

# Non-healing foot ulcers in diabetes mellitus and role of biopsy: a report of two cases

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## ABSTRACT

Diabetic foot ulcers are a severe complication of diabetes mellitus and are commonly associated with peripheral artery disease and/or neuropathy. An inadequate treatment or the presence of concomitant infection may result in a delay in wound healing. However, in some circumstances, non-healing wounds may hide other underlying diseases, which in some cases may be malignant. A biopsy can be a useful tool to investigate chronic wounds to achieve early diagnosis with the aim of establishing an adequate treatment and to improve the prognosis. We present two clinical cases in which biopsy revealed the presence of malignancy in non-healing chronic ulcers.

**Keywords** diabetic foot ulcer; tissue biopsy; chronic wound; skin cancer; melanoma

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## KEY MESSAGES

- In diabetic patients, chronic foot ulcers may hide other underlying diseases, which in some cases may be malignant.
- This paper describes two clinical cases in which skin cancer was misdiagnosed as diabetic foot ulcer.
- Biopsy is crucial to exclude diseases other than diabetes that can be malignant. Early diagnosis is essential to establish adequate treatment and improve prognoses.

## INTRODUCTION

Diabetic foot ulcers (DFU) are one of the most severe complications of diabetes mellitus and are associated with high morbidity and mortality rate, as well as placing a high economic burden on the healthcare system.<sup>1-3</sup> More than a quarter of non-healing DFU may lead to lower extremity amputation within a period of 18 months after the wound's first manifestation.<sup>4</sup>

Diabetic neuropathy and peripheral arterial disease (PAD) are usually the main causes of DFU.<sup>5</sup> Wound healing delay may result from conditions such as: inadequate treatment, impaired arterial or venous circulation, concomitant infection, immunocompromised status, and older age.<sup>6</sup> However, in some circumstances non-healing ulcers may hide other underlying diseases, which in some cases may be malignant.<sup>7</sup> Thus, guidelines and experts recommend biopsying atypical chronic ulcers for differential diagnoses or inappropriate clinical progression.<sup>8</sup> A biopsy can detect cancer and provide further information on the nature of the wound, including its potential for infection and its impediments to healing.<sup>9</sup> We report here on two cases of diabetic patients presenting with chronic wounds poorly responsive to treatment, in which skin biopsy performance was crucial for an accurate diagnosis.

## CASE 1

An 88-year-old Caucasian male patient with type 2 diabetes mellitus (T2DM) came to our Diabetic Foot Clinic for the evaluation of a non-healing ulcer involving the left plantar rear foot, present for more than two months (Figure 1).



Figure 1. Foot lesion in the first patient.

In addition to T2DM, his medical history included: hypertension, diabetic peripheral neuropathy (NP) and chronic obstructive pulmonary disease. The patient had no previous history of non-healing wounds, PAD, or of being immunocompromised.

The average wound area was 14cm<sup>2</sup> by the manual planimetric method; the lesion was characterised by hyper-granulation tissue and hyper-pigmentation of the peri wound skin. No signs of local infection were present. At the beginning, the ulcer had been treated with dressings, topical antiseptic and local offloading, with no evidence of improvement.

Due to the atypical appearance of the lesion, we decided to perform a biopsy, which was diagnostic for nodular melanoma (Figure 2). Disease staging confirmed the presence of metastases to the lungs and inguinal and hilar lymph nodes. In consideration of the patient's age and comorbidities, no specific treatment was performed. The patient died six months after the diagnosis.

## CASE 2

A 63-year-old Caucasian male came to our attention due to a non-healing plantar ulceration developed on his right forefoot (Figure 3). The patient had a seven-year history of T2DM, complicated by NP. There was no significant vascular defect; no history of trauma or previous DFU was reported. Medical history included hypertension, chronic renal disease, and previous myocardial infarction.

The ulcer of 33cm<sup>2</sup> was covered and surrounded by abundant hyperkeratosis; after keratolysis, inspection revealed the presence of exuberant granulation tissue with bleeding tendency. The wound was present for less than a year and had been treated with local dressing, rest, and an offloading device.

Given the chronic nature of the wound, an X-ray was performed and revealed osteomyelitis in the proximal end of the right fourth metatarsal bone. Furthermore, considering the unusual characteristics of the lesion, we also decided to perform a biopsy. In this case histopathology was remarkable for a well-differentiated squamous cell carcinoma (SCC), with an ulcerated pattern, infiltrating the skeletal muscle (Fig. 4). Lisfranc amputation procedure was performed. A computed tomography scan excluded metastatic spread of the disease. After the surgical wound healing process, the patient remained active and was able to walk by wearing

proper footwear and a custom-made insole, without the need of further walking aids.

## DISCUSSION

Melanoma and SCC are two of the most common skin cancers with high mortality rates worldwide.<sup>10,11</sup> Among all melanomas, the nodular subtype has poorer prognoses,<sup>12</sup> especially when arising on the foot, accounting for 35% of ultimately fatal cases of melanoma.<sup>13</sup> Malignant melanoma has a high tendency to disseminate: after primary tumor excision about 30% of patients develop metastasis in various organs<sup>14</sup>; in the presence of nodal metastasis, the five-year survival rate decreases by approximately 50%.<sup>15</sup> Nodular melanomas rarely occur on the foot; typically, they might seem symmetrical with well-defined borders or ill-defined, resembling a cauliflower.



Figure 3. Foot lesion in the second patient.



Figure 2. Histological pattern of nodular melanoma.

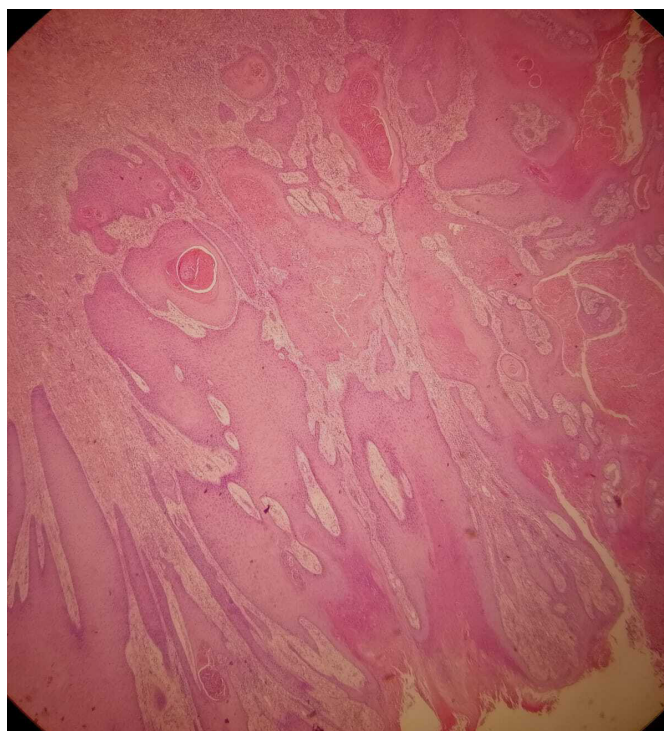


Figure 4. Histological pattern of squamous cell carcinoma.

Their pigmentation ranges from black/brown to red/pink. The growth occurs vertically, progressing quickly and aggressively into deeper tissues. This is a specific characteristic for this subtype of melanoma.<sup>16</sup> In the first case reported, the ulcer presented an exuberant granulation tissue with surrounding hyperpigmentation, similar characteristics to those just described. For this reason, we decided to perform a wound biopsy.

In the second case, the patient presented a non-healing plantar forefoot lesion covered and surrounded by abundant hyperkeratosis, resembling a neuropathic ulcer, but a biopsy revealed a high-risk SCC. The metastatic potential of a high-risk SCC is similar to that of melanoma<sup>17</sup> and the annual disease-specific mortality is estimated to be 1.5–2.1%.<sup>18</sup> Factors associated with local recurrence and metastases are: diameter >2cm, depth >2mm or beyond subcutaneous fat, perineural involvement, poor differentiation. Furthermore, SCC arising from a leg ulcer, burn scar and other chronic wounds have a reported metastatic risk of 26%.<sup>19</sup> An uncommon type of well-differentiated SCC is verrucous carcinoma, a slow-growing lesion that does not frequently metastasize, although it is highly prone to recurrence and local invasion.<sup>20</sup> Verrucous carcinoma, in its subtype called cuniculate epithelioma, is most commonly found on the weight-bearing surface of the foot and appears as an exophytic tumor, warty or cauliflower-like, with keratin-filled sinus tracts and malodorous exudate.<sup>21</sup> The first-line treatment is surgical excision despite being particularly challenging due to the anatomic location and requirement for margin control while preserving healthy tissue, covering abnormalities, and maintaining acceptable function.<sup>20</sup>

Despite only few cases having been reported so far, SCC has been described as a complication of DFU<sup>22</sup> or chronic osteomyelitis,<sup>23</sup> and both patterns were detected in our patient.

Chronic ulcers and burn scars may be linked to SCC, which usually starts in the upper layers of the skin in areas continuously exposed to an inflammatory stimulus for an extended period,<sup>24,25</sup> but no history of trauma was reported in our case. Chronic wounds that evolve in neoplasm are defined as Marjolin ulcers. The average latency period from the time of the initial triggering wound to the discovery of malignant degeneration is between 30 and 35 years,<sup>26</sup> but also rare cases of acute Marjolin ulcer have been reported, occurring within 12 months of the ulcer development.<sup>27</sup> In our patient the wound had been present for almost a year, which highlights how unusual the case was. Marjolin ulcers are often aggressive and carry a poor prognosis: metastases are found in up to 27% of cases and the recurrence rate after surgical resection is up to 50%.<sup>28</sup> Melanoma and SCC are two malignant diseases, which can be misdiagnosed when present in the diabetic foot as they can mimic DFU, as neuropathic ulcers. Both patients had T2DM complicated by NP. Moreover, the ulcer site was in typical pressure point in both cases; in the second patient the ulcer was located on an area of hyperkeratosis, appearing as pressure ulcer. Therefore, both lesions received the same treatment as neuropathic ulcers, but, due to a lack of improvement, a skin biopsy was performed.

Clinicians should consider biopsy to rule out other ulcer causes if the ulcer does not heal following therapy and no cause for an intractable ulcer has been identified.<sup>8</sup> The biopsy should

be taken from the wound edge, including epidermis, dermis and sufficient subcutaneous tissue. Among several types of skin biopsy techniques, the excisional is the preferred one when evaluating cutaneous tumors.<sup>29</sup> However, there is no consensus regarding the appropriate timing for a wound biopsy in a chronic lesion. In general, a biopsy procedure should be conducted on wounds not responding to six or more weeks of standard treatment or continuously opened without signs of healing for three months.<sup>30</sup> This procedure is crucial to exclude diseases other than diabetes that can sometimes be malignant. An early diagnosis could avoid systemic dissemination, limb loss, and death of the patient.

## CONCLUSION

In conclusion, our cases demonstrate that lower extremity ulcers in diabetic patients may have an etiology other than diabetes. The medical history and the presence of atypical characteristics must suggest the execution of further diagnostic investigations, as biopsy, to exclude other diseases, which in some cases may be malignant. Therefore, early diagnosis is essential to establish adequate treatment and improve prognoses.

## FUTURE RESEARCH

Further studies are needed to identify which characteristics are suspicious in chronic wounds and to establish the appropriate timing for skin biopsy performance.

## ABBREVIATIONS

DFU: diabetic foot ulcers

PAD: peripheral arterial disease

T2DM: type 2 diabetes mellitus

NP: peripheral neuropathy

SCC: squamous cell carcinoma

## STATEMENT OF ETHICS

All diagnostic and therapeutic procedures were in accordance with ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from the patients included in the study.

## CONFLICT OF INTEREST

The authors have no conflicts of interest.

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