Hypopigmentation Associated With an Adenovirus-Mediated gp100/MART-1–Transduced Dendritic Cell Vaccine for Metastatic Melanoma

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**Background:** Reports of vitiligo associated with metastases and rare cases of spontaneous regression of disease have fueled enthusiasm for immunologic approaches to the treatment of advanced melanoma. More recent strategies have focused on using antigen-presenting dendritic cells as vaccines.

**Observations:** We observed 3 cases of leukoderma associated with a novel adenovirus-mediated gp100/MART-1–transduced dendritic cell (MART indicates melanoma antigen recognized by T cells). All 3 patients had advanced metastatic melanoma. Despite the development of this leukodermic response, all patients experienced disease progression while under treatment.

**Conclusion:** We provide the initial evidence for effective induction of a leukodermic response with a gp100/MART-1–transduced dendritic cell vaccine.

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**Because of the lack of effective therapies, the prognosis is poor for patients with advanced metastatic disease.** Recently, as evidence from the literature points to a critical role for the immune system in tumor surveillance and destruction, much attention has been devoted to immunologically based therapies.

Patients with melanoma have been reported to develop vitiligo-like changes called melanoma-associated hypopigmentation (MAH). One hypothesis is that MAH occurs as an adverse effect of the immunologic destruction of tumor (ie, normal melanocytes are destroyed as a bystander effect). This is consistent with several case series that suggest a better-than-expected outcome for patients with cutaneous melanoma who develop MAH. However, since the effect is dramatic and the number of known cases is small, these MAH series are susceptible to reporting bias; furthermore, survival rates reported in these studies were based on historic rather than contemporaneous controls.

In addition to the descriptive studies of MAH, vitiligo-like changes have also been reported in clinical trials for metastatic melanoma, especially those using immunotherapy. Rosenberg and White reported vitiligo in 26% of patients with melanoma who responded to high-dose interleukin 2; all patients with vitiligo had objective responses: none of the nonresponders or patients with renal cell carcinoma who received interleukin 2 developed vitiligo. Furthermore, using vaccination approaches, Trefzer et al. and Jager et al. reported vitiligo in patients who had stable disease or regression of metastases. One possibility for these observations is that the vitiligo results from sensitization to antigens shared by melanocytes and melanoma cells.

In contrast to biotherapy with interleukin 2, more recent strategies have focused on using dendritic cells (DCs) as vaccines to enhance antigen-specific immunity. Dendritic cells are theoretically advantageous in a vaccination paradigm since they combine specificity and potency in the activation of antitumor cytolytic T lymphocytes. Although there is general agreement as to the potential benefits of DC therapy, there is a lack of consensus regarding the best vaccination protocols. Several DC trials for metastatic melanoma have been recently published. Nestle et al. observed objective responses in 5 of 16 patients (2 complete and 3 partial responses) when DCs were loaded with peptides derived from tyrosinase, MART-1, gp100, MAGE-1, and MAGE-3 and injected directly into the lymph nodes (MART indicates melanoma antigen recognized by T cells; MAGE, melanoma-associated antigen). Using a similar panel of peptides...
PATIENTS, MATERIALS, AND METHODS

We adopted a novel vaccination approach using adenovirus-mediated transduction of melanocyte-specific antigens gp100 and MART-1 into DCs. Since the exogenously introduced gene is processed by the DC’s natural antigen-presenting machinery, the entire spectrum of gp100 and MART-1 peptide epitopes are theoretically available for cytolytic T-lymphocyte activation. In our phase 1 vaccine trial of gp100/MART-1–transduced DCs for metastatic melanoma, we found that 3 of 12 patients who underwent vaccination developed leukoderma. However, all 3 patients also experienced disease progression while under this treatment; therefore, the response was not associated with tumor eradication.

This trial was approved by the Massachusetts General Hospital Institutional Review Board and the Food and Drug Administration. All patients provided written informed consent. Vaccinations were performed every 2 to 3 weeks. Although patient peripheral blood samples were collected for final analysis, immunologic end points for this phase 1 trial are not available.

but intravenous vaccination, Mackensen et al reported a partial clinical response in 1 of 14 patients. Finally, when Thurner et al loaded DCs with a single MAGE-3A1 peptide and vaccinated patients by intradermal and intravenous routes, they observed partial regression in 6 of 11 patients. In terms of cutaneous immunologic responses, Nestle et al observed regression of a single melanocytic nevus in 1 patient, and Mackensen et al reported the development of generalized vitiligo in 1 patient of 14. In both cases, the patients’ disease progressed despite their having undergone the vaccination.

REPORT OF CASES

CASE 1

A 42-year-old man presented with a 1.2-mm-thick level IV melanoma on the right flank in July 1996. Three years later, the patient developed adenopathy in the right axilla, and a dissection revealed 9 of 18 lymph nodes with metastatic deposits. The patient was treated with interferon alfa-2a for 6 months, but his disease eventually progressed with a tracheal node metastasis.

The patient was then enrolled in our gp100/MART-1 adenovirus–transduced DC vaccine trial. In June 1999, the patient received an injection of $7.5 \times 10^6$ DCs. Two weeks after his first vaccination, the patient experienced progression of pulmonary and adrenal disease and was enrolled in the gp100/MART-1 adenovirus–transduced DC vaccine trial. He initially received a dose of $7.5 \times 10^6$ DCs. Two weeks after his first vaccination, the patient’s disease progressed to adrenal and liver involvement. By his third vaccination, the patient experienced progression of pulmonary and abdominal disease and recurrence of his axillary disease.

One week prior to the fourth vaccine dose in June 1999, the patient noted the appearance of leukoderma that was confluent on his distal fingers (Figure 1). A Wood light examination of the affected areas showed chalky white pigment loss consistent with total depigmentation. Confirmatory biopsy specimens of normal and leukodermic areas under MART-1 (Figure 2) and hematoxylin-eosin (data not shown) staining demonstrated a complete absence of MART-1–positive melanocytes in a leukodermic area (data not shown).

Despite the apparent leukodermic response, computed tomographic scans 2 months later showed further growth of paratracheal and anterior mediastinal nodal deposits along with development of new subdiaphragmatic, pararenal, and splenic metastases. By the end of his fifth and final vaccine dose, the patient’s leukoderma had generalized to involve the trunk, neck, and upper extremities. With progressive thoracic, cutaneous, and bony disease, the patient began dacarbazine and palliative radiation therapy to the mediastinum in April 2000.

CASE 2

In June 1996, a 65-year-old man presented with left axillary lymphadenopathy that revealed metastatic melanoma. The patient had no history of cutaneous melanoma, and no primary tumor was found on skin examination. The patient began a year of high-dose interferon alfa-2a therapy but subsequently developed left supraclavicular and pectoral nodal disease.

In February 1999, the patient developed pulmonary disease and was enrolled in the gp100/MART-1 adenovirus–transduced DC vaccine trial. He initially received a dose of $7.5 \times 10^6$ DCs. Two weeks after his first vaccination, the patient’s disease progressed to adrenal and liver involvement. By his third vaccination, the patient experienced progression of pulmonary and abdominal disease and recurrence of his axillary disease.

One week prior to the fourth vaccine dose in June 1999, the patient noted the appearance of leukoderma that was confluent on his distal fingers (Figure 3) and scattered as small irregularly shaped macules on his upper chest and back. With his fifth vaccination, the patient had partial regression of a supraclavicular node. Furthermore, with his final vaccination, the patient’s leukoderma lesions increased in number and size to involve his forehead, shoulders, and both hands, including the wrists. Despite the widespread pigmented involvement, the patient developed ulcerating gastric metastases and died.

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CASE 3

A 74-year-old woman with no history of cutaneous melanoma presented with right axillary metastasis in April 1998. Initially, palliative radiation therapy for chest wall disease and a nodal dissection was performed. A year later, however, the patient developed bilateral lung metastases and was enrolled in a gp100/MART-1 adenovirus-transduced DC vaccine trial in September 1999. The patient initially received a dose of $7.5 \times 10^6$ cells along with low-dose interleukin 2 treatment ($0.9 \times 10^6$ U/m$^2$ per day on days 4-19 of each cycle).

After the third vaccine dose in November 1999, the patient developed islands of leukoderma extending from the shoulder blades up to the nape of the neck posteriorly and to the midchest anteriorly. A restaging computed tomographic scan at the onset of the pigment loss demonstrated a dramatic increase in the number of pulmonary nodules and liver lesions suggestive of metastasis. The patient’s leukoderma stabilized after the initial onset.

One month after her final vaccine dose, the patient’s melanoma rapidly progressed with increased bony destruction, new liver lesions, and widespread pulmonary infiltration. No further treatments were given, and the patient died in March 2000.

COMMENT

Three patients with stage IV melanoma participating in the adenovirus-mediated gp100/MART-1–transduced DC vaccine trial developed leukoderma during the trial. Since the prevalence of spontaneous MAH among patients with melanoma is 3% to 6%, the leukoderma seen in our patients is unlikely to represent a chance association between our vaccine trial and MAH. A further link between the cutaneous response and vaccination is supported by the temporal relationship between initiation of treatment and subsequent loss of pigmentation. Since the mechanism underlying leukodermic responses in melanoma is still largely speculative, we propose that the term vaccine-associated leukoderma be used to distinguish our observations from spontaneous MAH.

Biopsy specimens of the lesional and normal skin in 1 patient (case 1) showed an apparent absence of melanocytes consistent with melanocyte destruction. In studies of MAH, Koh et al2 described 2 distinct patterns: (1) an absence of melanocytes and (2) macromelanocytes of reduced density with decreased numbers of melanosomes or increased numbers of premelanosomes.2 One possibility is that the macromelanocytes observed in spontaneous MAH represent immunologically targeted melanocytes undergoing destruction since these macromelanocytes have been found in active borders of vitiligo.14

In our patients, the occurrence of leukoderma was not accompanied by any beneficial clinical response. Several possibilities exist to explain our findings. First, melanoma cells may use mechanisms such as down-regulation of major histocompatibility class I molecules15 to evade immune destruction. Alternatively, the vaccine may place selective pressure on residual tumors to lose specific gp100 and MART-1 epitopes that are targeted by the vaccine. This immunoselection has been demonstrated in one MAGE-3A1 pulsed-DC vaccine trial in which excised metastases at the study entry were MAGE-3 positive, and all samples removed after vaccination were MAGE-3 negative.16 Finally, since the adenovirus-
transduced DCs present a variety of epitopes, cytolytic T lymphocytes with different specificities may be responsible for antimalanocyte and antimalanoma effects. In murine models using B16 melanomas, vaccination with tyrosinase-related protein 1 leads to tumor eradication with vitiligo while vaccination with tyrosinase-related protein 2 results in tumor clearance without skin depigmentation. 16,17

Although our case series is too limited to afford prognostic information, the presence of a minor response (case 2) among our patients with vaccine-associated leukodermia is consistent with results from other DC vaccine trials 8,9 but in direct contrast to published results for other immunotherapeutic trials. Rosenberg and White 5 reported in their study that all patients with melanoma who developed vitiligo also had an objective response to interleukin 2.18,19 In these trials, the few patients with vitiligo also experienced stabilization of disease. Trefzer et al 6 vaccinated 16 patients with stage IV melanoma with fused tumor/antigen-presenting cell hybrids and described 2 patients with regionally restricted vitiligo after vaccination. In both cases, the patients with melanoma who developed vitiligo also had an objective response to interleukin 2. Vitiligo has also been described in patients with melanoma vaccinated with melanoma cell lines engineered to produce interleukin 2. 2,18,19 In these trials, the few patients with vitiligo also experienced stabilization of disease. Trefzer et al 6 vaccinated 16 patients with stage IV melanoma with fused tumor/antigen-presenting cell hybrids and described 2 patients with regionally restricted vitiligo after vaccination. In both cases, the patients had stable disease for more than 24 months. Finally, Jager et al 10 reported progressive hypopigmentation in 1 patient who experienced continued regression of metastatic disease under long-term immunization with MART-1, tyrosinase, and gp100-derived peptides. The fact that peripheral cytolytic T lymphocytes can be targeted to the skin has been shown in a single patient with melanoma who received an infusion of a MART-1-specific CD8 T-cell clone and subsequently developed inflammatory skin lesions that harbored MART-1–specific CD8 T cells with consequent loss of MART-1–staining melanocytes. 20 Although these vaccine and immunotherapy trials support a close association between favorable outcome, we did not observe this relationship. Moreover, since patients with vitiligo can develop cutaneous melanomas, 11 the autoimmune aggression seen in vitiligo must be distinct from potent antitumor immunity. 12

In summary, we describe a leukodermic response with a gp100/MART-1–transduced DC vaccine. Although this vaccination strategy represents a novel approach to overcome immune tolerance, eventual clinical success will require further studies to optimize antigen presentation, to better define epitope specificity, and to elucidate mechanisms that allow tumors to escape immunologic killing.

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REFERENCES