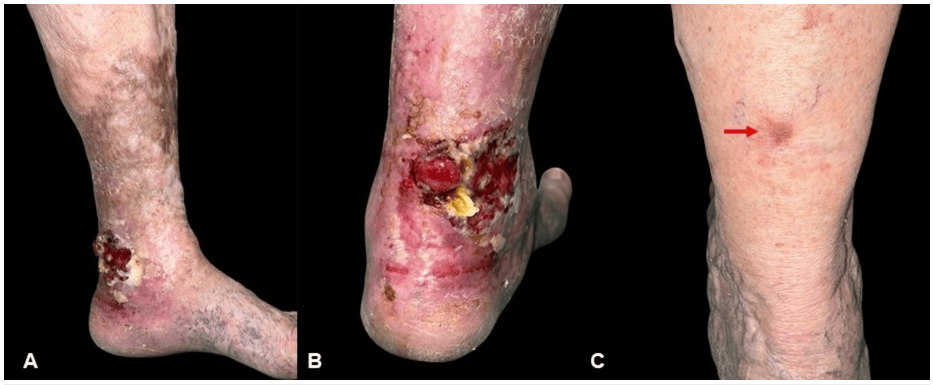


FIGURE 1: Clinical presentation before treatment

(A, B) Chronic ulcer located on the left medial malleolar/retromalleolar region, with an erythematous friable exophytic nodule and fibrinous-necrotic areas, consistent with a Marjolin-type basal cell carcinoma arising in a chronic venous ulcer. The surrounding skin shows marked signs of chronic venous disease, including hyperpigmentation, varicosities, edema-related changes, and lipodermatosclerotic-appearing induration.

(C) Contralateral right lower leg lesion corresponding to an independent, non-ulcer-associated basal cell carcinoma, presenting as a small erythematous plaque/nodule on a background of chronic venous changes.

Biopsies of both lesions confirmed BCC: a nodular adenoid and trabecular subtype in the left leg ulcer, invading the reticular dermis without perineural involvement (Figure *2*), and a nodular adenoid subtype in the right leg plaque, similarly confined to the reticular dermis without perineural invasion. The findings on the left leg, arising within a chronic venous ulcer, were consistent with a BCC-type Marjolin ulcer.

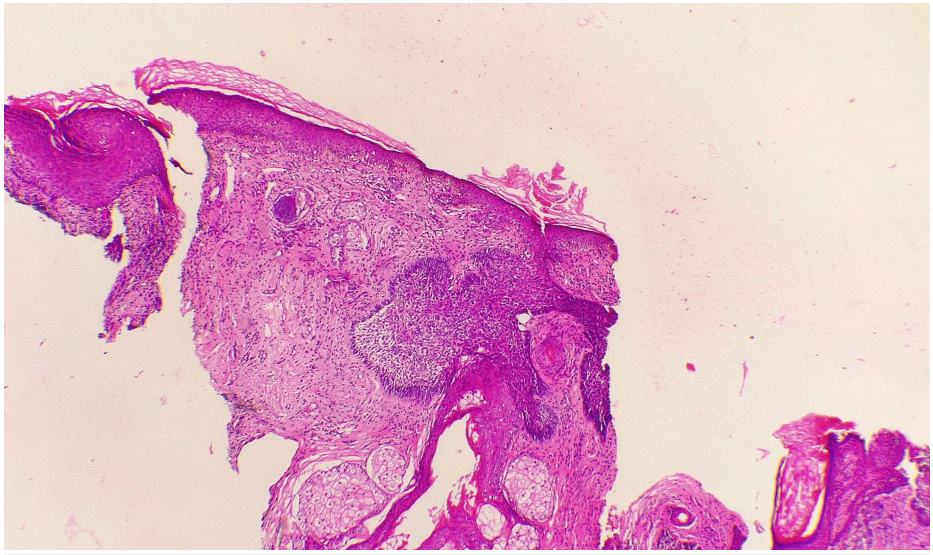


FIGURE 2: Histological findings

Dermal proliferation of nests and lobules of basaloid cells, with peripheral nuclear palisading and retraction clefts between the tumor islands and the surrounding stroma.

Multidisciplinary discussion classified the left-sided tumor as high-risk BCC, while the right-sided lesion was deemed medium-risk and treated with topical imiquimod 5% cream applied five days per week for six weeks, starting at diagnosis concurrently with vismodegib, with complete clinical resolution. Vascular assessment

with venous duplex ultrasound showed peripheral vascular disease, supporting the suspicion of compromised microvascular perfusion of the distal left leg. At a subsequent tumor board, wide local excision with flap reconstruction of the left leg lesion was considered unfavorable. Even in the absence of deep structural involvement, the ulcer measured 8.5 × 5 cm and extended from the medial malleolus to the posterior distal third of the leg, so excision with adequate margins would have left a subsequent large tumor defect board over the malleolar region requiring flap reconstruction in a poorly vascularized bed, with a high anticipated risk of flap or graft failure, non-healing, and infection in a patient with long-standing CEAP 6 disease, prior deep venous thrombosis, and diabetes mellitus. Radiotherapy was also considered less suitable because of the lower-limb location, the chronically ulcerated and poorly perfused tissue bed, and the risk of radiation-induced non-healing ulceration. For these reasons, amputation was proposed as the most oncologically definitive approach option, offering a single-stage procedure with a higher likelihood of primary wound healing. The patient declined amputation.

Systemic therapy with vismodegib 150 mg orally once daily was then initiated in January of 2026 as a limb-sparing alternative. Baseline contrast-enhanced MRI confirmed disease confined to the skin and superficial subcutaneous tissue, with a maximum thickness of 0.3 mm, without invasion of deep muscular planes, tendon, or bone (Figure *3*). After five cycles, imaging showed no significant interval change, and therapy was continued with ongoing clinical, laboratory, and radiologic surveillance. A repeat MRI six months later remained stable, again without marrow involvement, mass formation, or diffusion restriction.



FIGURE 3: Clinical findings after treatment

Hypopigmented atrophic scar at the site of the original basal cell carcinoma.

By approximately eight cycles, corresponding to roughly nine months of continuous treatment, the patient achieved a complete clinical response, with full re-epithelialization of the previously non-healing ulcer (Figure *3*). Follow-up MRI confirmed resolution of the ulcer, with only mild cicatricial cutaneous and subcutaneous change (Figure *3*). A confirmatory biopsy, obtained nine months after vismodegib initiation from the left external medial malleolar area at the site of the original tumor, demonstrated only scar tissue, with no evidence of residual tumor. Vismodegib was continued for two additional months after the complete response as a "holiday treatment strategy." At the last follow-up, two months after treatment completion, the patient remained free of clinical recurrence.

Treatment was well tolerated throughout, with mild adverse effects limited to alopecia, dysgeusia, and muscle cramps. Laboratory parameters remained within normal limits, and the patient maintained excellent adherence over the course of therapy.

Discussion

Marjolin ulcer classically denotes malignant transformation within a chronic wound, scar, or area of long-standing tissue injury, and the overwhelming majority of reported cases are squamous cell carcinoma [1].

BCC arising within a chronic venous ulcer is comparatively rare: reported rates of BCC arising from venous stasis ulcers range from 1.5% to 15%, and in a 25-year population-based cohort from Olmsted County, BCC accounted for 41.5% of malignancies identified in chronic leg wounds, occurring in near-equal proportion to squamous cell carcinoma [2,3]. This relative rarity, together with the advanced age and vascular comorbidity typical of affected patients, underscores the value of documenting this case.

The terminology used to describe this entity deserves comment. The term "Marjolin ulcer" has historically been used and is still most often used to denote squamous cell carcinoma arising in burn scars and other chronic wounds, and some authors restrict it to that histology [1]. Others apply it more broadly to any malignancy arising within a chronic wound or scar, including BCC [3]. We use the term "Marjolin ulcer-type BCC" descriptively to emphasize the clinical context of malignant transformation within a long-standing chronic venous ulcer, while acknowledging that its application to BCC remains debated. In addition, whether such tumors arise as a consequence of the chronic wound or represent coincidental BCCs involving an ulcerated area cannot be established with certainty in an individual patient.

Diagnostic delay is a recurring theme in the literature on malignant transformation of chronic wounds. In a tertiary wound-care cohort, mean ulcer duration before biopsy was 11.3 months, exceeding guideline-recommended timelines, with disproportionate pain, necrosis or bleeding, and atypical appearance identified as the most common red-flag features prompting biopsy [4,6]. In the present case, the ulcer had been present for two decades, but it was the emergence of a friable, exophytic, actively bleeding nodule - consistent with these described warning signs - that triggered diagnostic biopsy. This reinforces the recommendation that any chronic venous ulcer failing to improve within 4-12 weeks or developing atypical morphologic change warrants prompt histologic evaluation [4,6].

Therapeutic decision-making in this case was shaped by the patient's poor surgical candidacy and explicit refusal of amputation. Vismodegib is approved for locally advanced BCC in patients who are not candidates for surgery or radiotherapy, a scenario directly applicable to this case. Efficacy data in unresectable, locally advanced BCC are consistent across studies: a pooled analysis of interventional trials reported combined complete and partial response rates of 62.1% overall, rising to 64.7% specifically among patients with locally advanced disease, while a real-world disease registry reported an overall response rate of 85.1% with vismodegib [5-8]. The complete clinical response achieved in this patient, with ulcer closure after several treatment cycles, falls within this reported efficacy range.

The decision to propose amputation despite the absence of deep invasion reflected the limitations of local alternatives rather than tumor depth. Excision with adequate margins would have required flap reconstruction of a large malleolar defect in a limb with chronic venous hypertension, prior deep venous thrombosis, diabetes, and suspected microvascular compromise, conditions associated with a high risk of reconstructive failure, while radiotherapy to a chronically ulcerated, poorly perfused lower-limb bed carries a substantial risk of non-healing. In this context, guidelines support Hedgehog pathway inhibitors as a reasonable option for patients in whom curative surgery or radiotherapy is inappropriate [4,5].

The optimal duration of vismodegib therapy after a complete response remains undefined. In clinical trials and registries, treatment was generally continued until progression or unacceptable toxicity, and adverse events became more frequent with treatment beyond 12 months, often leading to discontinuation [9,10]. Current guidelines therefore support individualized decisions on treatment duration, including treatment interruption after maximal response, with close surveillance for recurrence [4,5]. In our patient, vismodegib was continued as a holiday strategy of treatment after histologic confirmation of complete response, and surveillance consisted of clinical examination every three months and MRI every six months during the first two years.

The tolerability profile observed - alopecia, dysgeusia, and muscle cramps, without need for discontinuation - closely mirrors the toxicity pattern consistently reported across vismodegib trials and real-world registries, in which muscle spasms, alopecia, and dysgeusia/ageusia are the most frequent adverse events, generally grade 1-2 [5,7,8,10]. Notably, the incidence of common adverse events increases with treatment duration beyond 12 months, underscoring the importance of the ongoing clinical and laboratory surveillance maintained throughout this patient's extended treatment course [7-10].

Clinical, radiologic, and histologic correlation was central to documenting response. MRI allowed exclusion of bone or deep muscular plane involvement at baseline and longitudinal monitoring of cutaneous thickening during treatment, consistent with the established role of high-resolution skin MRI in characterizing tumor depth and extent in cutaneous malignancy and in monitoring treatment response [9,11]. The absence of tumor infiltration on follow-up biopsy, in the context of cicatricial imaging changes and clinical ulcer resolution, concordantly supports complete response.

The coexistence of two histologically distinct nodular BCCs in this patient - one arising within a chronic venous ulcer as a Marjolin-type lesion and a second, contralateral tumor arising de novo - reflects the well-established propensity of BCC to present as multiple primary tumors, even in immunocompetent individuals. Population-based registries report that 24-40% of BCC patients develop additional primary

tumors, with roughly one-quarter to one-third of patients experiencing a subsequent BCC within three years of their index diagnosis; nodular histology, male sex, and older age are independently associated with multiplicity [10-13].

Synchronous presentation of a Marjolin ulcer-type BCC together with a separate, non-ulcer-associated BCC remains scarcely documented, largely confined to isolated case reports rather than systematic series, consistent with the overall rarity of BCC-type Marjolin ulcers. The medium-risk right leg tumor was treated with imiquimod 5% cream, which achieves clinical and histological clearance in 77-86% of nodular BCC at five years [12,14]. In this patient, imiquimod achieved lesion clearance and offered an appropriately conservative, non-invasive option for a lower-risk tumor while systemic therapy was directed at the contralateral high-risk lesion.

Taken together, this case demonstrates that malignant transformation should be actively sought in chronic venous ulcers and that synchronous, independent BCCs may coexist with a Marjolin ulcer-type lesion, warranting individualized, risk-stratified treatment of each tumor. It further suggests that Hedgehog pathway inhibition with vismodegib may be an effective, well-tolerated, limb-sparing alternative to amputation in selected patients with locally advanced BCC who are poor surgical candidates, as shown by the complete clinical and histologic response achieved in this patient while preserving limb function. As a single case report, these findings cannot be generalized, and larger series with long-term follow-up are needed to define the durability of the life response and the optimal treatment duration in this setting.

Conclusions

This case reinforces that chronic venous ulcers resistant to standard wound care warrant biopsy to exclude malignancy and that such transformation is not limited to squamous cell carcinoma. It further demonstrates that synchronous, histologically independent BCCs can coexist in patients with chronic venous disease, supporting individualized management of each lesion. Finally, in this patient, vismodegib achieved a complete clinical and histologic response while preserving the limb, suggesting that it may be a useful limb-sparing alternative to amputation in selected patients with locally advanced BCC unsuitable for reconstructive surgery. Further studies are needed to confirm these observations.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Critical review of the manuscript for important intellectual content: Juan Carlos Jaimes, Lina Gonzáles Cardona

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. The Ethics Committee of Instituto Nacional de Cancerología issued approval 038-26. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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