
Letter

I read with interest and appreciated the paper of Kiniwa et al. (1), which was published in a recent issue of Cancer Research. They identified a novel melanoma/melanocyte antigen (KU-MEL-1), isolated from a patient with vitiligo and T-cell-infiltrated metastatic melanoma, that induced IgG responses in patients with various cancers and Vogt-Koyanagi-Harada disease but did not in 12 vitiligo patients. The T-cell infiltration of the tumor and the vitiligo supported the possibility that immune response contributed to the good prognosis for this patient. I wish to comment on the work of Kiniwa et al. (1) and present our findings in patients with vitiligo and melanoma.

In our six patients, vitiligo began to manifest after the age of 40 years. In five of six cases, the melanoma arose from a pigmented mole. There was a very close relationship in time between the appearance of vitiligo and the so-called stirring symptoms, enlarging and darkening of the naevus (2). According to others’ findings as well (3, 4), indirect evidence supports the causal relationship between vitiligo and melanoma. However, we did not find pronounced lymphocytic infiltration and progressive destruction of the tumor cells in a single case and failed to demonstrate humoral antibodies against melanocytes (2). Despite this fact, none of our patients died of melanoma within 5 years.

Novel KU-MEL-1 protein identified by Kiniwa et al. (1) also supports, but does not prove, the view that there is an immunologically mediated causal relationship between vitiligo and melanoma. Their study lacks relevant clinical data as well. The vitiligo of 12 patients without melanoma was not specified (genuine or old age vitiligo). The onset of vitiligo associated with melanoma was not described. The development of vitiligo in patients with melanoma or other tumors was also observed as a consequence of radiotherapy or chemotherapy (2, 5). Their patients with metastatic melanoma had a good prognosis after treatment. The follow-up procedure, the results of tests, and the length of follow-up were not reported. Patients with vitiligo have an increased risk of melanoma (4), and vitiligo in patients with melanoma portends a longer survival than expected (3).

The question, whether the melanoma in vitiligo patients is biologically less aggressive or whether melanoma causes vitiligo by immunologically mediated processes, or both, has not been answered.

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References


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Reply

We thank Dr. Fodor for his comments on our paper, Kiniwa et al. “Tumor antigens isolated from a patient with vitiligo and T-cell-infiltrated melanoma,” Cancer Res., 61: 7900–7907, 2001 (1). Dr. Fodor has raised two important questions related to our report: whether vitiligo associated with melanoma or generalized vitiligo is caused by autoimmune responses, and whether melanoma with vitiligo is biologically less aggressive. Answers to these questions may explain the previous observation that melanoma patients with vitiligo have a relatively good prognosis, and they may also have implications for the diagnosis and treatment of melanoma and vitiligo. Our study, however, was not intended to solve these questions but rather to focus on the identification of antigens useful for the development of diagnostic and therapeutic methods for pigment cell disorders, including melanoma. We identified a new molecule, KU-MEL-1, that was preferentially expressed in melanoma and melanocytes and that induced IgG antibodies in some patients with melanoma and Vogt-Koyanagi-Harada disease, an autoimmune disease against melanocytes. Our recent unpublished observation that the anti-KU-MEL-1 Ab (1) was frequently detected in the sera of melanoma patients who were immunized with dendritic cells pulsed with autologous tumor cell lysates indicated the relatively high immunogenicity of KU-MEL-1. Thus, KU-MEL-1 may be useful for immunotherapy, at least for inducing CD4+ helper T cells and possibly of CD8+ cytotoxic T cells, in addition to its possible involvement in Vogt-Koyanagi-Harada disease as an autoantigen.

The patient whose serum was used for the isolation of KU-MEL-1 developed vitiligo at the age of 80 in 1996, 10 years after the appearance of a pigmented macule in her sole in 1986. The histopathological observation that the excised primary lesion did not contain part of a naevus suggested that the pigmented lesion was already a melanoma when it was found in 1986. The progression of melanoma appeared to relate to the development of the vitiligo, which finally extended to 20% of her body. The primary lesion and a metastatic lesion in the paraaortic iliac artery lymph node were excised when they were diagnosed as melanoma in 1998. The primary lesion was found to have partial regression with T-cell infiltrates; however, we could not perform histological analysis of the vitiligo lesion. The patient was regularly followed up and has been disease-free for 3 years and 10 months after the surgical excision and administration. After the treatment, the vitiligo lesions showed no change. The anti-KU-MEL-1 Ab was no longer detected in recently obtained sera, suggesting the possible complete disappearance of melanoma. No clear correlation was observed in our study between the development of vitiligo and the presence of the anti-KU-MEL-1 Ab in patients with melanoma. In fact, anti-KU-MEL-1 Ab was not detected in sera from 12 patients with vitiligo, including 10 patients with generalized vitiligo, 1 patient with raised border with lymphocyte infiltration, and 1 patient with segmental vitiligo. Therefore, we cannot conclude that the vitiligo in our patient was caused by autoimmune responses against melanocyte-antigens, including KU-MEL-1.

However, we would like to comment on the important issues raised by Dr. Fodor based on many published papers and from our own research on melanoma and melanocytes (2, 3). Van den Wijngaard et al. (3) have extensively reviewed the recent literature that supports the...
autoimmune nature of generalized vitiligo and vitiligo associated with melanoma (3). Studies show that some types of vitiligo are likely to be induced by autoimmune responses to melanocyte antigens. For example, in patients with generalized vitiligo, the vitiligo lesions are predominantly infiltrated with skin-homing CD8+ T cells that are positive for cutaneous leukocyte-associated antigens (4). In addition, using the HLA tetramer or enzyme-linked immunospot analysis, an increase in CD8+ T cells specific for melanocyte-specific proteins, MART-1, gp100, and tyrosinase, which were previously isolated by us as melanoma antigens recognized by tumor-infiltrating T cells (5, 6), is seen in the peripheral blood mononuclear cells of vitiligo patients (7, 8). Antibodies to the melanocyte-specific proteins TRP1 and gp100 are also detected in vitiligo patients (9), although the role of these antibodies in the destruction of melanocytes is not clear. In patients with melanoma, vitiligo development, particularly after immunotherapy, appears to be associated with a good prognosis (10–13). In some cases, an autoimmune response is clearly indicated by the presence of T cells specific for MART-1, gp100, and tyrosinase in the vitiligo lesions of melanoma patients (14).

These observations indicate that some types of vitiligo are caused by autoimmune responses to melanocyte-specific antigens, which may, at least in part, explain the good prognosis of melanoma patients with vitiligo, particularly those with vitiligo that develops after immunotherapy, although some cases may not show any evidence of the immune reaction as in the six cases reported by Dr. Fodor (15). Additional evaluation is necessary to clarify what percentage of vitiligo cases are caused by autoimmunity that may also contribute to a good prognosis for melanoma, as well as whether biologically less aggressive melanoma may be developed in association with vitiligo.

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References

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