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The Relationship between melanoma and vitiligo

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Abstract: Cutaneal skin cancer represents the foremost aggressive sort of carcinoma, whereas vitiligo is an autoimmune disorder that results in progressive destruction of skin melanocytes. However, vitiligo has been related to cutaneous melanoma since the 1970s. Most of the antigens recognized by the immune system are expressed by each melanoma cells and traditional melanocytes, explaining why the autoimmune response against melanocytes that led to vitiligo could be also present in melanoma patients. Leukoderma has been also observed as a side effect of melanoma immunotherapy and has always been associated with a favorable prognosis. During this report, we tend to discuss several characteristics of the immune system responses shared by melanoma and vitiligo patients, also because of the significance of the incidence of leukoderma throughout immunotherapy, with special attention to checkpoint inhibitors.

Introduction: Vitiligo is a chronic systemic acquired disease that has an unforeseeable clinical course, characterized by the occurrence of macules and achromic or hypochromic patches on the skin and mucous membranes due to the vanishing of melanocytes in the affected area. Along with the skin and mucosal involvement, melanocytes in the ocular (mostly in the uveal tract) and auditory apparatus (in vascular streaking and the modiolus of the cochlea) can be reduced, ocular diseases such as uveitis or even neurosensorial hearing loss may also occur. Yet, Psychological impact is one of the main outcomes of the disease, ago vitiligo can have strong effects on patients 'self-respect, with an increase in severe depression cases and a sharp sense of social discrimination resulting in quality of life deterioration(3). Melanoma is one of the most common malignant skin tumors with permanently rising incidence worldwide, essentially in fair-skinned populations (2). It is usually diagnosed at an average age 50, but for the time being is also diagnosed more frequently in younger adults, and very seldom in childhood. There is no specific or unique clinical presentation of melanoma. Clinical presentation of melanomas varies relying on the anatomic localization and the type of growth (2). The past several contracts of exploring in tumor immunology have discovered a strong connection between tumor immunity and autoimmunity. This relationship is first understood in the context of the prolonged overlap between antigens expressed by a tumor and its normal tissue counterpart. The development of vitiligo in conjunction with melanoma is the best example of a study of tumor immunity and autoimmunity.

Vitiligo, or the autoimmune devastation of melanocytes, is a distinct positive predictive factor for melanoma patients, and its happening is increased by certain immunotherapies that pay T cell responses to melanoma. For years autoimmunity has been viewed as a side effect of robust anti-tumor immunity. New research now explains that autoimmune melanocyte killing also directly maintains T cell immunity to melanoma. The critical of autoimmunity in shaping anti-tumor immunity now informs the interpretation of immunotherapeutic responses in the lab and the clinic. In this research perspective, we explore the history linking melanoma and vitiligo in patients, and the characteristics of memory T cell responses that are governed by vitiligo. Finally, we discuss the importance of autoimmunity for the success of tumor immunotherapy (1).

Aim: Discuss several characteristics of the immune system responses participate by melanoma and vitiligo patients, as well as the significance of the appearance of leukoderma through immunotherapy.

Methods: The three in vitro assays applied to locate the antibody reactivities utilizing a mouse melanoma cell line B-16-F10 and M-14 human melanoma cells as a goal are as follows: enzyme-linked immunosorbent assay (ELISA), proliferation assay, and morphologic checking in the presence of antibodies purified from sera of patients with vitiligo. In the Vivo studies, experimental melanoma was intravenously induced in C57BL/6 mice, and the mice were treated by daily intraperitoneal injections with purified immunoglobulin G (IgG) fraction derived either from patients with vitiligo or from healthy subjects (4).

Results: The binding of immune globulin derived from patients with vitiligo was by incontestable ELISA. Exposure of malignant melanoma cells to the vitiligo autoantibodies was followed by inhibition of their proliferation capability. Also, morphologic alterations exemplified by detachment of the cells from their solid support related to melanin release were ascertained within the in the B-16-F10 cells. Less pathological process foci developed within the lungs of the mice treated with the refined immune globulin from the sera of patients with vitiligo compared with those treated with refined immune globulin fraction from healthy subjects(4).

In this report for biomarkers (table1), several studies showed an association between a high range of current neutrophils and/or neutrophil-to-lymphocyte quantitative (NLR)

and responsiveness to therapy. Thus, neutrophils could also be the expression of an immunosuppressive environment evoked by the malignant melanoma itself and their presence could distinguish between responsive and not-responsive individuals. NLR has also been investigated in vitiligo patients.NLR values were found to be significantly higher in patients who had generalized vitiligo than in those with localized vitiligo and healthy controls. Other biomarkers, proposed to be predictive for response to immunotherapy with checkpoint inhibitors, such as PD-1/PD-L1or CTLA-4expression, presence of an IFN- signature, or augmented inflammatory cytokines, are also hallmarks of active vitiligo. Expression of PD-L1 on tumor cells may play an important role in blocking T cell immune responses. In a study on melanoma patients receiving anti-PD-1 antibodies, intratumoral positivity to PD-1 significantly correlates with response to immunotherapy. Other evidence indicates that response is associated more with PD-L1 expression in tumor-infiltrating immune cells than on tumor cells themselves. A study of patients with metastatic melanoma showed that exosomes released from melanoma cells carry PD-L1 their surface and that the increase in levels of vitiligo, PD-1 expression in CD8+ T cells is positively associated with disease activity. An immune-active microenvironment favors the response to checkpoint inhibitors. High-treatment expression of IFN- or IFN--inducible factors, such as CXCL9, CXCL10, or CXCL-11, was associated with response in melanoma patients. Interestingly, in vitiligo an IFN-signature is present and high serum levels of CXCL-9 or, more prominently, of CXCL-10 are present in patients with progressive disease IFN-uses the Janus kinase (JAK)/signal transducers and activators of transcription (STAT)pathway to activate inflammatory chemokines and cytokines, and expression of both JAK1 and STAT3is up-regulated in vitiligo. Thus, JAK inhibitors are evaluating as possible therapeutic options for vitiligo as they down-regulate IFN- signaling. Importantly, JAK1 or JAK2 mutations are also associated with acquired resistance to checkpoint inhibitor immunotherapy in melanoma patients. High pretreatment expression of CTLA-4 in the tumor tissue or tumor-infiltrating lymphocytes positively correlates with response to treatment with anti-PD-L1 antibodies. Variants in the gene coding for the CTLA-4 gene are associate with response to immunotherapy with a checkpoint inhibitor in melanoma patients. The inflammatory response in vitiligo is also thought to be mediated by a polymorphism in the CTLA gene.

Table 1. Biomarkers of response to checkpoint inhibitor immunotherapy that are also associated with vitiligo development(2)

Biomarker	Immunotherapy	Vitiligo
NLR	High NLR positively associates with the response.	High NLR in patients with generalized disease.
PD-1/PD-L1	The expression of PD-L1 positively correlates with response.	High levels of PD-1 on CD8+ T cells positively associate with disease activity.
IFN- γ and IFN-related genes	Expression of CXCL-9, CXCL-10, CXCL-11 in the tumor microenvironment positively correlates with Response.	High serum levels of CXCL-9 and CXCL-10 indicate vitiligo active Phase.
Janus kinase (JAK)/signal transducers and activators of transcription (STAT)	JAK mutations are related to resistance to immunotherapy.	JAKs and STATs are over-expressed in vitiligo.
CTLA-4	High pretreatment expression of CTLA-4 in tumor tissue or tumor-infiltrating lymphocytes positively correlates with response. Polymorphisms in the CTLA-4 gene are associated with response.	Polymorphisms in CTLA-4 gene are involved in vitiligo development.

Discussion: A remarkable facet of vitiligo is its relationship with cutaneous melanoma. Melanoma-associated leukoderma spontaneously occurs in a fraction of melanoma patients and correlates with a favorable prognosis. A retrospective study indicated that melanoma patients with concomitant leukoderma had a higher survival rate. In some cases, leukoderma appearance revealed a regressing melanoma supporting the need for a detailed examination of patients with skin coloration for the presence of primary tumors. Two reports of skin cancer arising among a replacement depigmented patch are recently revealed. Some proof indicates that melanoma-associated leukoderma has clinical options distinct from vitiligo, together with the advanced age of onset, absence of a case history of vitiligo or immediate allergy, equal distribution among men and women, localization of depigmentation, and multiple flecked depigmented macules. Nevertheless, histological and immunohistological differences have not been found. Association between vitiligo and melanoma is thought to be the consequence of an immune response against antigens shared by melanoma and normal melanocytes. Indeed, humoral responses to similar antigens have been proven. In 1995, Cui and Bystryn showed the presence of autoantibodies to melanocytes in 80% of melanoma and 83% of vitiligo patients. These antibodies were directed to analogous antigens with comparable frequency in both diseases. Moreover, Fishman et al. showed that autoantibodies isolated from vitiligo patients had a destructive effect on melanoma cells both in vitro and in vivo. Other authors reported the presence of autoantibodies against melanocyte differentiation antigens, such as tyrosinase, in the sera of both vitiligo and melanoma patients. As autoantibodies rarely succeed in tumor clearance, the authors proposed that differences in the number of antibodies recognizing these epitopes could characterize vitiligo versus melanoma immune responses, with higher titers in vitiligo patient sera. T cell antigen receptor (TCR) sequencing provides information about T cell antigen specificity because T cell clones having an identical TCR sequence recognize the same antigen. A previous study has shown in vivo accumulation of an identical T cell clone in primary melanoma and vitiligo-like halo around the tumor, supporting the idea that tumor T cells recognizing antigens common to both melanoma and melanocytes may contribute to tumor destruction. Because these CTLs rarely achieve melanoma eradication, similarly to what proposed for autoantibodies, Palermo and colleagues indicated that qualitative differences in CTL reactivity against

melanocytes could differentiate vitiligo and cutaneous melanoma, with vitiligo CTLs having a higher affinity to melanocytes(2).

Conclusions: The results of this report indicate that coloration is considerably related to a positive prognosis, and the appearance of melanoma-associated leukoderma represented not solely a proof of effective response to therapy with stop inhibitors however could be additionally helpful for the upkeep of such a response through time with the generation of anti-melanoma memory T cells and This aspect has been studied in animal models.

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