Actas Dermosifiliogr. 2014;105(2):122–127

ACTAS Dermo-Sifiliográficas

Full English text available at www.actasdermo.org

REVIEW

Immunological Basis of Melanoma-Associated Vitiligo-Like Depigmentation☆

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Received 16 March 2012; accepted 20 June 2012
Available online 25 February 2014

KEYWORDS
Melanoma;
Vitiligo;
Leukoderma;
Autoimmunity

Abstract Vitiligo is a skin condition characterized by white, hypopigmented macules. Melanocyte loss is a feature of the disease, and it has been hypothesized that an autoimmune mechanism could be responsible for the depigmentation. Melanoma is a malignancy that develops in melanocytes; if not detected and treated early, it is often deadly. Leukoderma, a condition characterized by depigmentation of the skin, is sometimes associated with malignant melanoma. An immune response against melanocyte antigens leading to destruction of either melanoma cells or melanocytes has been observed in both vitiligo and melanoma. Studies in animal models and humans have shown that humoral and cell-mediated immune responses are involved in modulating cytotoxic activity against tumor cells and normal melanocytes. The study of factors associated with anti-tumor immunopathogenic mechanisms —autoimmunity for example—may provide us with tools for the diagnosis and treatment of diseases such as vitiligo and malignant melanoma.

PALABRAS CLAVE
Melanoma;
Vitíligo;
Leucodermia;
Autoinmunidad

Bases inmunológicas de la hipopigmentación vitiligoide asociada a melanoma

Resumen El vitíligo es una patología cutánea que se manifiesta en forma de manchas hipocrómicas y acrómicas. Se caracteriza por la pérdida de melanocitos y se ha hipotetizado que un mecanismo autoinmune podría estar estrechamente relacionado con este fenómeno de despigmentación. El melanoma es una neoplasia maligna derivada de los melanocitos, que es letal si no se trata oportunamente. La leucodermia es un fenómeno de despigmentación cutánea, que ocasionalmente se puede asociar a melanoma. Tanto en los pacientes con vitíligo como con melanoma se ha observado una respuesta inmune contra antígenos de las células melanocíticas, ya sea para la destrucción de los melanocitos normales como de las células tumorales. A través de diversos estudios en humanos y modelos animales se ha observado que,

☆ Please cite this article as: González R, Torres-López E. Bases inmunológicas de la hipopigmentación vitiligoide asociada a melanoma. Actas Dermosifiliogr. 2014;105:122–127.

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1578-2190/$ - see front matter

tanto la inmunidad humoral como la celular tienen un papel inmunorregulador en la citotoxicidad contra el tumor o contra las células melanocíticas. El estudio de los factores asociados a los mecanismos de inmunopatogenicidad antitumoral, así como a la autoinmunidad es, en potencia, una vía alternativa para el diagnóstico y tratamiento de patologías como el vitíligo y el melanoma maligno.

Introduction

Vitiligo is a disorder characterized by well-delimited white, hypopigmented macules with no detectable melanocytes. The condition is usually acquired, although congenital and familial cases have been reported.[1] The main burden of the disease is its effect on the psychological state of the patient. The worldwide prevalence is estimated to be 0.5%[2] and the incidence is approximately 1% to 2% in the general population. Clinically, vitiligo presents as round or oval white, hypopigmented macules with regular borders. It can sometimes show a trichrome coloration (band of tan color between the white macule and healthy skin) or quadrichrome coloration (perifollicular or marginal macular hyperpigmentation in cases of repigmenting vitiligo). Another clinical form is inflammatory vitiligo, with a raised red border similar to pityriasis versicolor. The distribution patterns of vitiliginous lesions include focal vitiligo (isolated lesion), segmental vitiligo (unilateral macular lesions which generally cover a dermatome), generalized vitiligo (most common form, disseminated macules of variable size, usually with a symmetric distribution and a certain predilection for extensor surfaces), and vitiligo universalis (severe form that affects more than 80% of the body surface).

Certain proteins located in melanosomes are required for the synthesis of melanoma, the pigment responsible for color in eyes and skin and its appendages.[3] These molecules are denoted melanosomal proteins and are classified into 2 groups:

Tyrosinase and tyrosinase associated protein 1 (encoded by the *TYRP-1* gene) and protein 2 (encoded by the *TYRP-2* gene), which catalyze the biochemical steps in the biosynthesis of melanin

Melanoma-antigen recognized by T cells (MART-1), Pmel17, Rab7, and Rab27, responsible for retaining the melanosomal structures and/or transporting the melanogenic proteins or melanin pigments

All these proteins are important from the pathogenic, diagnostic, and therapeutic point of view in a large number of pigmentary disorders (vitiligo, piebaldism, melanocytic nevus, and melanoma, among others).

To date, different theories have been put forward to explain the possible pathogenesis of vitiligo, with the immunology-based theory being the most widely accepted. On the one hand, it has been shown that vitiligo can be associated with other autoimmune disorders, especially autoimmune thyroiditis. On the other, in these patients, antibodies against melanocyte antigens such as tyrosinase, TRYP-1, and TRYP-2 have been detected. In addition, there are studies that show that cellular immunity also has an impact on the development of vitiligo. Infiltrates have been found to contain $CD8^+$ T cells that are reactive with melanocyte self-antigens such as Melan-A/MART-1, tyrosinase, and gp-100.[1]

Treatment for vitiligo depends on the presence and severity of associated comorbidities. Therapy is based on topical immunosuppressive agents (corticosteroids and calcineurin inhibitors) and phototherapy to induce repigmentation. In cases of extensive depigmentation, depigmentation of healthy skin is indicated using hydroquinone monobenzyl ether.[1]

Melanoma is a fatal mucocutaneous or ocular neoplasm that can be sporadic or familial. The neoplasm is associated with a range of genetic factors. Other predisposing factors are exposure to intense sunlight associated with sunburn and a clear phototype (Fitzpatrick skin type I and II, mainly), although patients with darker phototypes can also present with the neoplasm. Melanoma accounts for approximately 5% of all cancers in men and 4% in women.[4] The incidence of cutaneous melanoma among Caucasians is reported to be increasing by between 3% and 7% each year.[5]

The clinical presentations of cutaneous melanoma have been widely reported in dermatology and oncology texts, and so the present review will not cover them in depth. It is however important to mention that lesions are usually macular or nodular, with irregular borders, and generally hyperpigmented with a variety of colors ranging from light coffee to blue and grey. Regions of hypopigmentation (regression) may even be present. Some form of recurrence or metastasis (regional or distant) is reported in between 15% and 36% of patients with early-stage melanoma (I and II) during the clinical course of their disease.[4] The accepted prognostic factors in the classification of the American Joint Committee on Cancer (AJCC) from 2009 include tumor thickness, level of invasion (only for T1 melanomas), mitotic rate per mm^2, ulceration, presence of satellite, lymph node, and pulmonary metastases, high levels of lactate dehydrogenase,[6] and antitumor lymphoid response. The latter factor specifically refers to tumor-infiltrating lymphocytes, whose density in the infiltrate is directly proportional to improved prognosis.[4] The function of this infiltrate would therefore seem to be to generate an innate antimelanoma immune response, although unfortunately this is insufficient to fully eradicate the neoplasm in many cases.[3] Other prognostic factors that have also been taken into consideration are age, sex, anatomic site of the tumor, and regional lymph node involvement.[4]

Melanoma is a highly immunogenic neoplasm. In other words, it stimulates the immune system to generate a humoral (antibody-mediated) and essentially cellular (cytotoxic lymphocyte-mediated) response to cytoplasmic antigens as well as to the membrane of melanoma cells.[3] Melanoma-associated antigens can generally be classified into 2 groups: