Double skin tumors with an atypical clinical picture

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The authors present a rare case of double skin tumors: acral lentiginous melanoma and metatypical carcinoma. The tumors were manifested as gradually enlarging ulcerations on the leg and sole of the foot that did not respond to standard treatment. The skin biopsies showed advanced acral lentiginous melanoma on the sole and metatypical carcinoma of the lower leg. Soon after the diagnosis was made, the melanoma generalized. The article discusses the differential diagnosis of both leg ulcerations, correct diagnostic procedures, and characteristic features of both tumors that are important questions for general practitioners, dermatologists, and surgeons.

**Case report**

A 74-year-old male presented with a long history of relapsing lower leg ulcers resulting from chronic venous insufficiency. The family history was uneventful. The personal history included cholecystectomy due to lithiasis performed 25 years earlier and long-term treatment with venotonics and vasodilators. The patient had recently been treated by a general practitioner and then by a surgeon for a progressing lesion of ten months' duration on the sole of the right foot as well as for a minor ulcer on the right shin. The lesion on the sole suggested a neurotrophic ulcer; however, detailed examinations did not reveal diabetes or a neuropathological etiology. The shin lesion was considered a relapsing ulcer of venous origin. Local treatment with commonly used enzymatic and antiseptic preparations was not effective. Instead, both lesions were gradually enlarging.

On admission to the hospital, the clinical examination revealed varices of both legs, hyperpigmentation due to hemosiderin deposits, and perimalleolar scarring of the right lower leg resulting from healed ulcers.
On the right sole at the level of the metatarsophalangeal joint of the 2nd and 3rd toe there was an oval lesion 20 × 27 mm with a clear granulating base; a brown discoloration was visible on the proximal side (Figure 1). On the anterior aspect of the right lower leg there was an ulcer 21 × 15 mm with a clear base and a central prominence (Figure 2). Except for the ulcer, the skin was unchanged; a physical examination of regional lymph nodes also showed nothing. Routine laboratory tests were within normal limits, as was the chest X-ray. Due to the long duration of the ulcerations and lack of response to standard therapy, two biopsies were performed. Histopathology of the ulcer on the sole disclosed an acral lentiginous melanoma in an advanced stage with vertical growth. It was diagnosed as Clark stage IV–V, with a depth of 4 mm according to the Breslaw index, and with invasion into dermal lymphatic vessels (Figures 3 and 4). The histopathology was confirmed immunohistochemically by positive HMB-45 staining. A biopsy from the lesion on the shin disclosed a metatypical carcinoma (Figure 5).

Following the diagnosis, a total excision of the metatypical carcinoma was carried out and radical excision of the melanoma with protective margins of 3 cm and amputation of toes II and III were performed.
The excision of the sentinel lymph node verified microscopic metastases. Elective lymph node dissection of the right inguinal area followed; histopathology showed extensive metastases. The surgical intervention was therefore followed by radiotherapy of the inguinal area $7 \times 5$ Gy (MeV). Two months later metastases to the liver were verified, and palliative radiotherapy and systemic treatment with corticosteroids were indicated.

**Discussion**

Malignant melanoma (MM) is a highly destructive tumor. Its incidence has increased significantly over the last few years, and today the incidence varies between 12 and 14 cases per 100,000 inhabitants in Europe, and 40 cases per 100,000 inhabitants in the US and Australia (1). Excessive exposure to ultraviolet radiation is considered one of the main factors responsible for the increase in incidence because of the alteration of the ozone layer surrounding the Earth. UV radiation is responsible for irreparable alterations in the DNA of melanocytes. People with pale, less-pigmented skin – phototypes I and II – face the greatest danger, but melanoma often occurs in sites not exposed to UV radiation. Evidently there are also other etiopathogenetic factors. The high incidence (ca. 20%) of acral lentiginous melanomas in the black population (1, 3) serves to illustrate this.

The main clinical-histological subtypes of MM are superficially spreading MM (57%), nodular melanoma (21%), lentigo maligna melanoma (9%), and acral lentiginous melanoma (4%). The other types include amelanotic, mucosal, and unclassifiable MMs (3).

The prognosis of malignant melanoma is based on clinical and histopathological criteria (4). The most significant and independent prognostic factor is the tumor thickness measured with an ocular micrometer from the granular layer of the epidermis to its deepest level according to the Breslow index. The state of the sentinel lymph nodes is the second most important prognostic factor; micrometastases significantly worsen the prognosis even in patients with a Breslow tumor thicknesses of 1 to 4 mm (5, 6). An independent but less significant prognostic factor is the depth of invasion measured according to Clark stages.

Other prognostic criteria are the localization of MM. Lesions on the trunk have a worse prognosis than those on the limbs, and those on the arms have a better prognosis than those on the legs. Hemorrhagic, ulcerating, and amelanotic MMs always have a bad prognosis. Nodular and acral lentiginous MMs are always less favorable. A high number of mitoses and aneuploidy of tumor cells determined by flow cytometry make the prognosis worse. On the other hand, a dense inflammatory infiltrate of the base is prognostically favorable. In general, males have a worse prognosis than females. Traditional serological markers of melanoma activity such as levels of melanin and S-100 protein in the serum are less reliable. The most accurate serological marker is probably the level of melanoma inhibitory activity (MIA).

The parameters mentioned above are not sufficient to evaluate the prognosis. It is known that even minor lesions may undergo early metastases; on the other hand, even histologically advanced MM may be dormant for many years (7). Therefore, the search for further prognostic factors is recommended. The investigations focus especially on the interactions between the tumor and adjacent stroma. The alteration of the stromal microenvironment is significant for tumor growth and invasion (8). The molecular mechanisms of tumor growth remain the subject of active research.

The pTNM staging of the disease is necessary for selecting appropriate therapy: pT = primary tumor, pN = regional lymph nodes, pM = distant metastases. This staging can be done only after the excision and histopathological examination.

Our patient was diagnosed with acral lentigious melanoma, underwent a radical excision, and was classified as IIIC (pT3b, N3, M0). Elective lymph node dissection in the right inguinal area and actinotherapy followed. Other recommended methods of treatment such as immunotherapy, chemotherapy, or hyperthermic cytostatic perfusion (4, 9, 10, 11) were not applied because of the patient’s poor general condition and the rapid progression of the disease.

This variety of MM frequently affects the ungual matrix or ungual bed; the localization may be also palmoplantar (12). It may be easily misinterpreted as a benign lesion (13). Viral warts, clavus, subungual hematomas, pyoderma, and junctional nevi in particular have to be excluded. In advanced ulcerating tumors it is necessary to consider ulcers of various etiology. Although in our patient there was no preceding history of pigmented lesions, discrete discoloration at the margin of the lesion suggested a malignant melanocytic lesion.

Histologically, acral lentigious MM shows radial growth characterized by the presence of atypical melanocytes in the basal layer of epidermis, sometimes crowded in nests. Usually the epidermis is hyperplastic with possible focal ulcerations. As the tumor advances there is usually invasion of the dermis by nests of epithelioid or fusiform cells. The presentation of superficially spreading or nodular MM is usually observed (14). The initial stages present difficulties for microscopic interpretations, especially if the biopsy is not large enough. In doubtful cases, immunohistochemical examination is suggested. The expression of S-100 protein, Melan-A, and HMB-45 are characteristic of malignant melanoma (14).

In cases of a suspected MM it is appropriate to perform total excision of the lesion with protective edges, followed by histopathological evaluation.

The second tumor in our patient was a metatypical carcinoma. Its relation to squamous cell carcinoma is widely discussed (1). In the subclass of the so-called transient tumors, whose proportion within basal cell carcinomas varies between 3 and 12%, they may be also clas-
sified as basosquamous carcinomas, which are considered to be the collision of two individual tumors in the same lesion. Keratotic basal cell carcinoma with pronounced keratinization is another type. It is most probably of follicular origin (1, 15). As for the clinical morphology and behavior, it is similar to other types of basal cell carcinomas.

Metatypical carcinoma is a relatively rare tumor type. Clinically, it is characterized by locally aggressive behavior and the tendency to pronounced invasion and radioresistance (1). The described cases of metastatic basal cell carcinomas mostly represent this type of tumor. Histopathology showed basaloid cells of a spiky shape with a loss of the typical palisade pattern of the cells at the margins; certain spots of squamous differentiation were also observed. This distinction between the tumor and the dermis is quite typical, as is a rather deep invasion into the dermis. Nests and strands of more mature cells were also present in the case documented here. Perineural infiltration and invasion into the bones is rather uncommon (14, 15). None of the common carcinogens (excessive exposure to UV or X-rays, chemical carcinogens, or genetic background) were shown to be factors in our patient.

Although ulcerations of venous etiology prevail among leg ulcers, one should carefully consider other etiologies. Attention should be paid to all abnormal-looking ulcers, especially those not responding to standard therapy. An early and appropriate biopsy is a key procedure among diagnostic methods.

REFERENCES


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