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CASE REPORT

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Diagnosis of melanoma localized in ulcer associated with diabetic foot syndrome — case report

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ABSTRACT

Difficult-to-heal wounds, which include ulcers in diabetic foot syndrome (DFS), are characterized by long healing times, sometimes leading to sepsis and the need for amputation. The often months-long persistence of the ulceration creates conditions for uncontrolled proliferation of granulation tissue, which is a component of the wound, also in the direction of neoplastic lesions. The co-occurrence of such a condition with hyperglycemia can increase the risk of cancer development within the ulcer. This article presents the case of a 71-year-old man in whom a histopathological examination of a wound specimen was performed due to a lack of progress in the healing process. The patient was diagnosed with melanoma and was referred urgently to a referral centre, where a toe resection and sentinel node biopsy were performed. In addition, the article presents a diagnostic pathway that applies to patients with suspected proliferative disease in the wound associated with DFS.

Key words: diabetic foot ulcer, melanoma, management

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Introduction

The diagnosis of diabetic foot syndrome (DFS) should be considered whenever there are changes in the structures of the foot in a patient with diabetes mellitus complicated by the presence of neuropathy and/or ischaemic changes in the lower extremity arterial bed, especially if it involves patients with a metabolically unbalanced disease course [1]. Since the treatment process is usually lengthy in this group of patients, diagnostic inertia usually develops among physicians in getting used to the protracted process of therapy, which requires the patient to follow numerous recommendations such as the use of dressings, the wearing of pressure-relieving shoes and lifestyle changes [2]. Often, despite following the doctor's recommendations, the ulceration does not heal properly, and the wound size is not reduced. Often it is very hard to determine the aetiology of a chronic wound. In such cases, a dermatological and oncological diagnosis should be included in the management.

Case report

A 71-year-old obese [body mass index (BMI) 33 kg/m^2] man with type 2 diabetes mellitus (treated with insulin) diagnosed 10 years ago, hypertension, hypercholesterolemia, chronic coronary syndrome (status post-implantation of 3 drug-eluting stents into a right coronary artery in 2019), heart failure (left ventricular ejection fraction 40%), paroxysmal atrial fibril-

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Table 1. The history of the patient's visits to the diabetic foot clinic

Visit's number	Visit 1	Visit 2 (after 3 months)	Visit 3 (after 6 months)	Visit 4 (after 9 months) Result of histopathological examination: melanoma
Localization of the wound	First toe of the right foot	First toe of the right foot	First toe of the right foot	First toe of the right foot
Diameter of the wound	2.0 × 1.5 cm	2.3 × 2.0 cm	2.3 × 2.0 cm	2.3 × 2.0 cm
Depth of the wound	Superficial	Superficial	Superficial	Superficial
The presence of inflammation	Yes	No	No	No

lation (treated with rivaroxaban), chronic obstructive pulmonary disease, benign prostatic hyperplasia, and nicotinism (50 pack-years) was referred to the Diabetic Foot Clinic with persistent ulceration of the first toe of the right foot for 2 years.

The patient's lesioned foot showed impaired superficial sensation of pain, touch, temperature, and vibration, pitting oedema of both lower extremities and a superficial wound measuring 2.0 × 1.5 cm, with features of inflammation located on the plantar surface of the first toe of the right foot. Due to the signs of local inflammation, the wound was treated podiatrically, a dressing with silver ions was applied, and the use of pressure-relieving shoes and improved glycaemic control were recommended.

The inflammation had resolved with topical treatment by the time of the next visit (after 3 months). However, no progress in the healing process was observed at any of the visits (3, 6, 9 months) (Tab. 1), which prompted the attending physician to consider an aetiology of the wound other than DFS (Fig. 1). Accordingly, a histopathological examination was performed, and the result suggested a diagnosis of melanoma. The patient was urgently referred to the National Cancer Institute (NCI) for further diagnosis.

At the first visit to NCI, which took place 5 days after the initial diagnosis, a histopathological examination was performed again and BRAF mutation detection was ordered. Microscopic examination revealed melanoma [SOX10(+), HMB45(+), PRAME(+)], with a predominant "*in-situ*" component, confirming the earlier diagnosis. Determination of BRAF mutation was not possible due to an insufficient percentage of tumour cells in the specimen.

The patient was initially qualified for toe amputation and sentinel node biopsy. In the preoperative period, abdominal and chest CT (computed tomography), as well as PET-CT (Positron emission tomography) were performed. Imaging studies showed the presence of a solid subpleural nodule in the anterior part of the upper lobe (Fig. 2A), a cyst of the right kidney (37 mm)

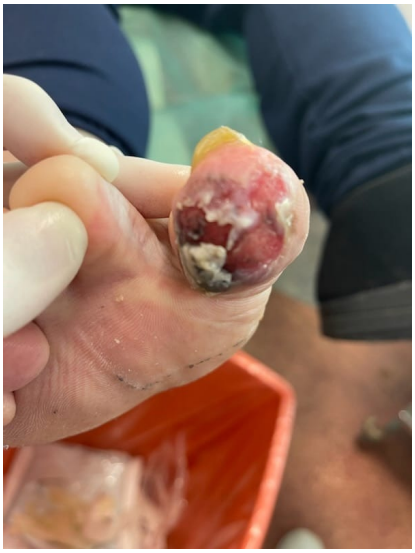

Figure 1. Wound 9 months after starting treatment at the diabetic foot syndrome clinic

(Fig. 2B), and the presence of diffuse atherosclerotic lesions. No metastatic lesions were identified.

A sentinel node biopsy was taken from the right inguinal nodes. The first toe of the right foot was amputated and submitted for histopathological examination. Subsequently, the distal fragment of the first metatarsal bone of the right foot was occluded. The surgical procedure was performed without complications and deviation from standard medical procedures. As a result of the histopathological examination, a definitive diagnosis of pT1b [3] stage acute melanoma with signs of regression and the presence of lymphoid infiltration was made. The depth of infiltration on the Breslow scale was estimated at 0.8 mm and the mitotic rate at 0–1/mm^2. Angio- and neuroinvasion was not found, and there were no satellite nodules. No melanoma metastases were observed in the sentinel nodes.

The patient was instructed the day after surgery about the need for regular medical follow-up and pos-

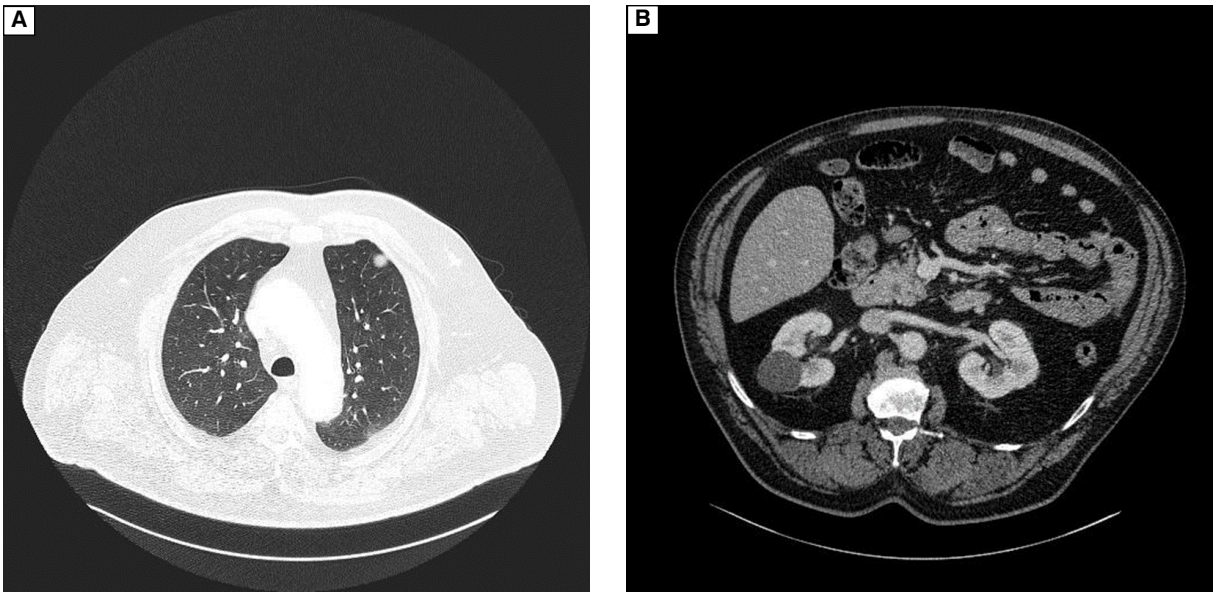

Figure 2. Solid subpleural nodule of the upper lobe of the right lung in the frontal part (**A**), right kidney cyst of 37 mm dimension (**B**)

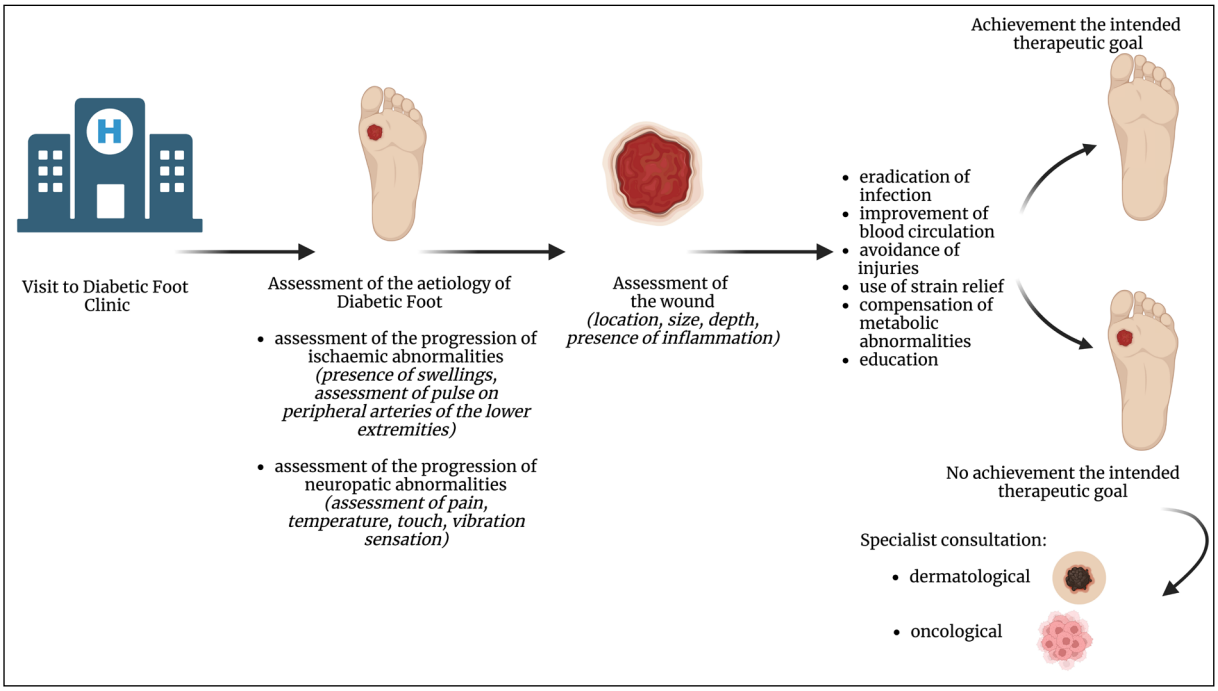

Figure 3. Diagram of the management of a patient with diabetic foot syndrome of malignant or autoimmune aetiology. Created with BioRender.com

sible postoperative complications and was discharged home. A follow-up PET scan 2 months after surgery revealed no lesions indicating neoplastic growth. Chest X-ray, abdominal ultrasound, and oncological and dermatological follow-ups were recommended every 6 months.

Discussion

Diabetic foot syndrome is characterized by changes in the deep layers of the skin of the foot originally caused by neuropathy and/or blood supply disorders. In contrast, the direct causative factor is usually trauma,

caused by mechanical, chemical or thermal factors. In the absence of pain in most patients, the wound goes unnoticed for a long time, resulting in the patient being brought to the hospital/outpatient clinic with developed features of infection. Classic management of DFS includes surgical debridement of the wound, infection treatment, use of adjunctive methods such as negative pressure wound therapy (NPWT), and wearing pressure relieving shoes to reduce the pressure exerted on the lesion [4]. Ulcer healing can take many months, but up to 77% of wounds resulting from DFS manage to heal within 1 year after diagnosis [5]. The prolonged healing process is most often due to inadequate metabolic compensation of diabetes, failure to consider the features of ischaemia at diagnosis and attempt possible revascularization, and lack of cooperation from the patient [6]. In the case described here, the patient had been observing a toe ulcer for two years before presenting to the doctor. Failure to achieve therapeutic goals for nine months of treatment prompted the treatment team to deepen the diagnosis. Initially, inflammation was present in the patient, but the treatment administered helped reduce the infection. Despite this, no reduction in the size of the ulceration was observed. When the wound does not heal properly despite the standard treatment methods, extended dermatological and oncological diagnostics should be considered. Diagnosing the aetiology of chronic wounds is a very challenging process. The differential diagnosis of DFS is very broad and includes neoplasms (squamous cell carcinoma, basal cell carcinoma, Kaposi's sarcoma, malignant melanoma, neuroendocrine carcinoma of the skin, mycosis fungoides), infections, decubitus ulcers, pressure ulcers (*Martorella*) and venous ulcers [5]. In the case described here, the patient's failure to comply with the recommendation to use pressure-relieving shoes was an additional complication to the diagnosis, which may have been the reason for the long duration of the ulceration. However, histopathologic examination revealed the presence of acral melanoma, which made a definitive diagnosis.

The incidence of acral melanoma is 1–8% among diagnosed melanomas in the European population [7]. Its incidence is not strictly related to UV exposure [7]. It has been suggested that genetic factors have a greater influence on its formation [8]. Chronic skin wounds, such as DFS, also can have an impact on acral melanoma formation, however, the inflammatory process is more often associated e.g. with squamous cell carcinoma [8, 9]. Acral melanomas are often associated with a poor prognosis, partly due to difficult and delayed diagnosis. Misdiagnosis is noted in 25–33% of cases of acral melanoma compared to 10% of cases of other types of melanoma [10]. Older patients with diabetes (> 65 years old) are at higher risk for malignant lesions masked as diabetic foot ulcers [11]. Therefore, more frequent biopsies are suggested to correctly diagnose melanoma in these patients [12]. However, this procedure carries the risk of complications in the form of delayed wound healing [13]. Typical management of melanoma includes surgical treatment and sentinel node biopsy [3]. In the case described here, amputation of the entire first toe of the right foot was required to preserve surgical margins.

Studies indicate that type 2 diabetes may independently increase the risk of melanoma [14]. However, it is important to remember that diabetes and cancer are characterized by similar risk factors, such as obesity, age, and lifestyle of patients, which may increase the probability of their co-occurrence [15, 16]. A negative effect of diabetes on markers of increased melanoma aggressiveness (Breslow score depth of infiltration, sentinel node metastasis, mitotic index, and melanoma stage) was also described [17]. Diabetes medications may also influence cancer progression. *In-vivo* studies demonstrated the antitumor effect of metformin, which, enhances the activity of cytotoxic T cells inside the tumour and increases the antitumor activity of NK cells [18]. However, no beneficial effect of metformin therapy on reducing melanoma aggressiveness has been noted [17].

Multidisciplinary action by teams of diabetologists, dermatologists, and surgeons could significantly improve the diagnostic efficiency of malignant lesions masking as diabetic foot ulcers (Fig. 3). It is important to increase physicians' awareness of the difficulty of diagnosing acute melanoma in cases of DFS, especially in older patients. Speeding up the diagnostic process, for example, by using biopsies more frequently, could have a positive impact on patient survival and treatment success.

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