Cutaneous Vitiligo Following Management of Uveal Melanoma in 6 Patients

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**IMPORTANCE** The relationship of vitiligo to cutaneous melanoma is believed to be due to an immune response generated to melanoma antigens that cross-react with normal skin. There is little in the literature on the relationship between cutaneous vitiligo and uveal melanoma.

**OBJECTIVE** To describe the clinical profile, treatment, and outcome in patients with uveal melanoma who subsequently developed cutaneous vitiligo.

**DESIGN, SETTING, AND PARTICIPANTS** Retrospective case series of 6 patients with uveal melanoma who had developed cutaneous vitiligo and were examined at a tertiary eye care institution.

**MAIN OUTCOME AND MEASURE** Development of cutaneous vitiligo.

**RESULTS** The mean age at presentation was 62 years (range, 39-85 years). No patient had a personal history of cutaneous melanoma, autoimmune disease, or cutaneous vitiligo. The mean tumor basal diameter was 12.9 mm (median, 12.7 mm; range, 7-19 mm), with a mean thickness of 9.5 mm (median, 8.4 mm; range, 3-19 mm). Treatment included plaque radiotherapy in 4 patients and enucleation in 1 patient; 1 patient refused therapy. No patient had local tumor recurrence at the 71-month mean follow-up, but of the 3 patients who developed metastases at the 52-month mean follow-up, 2 were treated with a melanoma vaccine. The mean interval from initial presentation to onset of vitiligo was 77 months (range, 5-168 months). The vitiligo developed bilaterally with multiple well-defined lesions, affecting 5% to 40% of the cutaneous surface, generally in the upper body. During the 71-month mean follow-up (range, 4-205 months), there was 1 death.

**CONCLUSIONS AND RELEVANCE** Patients with uveal melanoma can develop vitiligo spontaneously or following vaccine therapy. Involvement is multiple and bilateral, predominantly affecting the upper body.

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the Wills Eye Institute approved this study. The study and data collection conformed to local laws and were compliant with the principles of the Declaration of Helsinki.

Data were reviewed regarding patient demographic information such as age, race, sex, and past personal or family history of cutaneous melanoma, autoimmune disorder, or cutaneous vitiligo. A detailed systemic and ocular history was obtained from the medical records, including best-corrected visual acuity, slitlamp biomicroscopy, intraocular pressure measurement, indirect ophthalmoscopy, and transillumination findings. B-scan ultrasonography was performed in all patients to quantify tumor dimensions. Additional imaging with computed tomography or magnetic resonance imaging was done when needed. Details of the uveal melanoma were recorded regarding tumor size (base and thickness in millimeters), location, related features, and treatment. Outcomes of therapy were recorded, including melanoma control, metastasis, and death. Details on the development of cutaneous vitiligo were recorded, including melanoma control, metastasis, and death.

Details on the development of cutaneous vitiligo with regard to the extent, location, time to onset, progression, and treatment were noted. Vitiligo outcomes included progression of disease and relationship to the primary uveal melanoma.

### Results

The demographic features and clinical characteristics of the 6 patients are listed in Table 1. The mean age at presentation was 62 years (median, 62 years; range, 39-85 years). Five patients were white and 1 was African American. There was no personal or family history of cutaneous melanoma, autoimmune disease, or cutaneous vitiligo. No patient received treatment before referral to our department.

### Discussion

Cutaneous vitiligo is a common skin disorder, recognized as patchy depigmentation and occurs in approximately 0.5% to
1% of the world population.2 There is no apparent predilection for sex, race, or skin type, and nearly half of affected patients manifest vitiligo by the third decade of life.1

The cutaneous surface of the body is endowed with complex adaptive immune mechanisms. In the past 50 years, studies on tumor immunology have revealed a link between tumor immunity and autoimmunity,11 with an extensive overlap between normally expressed antigens and those expressed by malignant neoplasms, such as melanoma.1 Spontaneous regression of cutaneous nevi is recognized in children and ado-

Table 3. Details of Cutaneous Vitiligo Following Uveal Melanoma in 6 Patients

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Time to Onset of Cutaneous Vitiligo From Date First Seen, mo</th>
<th>Vitiligo Site</th>
<th>Extent, %</th>
<th>Progression of Vitiligo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>62</td>
<td>Both arms</td>
<td>10</td>
<td>Yes</td>
</tr>
<tr>
<td>2a</td>
<td>87</td>
<td>Face</td>
<td>40</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neck</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Abdomen</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Right forearm</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Left forearm</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Both shins</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Back</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>Nasolabial folds</td>
<td>5</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>31</td>
<td>Both arms</td>
<td>10</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>168</td>
<td>Neck</td>
<td>10</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Both arms</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>6a</td>
<td>109</td>
<td>Both forearms</td>
<td>5</td>
<td>No</td>
</tr>
</tbody>
</table>

*Patients who got vaccine therapy for metastatic disease.

Figure 1. Vitiligo in a Patient Treated With Plaque Radiotherapy

A 39-year-old man (patient 5) with an amelanotic melanoma (A) 9.9 mm in thickness on ultrasonography (B) was treated with plaque radiotherapy. Seventeen years later, the right eye displayed cataract (C) and regressed melanoma (D). Cutaneous vitiligo was found on both arms (E and F), and there was no evidence of metastatic disease.
Adolescents, probably reflecting an active and robust immunosurveillance that eliminates normal and neoplastic melanocytes, thus preventing tumor development. Conversely, it also has been shown that immunodeficiency is associated with a higher incidence of melanocytic nevi. Furthermore, medication-related immunosuppression in transplant recipients can cause eruption of cutaneous nevi. Such nevi are reported to involute after discontinuation of immunosuppressive therapy. These observations directly support the theory of skin immunosurveillance against melanocytic proliferation. An important finding to further confirm this observation is the fact that cutaneous melanoma increases 4 to 7 times in immunosuppressed populations compared with age- and sex-matched controls.

Melanoma cells express a family of differentiation antigens that are shared by normal melanocytes. This family of proteins includes tyrosinase and related proteins TRP-1 (gp75), TRP-2 (dopachrome tautomerase), gp100, and MART-1 (Melan-A). Each of these proteins plays a crucial role in melanin synthesis. Two major mechanisms of vitiligo pathogenesis in patients with cutaneous melanoma have been proposed by the antibody-based theory and the T-cell-based theory. In the antibody-based theory, the host antibodies lyse melanocytes and melanoma cells. Studies have detected the presence of auto-antibodies recognizing tyrosinase, TRP-1, and TRP-2 from the serum samples of patients with melanoma and those with vitiligo. In the T-cell-based theory, the host CD8+ T cells react with host melanoma and cross-react with benign melanocytes, leading to destruction. Clonotypically, identical T cells have been found in cutaneous melanoma and vitiligo patches. Furthermore, most cells infiltrating vitiligo are CD8+ T cells that recognize melanocytes and melanoma cells.

The published incidence of melanoma-associated vitiligo has varied at 2.8%, 3.7%, 4.1%, and 5% and is higher than vitiligo in the general population. On the basis of age differences, lack of family history, and clinicopathologic findings, Koh et al have suggested that vitiligo associated with cutaneous melanoma may be different from autoimmune vitiligo unassociated with melanoma.

There is little in the literature on cutaneous vitiligo in patients with uveal melanoma. Individual observations of cutaneous vitiligo developing after enucleation or evisceration.
of eyes with uveal melanoma have been reported. In 1968, Nirankari et al. described a 57-year-old man who underwent evisceration for panophthalmitis from undetected ocular melanoma, and cutaneous vitiligo was detected 7 years later with subsequent orbital melanoma recurrence thereafter. A similar phenomenon of depigmentation of the cutaneous nevus into the halo nevus has been observed following treatment of uveal melanoma.7,10

The development of vitiligo in patients with cutaneous melanoma has been associated with increased survival rates, attributed to activation of a systemic immune response.4 In 1983, Nordlund et al. reported that the 5-year survival rate with patients who manifest melanoma-related vitiligo was significantly enhanced. In 1987, a more extensive study by Bystryn et al. reached similar conclusions. However, these studies drew patients with stage I or II disease. Recently, in a cohort of patients with metastatic cutaneous melanoma, Quaglino et al. reported that vitiligo was an independent positive prognostic factor correlated with significantly enhanced 5-year survival. In fact, vitiligo induction is recognized as a marker of effective melanoma tumor immunotherapy. Nordlund and Lerner suggested that vitiligo should be induced in patients after resection of primary melanoma. In a series of 374 patients with metastatic melanoma who were treated with high-dose interleukin 2, 22% developed treatment-related vitiligo.23

In conclusion, vitiligo can occur rarely in association with uveal melanoma. When present, it usually develops late in the clinical course with a predilection for bilateral, asymmetric involvement of the upper body. The potential prognostic benefit of this finding in these patients remains to be determined.

REFERENCES