

Low frequency of skin cancers in vitiligo patients

Mniejsza częstość zachorowań na raka skóry u pacjentów z bielactwem

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ABSTRACT

KEY WORDS:

vitiligo, malignant melanoma, nonmelanoma skin cancers.

SŁOWA KLUCZOWE:

bielactwo nabyte, czerniak, nieczerniakowe nowotwory skóry.

Vitiligo is a disease characterized by discoloration of the skin and hair as a result of damage of melanocytes. The exact mechanism of the disease is still unknown. Theories about the pathogenesis focus on autoimmune, neurogenic and autotoxic mechanisms. There is a decreased risk of incidence of skin cancers in patients with vitiligo. The relation between vitiligo and decreased frequency of cases of malignant melanoma (MM) may be a consequence of the immune response to antigens, which are common for melanocytes and MM cells. Genetic studies indicate a mutually exclusive relationship of melanoma and vitiligo. This disease is also associated with a polymorphism in the TYR gene which encodes tyrosinase. Studies also indicate a decreased risk of incidence of nonmelanoma skin cancers (NMSC) in patients with vitiligo.

STRESZCZENIE

Bielactwo jest chorobą charakteryzującą się odbarwieniami skóry i włosów w wyniku uszkodzenia melanocytów. Dokładny mechanizm tej choroby jest nadal nieznan. Teorie na temat patogenezy koncentrują się wokół mechanizmów: autoimmunologicznych, neurogenicznych i autotoksycznych. U pacjentów z bielactwem odnotowano zmniejszone ryzyko zachorowań na nowotwory skóry. Związek między *vitiligo* a zmniejszoną częstością występowania przypadków *melanoma malignum* (MM) może wynikać z odpowiedzi immunologicznej przeciwko antygenom, które są wspólne dla melanocytów i komórek czerniakowych. Badania genetyczne wskazują na wzajemne wykluczanie się bielactwa i czerniaka. Choroba ta również wiąże się z polimorfizmem w genie kodującym tyrozinazę (TYR). Badania wskazują także na zmniejszone ryzyko zachorowań na nieczerniakowe nowotwory skóry u pacjentów z bielactwem.

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INTRODUCTION

Vitiligo is characterized by discoloration of the skin and hair as a result of the damage of melanocytes [1]. The exact mechanism of the disease is still

unknown. Theories about the pathogenesis focus on autoimmune, neurogenic and autotoxic mechanisms. Higher incidence of antibodies against the surface antigens of melanocytes in patients with vitiligo suggests an immune pathogenesis. Autoreactive

CD8+ T cells may participate in the destruction of melanocytes. It is worth mentioning that vitiligo is often accompanied by other autoimmune diseases such as thyroid or Addison's disease, pernicious anemia and systemic lupus erythematosus [2–6]. The autocytoxic theory is based on the assumption that skin melanocytes in patients with vitiligo are more susceptible to toxic agents which could come from the external environment, such as phenol or quinones. Increased apoptosis of melanocytes can also be the result of the influence of toxic products released during transformation of melanin, e.g. of phenolic compounds mentioned above [7]. The neurogenic theory is based on abnormalities in the production of neurotransmitters in the adrenergic nervous system, which can lead to a decrease in melanin synthesis or melanocyte destruction. Evidence supporting this theory is the frequent stacking of depigmented areas along dermatomes [7, 8]. Currently, the most popular is the polyetiological theory, according to which the genetic background predisposes to depigmentation, in conjunction with the influence of a variety of other factors, such as pregnancy, infections, stress and imbalance in the diet [9].

There are three basic types of vitiligo:

- localized: focal, segmental, mucosal,
- generalized: acrofacial, vulgaris, mixed,
- universal [2, 10, 11].

The disease affects 0.5–4% of the total population. There is no significant correlation between gender or race and the incidence. Vitiligo may occur at any age, but approximately 50% of cases occur before the age of 20 [2, 10–12].

VITILIGO AND SKIN CANCERS

Many researchers have paid attention to the relationship between vitiligo and skin cancer [13]. It is noteworthy that there is a decreased risk of skin cancers in patients with vitiligo [14]. Tobin *et al.* observed that

discolored skin is not completely deprived of melanocytes and that they may, *in vitro*, regain their functions [15]. For this purpose, bovine catalase was added to the culture medium of melanocytes obtained from discolored patches, to deactivate reactive oxygen species [16, 17]. A similar phenomenon was observed after *in vivo* administration of pseudocatalase activated earlier with narrowband UVB radiation, which was also associated with inactivation of reactive oxygen species [17]. Impairment of the antioxidant system is observed in melanocytes of vitiligo patients. The melanin synthesis intermediates (3,4-dihydroxyphenylalanine, dopachrome, 5,6-dihydroxyindole), through increased production of free radicals, are toxic to melanocytes [17]. The relation between vitiligo and lower incidence of cases of malignant melanoma may be a consequence of the immune response to antigens, which are common for melanocytes and malignant melanoma (MM) cells. Both cellular and humoral responses play a role in this mechanism. It mainly involves antityrosinase antibodies and infiltrating CD8+ oligoclonal T cells. It is assumed that these actions lead to the destruction of melanocytes during the immune response to MM antigens [16]. Genetic studies indicate a mutually exclusive relationship of melanoma and vitiligo (the SNP alleles in the TYR gene are related to vitiligo and the minor alleles to melanoma) [18]. Vitiligo is also associated with a polymorphism in the TYR gene which encodes tyrosinase, the major enzyme involved in melanin synthesis [13].

Melanoma-associated leukoderma (MAL) is a poorly understood condition. There are at least three types of leukoderma associated with melanoma:

- primary melanoma regression, where the tumor is replaced with fibrous stroma, but complete regression is very rare (malignant melanoma with numerous fields deprived of pigment inside the lesion are shown in Figure 1),
- halo nevus (Sutton's nevus, Figure 2),

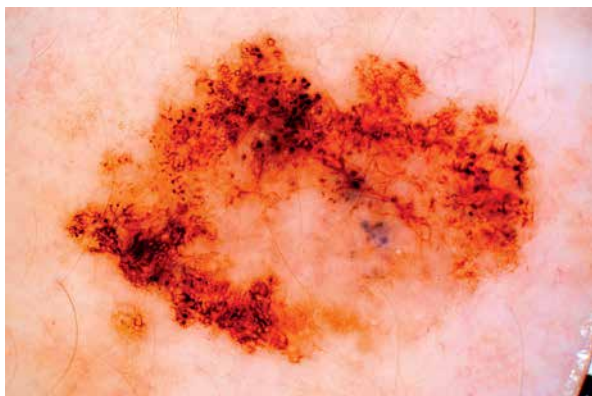


Figure 1. Malignant melanoma with numerous fields deprived of pigment

Rycina 1. Melanoma malignum z licznymi ogniskowymi odbarwieniami



Figure 2. Halo nevus (Sutton's nevus)

Rycina 2. Znamię Suttona (halo nevus)

- melanoma associated depigmentation/leukoderma - white patches occurring distantly from primary tumor [19].

Melanoma-associated leukoderma may develop in melanoma patients (2–16%), mainly in advanced stages and corresponding therapies. Also rarely MAL is seen before melanoma detection, or after detection and before treatment, sometimes in melanoma of unknown primary localization [19–21].

Although the efficiency of this antitumour response may not be sufficient for complete eradication of melanoma, longer survival has been observed in MAL patients on different antitumor therapies [22, 23]. Studies by Quaglino *et al.* [24] and Phan *et al.* [25] showed a higher response to high-dose interleukin 2 (IL-2) therapy in patients who developed MAL.

The association between melanoma and leukoderma is probably the result of the immune response against antigens that are present in normal melanocytes and melanoma cells. Cellular immunity takes place in melanoma progression and development of MAL [20, 25]. Therefore appearance of depigmented skin lesions in patients with melanoma may suggest a better prognosis. It is supposed that discoloration of the skin is a marker of developing immunity against melanoma [26]. Studies have shown that melanoma patients with skin depigmentation and halo nevi have a higher survival rate than expected [27].

Melanoma-associated leukoderma development and autoimmunity may be associated with more efficient activation of the immune system against antigens common to melanocytes and melanoma cells, which can mediate tumor regression and prolong patients' survival [13, 14, 16, 18]. Such an assumption may seem controversial because, despite the autoimmunity present in patients with vitiligo, there is a lack of a protective role of melanin. This may

suggest increased susceptibility to sun damage and subsequent risk of carcinogenesis [13, 17, 28]. At the same time, patients with vitiligo are recommended to use photoprotection products with a high sun protective factor (SPF). They are also advised to contact a dermatologist more frequently, which allows early detection and treatment of skin cancers [13, 28].

Studies also indicate a decreased risk of nonmelanoma skin cancers (NMSC) in patients with vitiligo. It is assumed that the overexpression of the wild protein p53, which is responsible for apoptosis, present in keratinocytes of these patients, prevents photodamage of the skin and development of tumors of epidermal origin. Patients with vitiligo have increased levels of glutathione peroxidase and superoxide dismutase [28–30] and overproduction of interleukin (IL)-1 and tumor necrosis factor (TNF)- α , which play a role in the induction of superoxide dismutase. At the same time, there is a decrease of transforming growth factor (TGF)- β and IL-10, which may indicate reduced susceptibility to skin carcinogenesis [31, 32]. An important function of glutathione peroxidase in protecting cells from oxidative damage was confirmed in a study of mice irradiated by UV. The UVR provoked a decrease of the enzyme level and this, in consequence, predisposed to formation of squamous cell carcinoma [29].

Teulings *et al.* conducted a retrospective comparative study of 1307 patients with vitiligo and their partners as a control group, to assess the incidence of melanoma and nonmelanoma skin cancers [14]. There was three times lower risk of developing melanoma and non-melanoma skin cancers in patients with vitiligo compared to those without hypopigmentations. Phototherapy (narrowband UVB, PUVA) did not increase the risk of neoplastic lesions in vitiligo [14]. Other authors [28] conducted a study to evaluate the effect of concomitant vitiligo on the risk of developing MM and NMSC in 10 040 patients who were compared to patients without vitiligo, hospitalized at the department of vascular surgery. In the group of patients with vitiligo the crude risk ratio for developing malignant melanoma was 24%. The incidence of MM in this group was 1.1‰ at the 5% significance level (confidence interval 0.5–2.0‰), while in the control group it was 4.5‰ [28].

The crude risk ratio for nonmelanoma skin cancers in patients with vitiligo was 19%. The incidence of NMSC was 3.8‰ at the 5% significance level (confidence interval 2.7–5.2‰). This ratio for those without vitiligo was 19.6‰ (significance level of 5%, confidence interval 18.0–21.4‰). In patients who underwent phototherapy the risk of developing cancer was significantly higher, but still lower than in those without vitiligo (Figures 3, 4). The results of the Paradisi *et al.* study indicate a lower risk

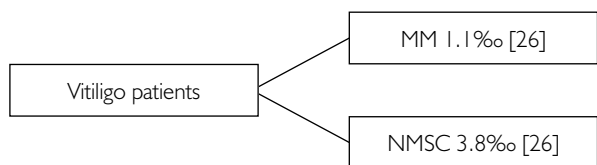


Figure 3. Incidence of malignant melanoma and nonmelanoma skin cancers in vitiligo patients

Rycina 3. Częstość występowania czerniaka i nieczerniakowych nowotworów skóry u pacjentów z vitiligo

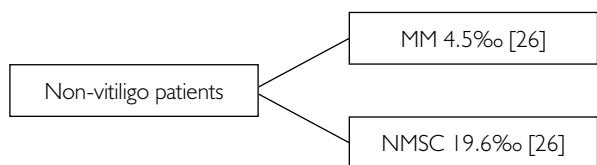


Figure 4. Incidence of malignant melanoma and nonmelanoma skin cancers in non-vitiligo patients

Rycina 4. Częstość występowania czerniaka i nieczerniakowych nowotworów skóry u pacjentów bez vitiligo

of developing skin cancer in patients with vitiligo despite increased exposure to UV radiation associated with frequently used phototherapy [29]. This may be related to the recommendation of the use of creams with a high SPF. Some studies suggest a slightly increased risk of developing skin cancers associated with the use of phototherapy [33]. Sunlight exposure is a risk factor of squamous cell carcinoma (SCC) and to some extent of basal cell carcinoma (BCC). There are data indicating that artificial light (tanning beds) also leads to skin neoplasms [34]. Also light therapies may carry some risk. In psoriasis patients it was observed that long-term PUVA or UVB therapy increased the risk of SCC development. Exposure to more than 350 PUVA treatments greatly increased the risk of SCC [35, 36]. However, UVB remains a low-risk treatment. Also the dose-dependent risk of melanoma has been documented in PUVA patients [37, 38].

Vitiligo patients are not exposed to so many UV treatment sessions as psoriasis patients, and mainly restricted fields are irradiated. British Association of Dermatologists clinical guidelines recommend narrowband (NB) UVB in preference to oral PUVA due to evidence of greater efficiency [39]. A newer method is excimer laser, which is effective in adults and children with vitiligo as monotherapy or in combination with other therapeutics [40]. It should be stressed that also UVA and psoralen + UVA are successfully used in vitiligo treatment [41, 42].

Data from Saudi Arabia show that the most frequently prescribed phototherapy in generalized vitiligo is narrowband ultraviolet B (NB-UVB) and in focal or segmental vitiligo excimer laser [37, 38].

In conclusion, patients with vitiligo are less prone to the development of MM and NMSC, and even the use of phototherapy does not increase this risk.

It is not without significance that vitiligo patients are more frequently monitored by dermatologists, and therefore they are diagnosed faster and undergo more effective treatment.

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Conflict of interest

The authors declare no conflict of interest.

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