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Metastatic Melanoma and Vitiligo: A Case Report

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SUMMARY Different clinical studies report the connection between malignant melanoma (MM) and vitiligo, as the etiology of both diseases evolves around melanocytes. A case is presented of a 70-year-old female patient with metastatic MM in lymphatic node of the right groin, which developed simultaneously with the "vitiligo-like patches" over the face and extremities. Some authors suggest that the appearance of depigmentation during the course of MM might be considered a good prognostic sign. However, our patient subsequently developed multiple lung metastases as well as metastases in lymphatic nodes of the other groin region. This case shows that MM and vitiligo may develop simultaneously, indicating the possibility of similar mechanisms in the destruction of both benign and malignant melanocytes.

KEY WORDS: malignant melanoma; vitiligo; melanocytes, melanoma-associated hypopigmentation

INTRODUCTION

Malignant melanoma (MM) is a cancer of melanocytes, which can sometimes develop simultaneously with vitiligo, a depigmenting disorder with the loss of melanocytes from the epidermis. Healthy skin contains melanin produced from the amino acid tyrosine by skin melanocytes, but in the skin affected by vitiligo, melanocytes are absent and there are signs of inflammation in the deeper layer of the skin (1,2).

Several clinical observations suggest that there is a certain immunological link between MM and vitiligo (3,4). However, the nature of immune disturbances associated with these diseases is yet not elucidated (4,5).

We present a case of a 70-year-old female patient with metastatic MM in lymphatic node of the right groin, which developed simultaneously with the "vitiligo-like patches" over the face and extremities.

CASE REPORT

A 70-year-old female Caucasian was referred to our department after biopsy of a brown reddish inflamed node in the right groin region. Histopathologic examination of the node showed connective and fatty tissue infiltrated with tumor cells. The tumor consisted of clusters of polygonal cells with prominent nucleoli and a substantial quantity of

Acta Dermatovenerol Croat
2006;14(2):100-103

cytoplasmic melanin showing high mitotic activity with up to 5 mitoses per high-power field (HPF), indicating metastatic MM (Fig. 1).

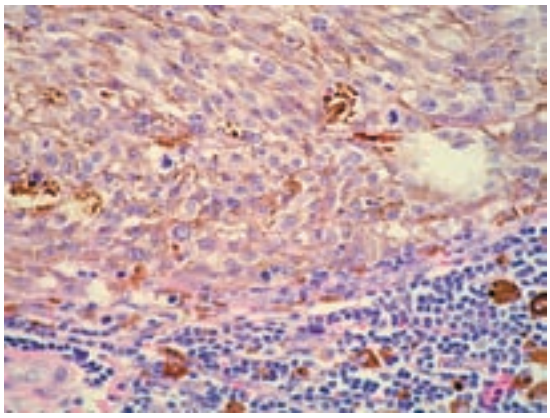

Figure 1. Connective and fatty tissue infiltrated with tumor made up of clusters of polygonal cells with prominent nucleoli and a substantial quantity of cytoplasmic melanin showing high mitotic activity of up to 5 mitoses per high-power field (HPF), indicating metastatic melanoma (HE, x400).

According to history data, at the same time when the inflamed node in the right groin appeared, the patient noticed emerging of small, multiple, well-demarcated, confluent depigmented patches over both wrists and dorsal sides of fingers. Depigmented macular lesions also spread gradually over the face during the period of 4 months, followed by the affection of groins and lower legs (Fig. 2).

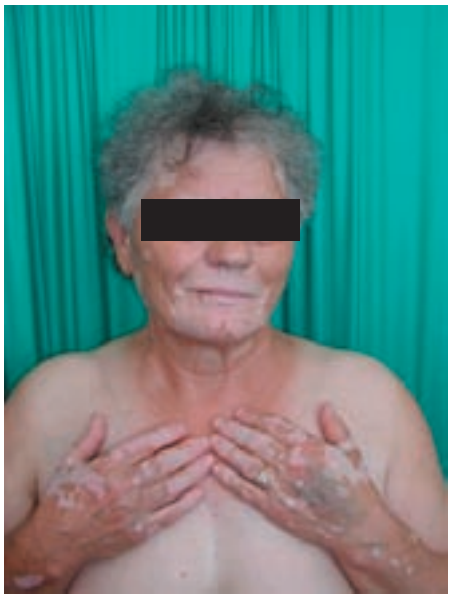

Figure. 2. Multiple, well-demarcated, confluent, depigmented patches over the face, both wrists and dorsal sides of fingers in the patient with histopathologically verified metastatic melanoma in lymphatic node of the right groin.

In spite of thorough clinical examination of the skin and mucous membranes, primary melanoma had never been discovered. Unfortunately, our patient subsequently developed multiple lung metastases as well as metastases in lymphatic nodes of the other groin region.

Previous patient's medical history included hysterectomy 18 years before (due to myomatous uterus), and cholecystectomy 8 years ago and, was otherwise unremarkable. It was also reported that the patient had been spending a lot of time in the sun, working in the field. The patient's family medical history included frequent non-skin cancers.

DISCUSSION

A variety of arguments obtained from clinical observations support the hypothesis that autoimmunity is important for the development of both MM and vitiligo. Although the cause of vitiligo has not yet been elucidated, there are three major hypotheses: autoimmune, neural and self-destruction hypothesis (1,2,6). Probably each of them plays a role in individual cases, however, there are convincing scientific arguments both for and against each hypothesis.

The autoimmune hypothesis of vitiligo implies an autoimmune reaction against melanocytes during the process of their normal turnover in the basal layer with the development of cytotoxic reactions and subsequent destruction of normal melanocytes (1,7). Many autoantibodies have been demonstrated in vitiligo patients, but those against melanocytes are among the hardest ones to find. Despite specific autoantibodies against melanocytes found in the blood of vitiligo patients, it is not known whether autoantibodies are the cause or the effect of the damage.

Some studies showed most patients with melanoma or with vitiligo to develop antibodies to similar antigens present both on melanocytes and on melanoma cells, supporting the hypothesis that the clinical link between these two diseases may be the result of immune responses to antigens shared by both normal and malignant pigment cells (5). The enzyme tyrosinase participates in melanin production in normal melanocytes and melanoma cells, thus the detection of antityrosinase antibodies in patients with vitiligo and melanoma supports the hypothesis that tyrosinase may be an autoantigen in these conditions (8).

Neural hypothesis for the development of vitiligo is based on the fact that vitiligo lesions often fol-

Acta Dermatovenerol Croat
2006;14(2):100-103

low a dermatomal pattern, suggesting that a neurochemical mediator is responsible for destruction of melanocytes. This fact indicates an association of nerve damage with the loss of pigment in the skin area served by the nerve. However, the distribution of depigmented patches in our patient did not correspond to dermatomal pattern.

Self-destruction hypothesis of vitiligo development is based on the assumption that toxic intermediatory products of melanin synthesis destroy melanocytes (1).

There are several reports on the appearance of ''vitiligo-like patches'' on the skin of patients with MM, called melanoma-associated hypopigmentation (MAH) (8). Several types of hypomelanosis may occur in patients with MM (9). The loss of pigmentation may involve the primary lesion itself (the form of an eccentrically placed hypopigmented macule, analogous to halo nevus), or it may occur in distant locations (a process known as melanoma-associated leukoderma). Unfortunately, primary melanoma has never been diagnosed in our patient. Therefore, it remains questionable whether in this case the loss of pigmentation included the primary lesion itself or it occurred in a distant location.

Furthermore, leukoderma may be hypomelanotic and mottled, or depigmented and milk-white. In some cases spontaneous repigmentation may occur. Clinically, it is frequently first observed on the trunk, with subsequent spread to extremities. On the contrary, our patient's depigmenting process began on the extremities, followed by the affection of the face.

The leukoderma observed in MM patients may develop as the result of an immune response against abnormal melanocytes. Some authors suggest that the appearance of depigmentation during the course of MM might be considered a good prognostic sign (3,5,9,10). On the other hand, our patient subsequently developed multiple lung metastases as well as metastases in lymphatic nodes of the other groin region.

Furthermore, one study in which the sera of patients with vitiligo, melanoma, MAH, and of healthy subjects were examined, defined antibodies to the B16 melanoma cell line and to tyrosinase, indicating the cross-antigenicity between melanocytes and melanoma cells (11). These results support the hypothesis on the participation of antibodies against melanoma-associated membrane antigens in the mechanism that leads to the development of MAH.

Besides humoral immunity, the role of cellular immunity in vitiligo was confirmed by histological and immunohistochemical studies in perilesional skin, and T-cell analyses in peripheral blood (7,12).

It has been observed that some factors found in melanoma patient sera contribute to the impairment of cytotoxicity, whereas other factors from the serum of vitiligo patients and control subjects enhanced their peripheral blood mononuclear cell antimelanoma cytotoxicity (4).

Examination of spontaneous vitiligo in human melanoma and animal model revealed the role of tumor-specific CD8(+) T cells (10). Namely, tumor antigen-reactive T cells can be detected in a large proportion of MM patients, in spite of their unclear efficacy on tumor control in vivo. It has also been noticed that immunologic destruction of tumors including melanoma is mediated primarily by activated T cells exerting this effect by recognizing peptides derived from endogenous proteins (3,13). These proteins may be either antigens encoded by tumor-specific or mutated genes, or melanocytic differentiation antigens, which are normal proteins restricted to the melanocyte lineage, such as tyrosinase, Melan-A/MART-1, and gp 100. In the majority of melanoma patients T cells specific to these antigens were found. T cells involved in the destruction of neoplastic melanocytes are identical clones of those that accumulate in melanoma-associated leukoderma, thus indicating the association between vitiligo-like leukoderma (resulting from destruction of normal melanocytes) and melanoma regression (resulting from destruction of cancer cells) (9).

CONCLUSIONS

Although some authors suggest that simultaneous occurrence of melanoma and skin depigmentation often presents a good prognostic sign, our case warns about the possibility of poor outcome, especially when it is impossible to detect primary melanoma. This case indicates the importance of an early and detailed examination of vitiligo patients, since both vitiligo and melanoma are diseases based on melanocytic changes which in case of melanoma may be fatal.

Despite many unknown mechanisms, understanding the nature of immune responses directed against normal melanocytes and their malignant counterparts may lead to better understanding of the mechanisms and factors involved in the pathogenesis of both vitiligo and melanoma.

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For skin protection in the spring – Nivea cream and oil, year 1935.
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