Amelanocytic Anhidrotic Alopecia Areata-like Phenotype After Allogeneic Hematopoietic Cell Transplant

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Background: Diffuse alopecia areata or canities subita is a rare variant of alopecia in which hair loss is associated with regrowth of white hairs and possible lightening of the skin. Preferential loss of pigmented hair in this disorder may be related to the melanin pigment system and/or melanocytes. Acquired generalized anhidrosis can be associated with autoimmune disease, cancer, graft-vs-host disease, or medications or can be idiopathic. Extensive anhidrosis may cause hyperpyrexia on exposure to heat, and protection from overheating is essential.

Observations: A 38-year-old man with idiopathic autoimmune aplastic anemia developed permanent diffuse skin and hair whitening and generalized anhidrosis after a successful allogeneic hematopoietic stem cell transplant. Results of a histopathologic examination, which has previously not been reported in this disease, demonstrated a complete lack of epidermal and follicular melanocytes and a dense perifollicular and periadnexal lymphocytic infiltrate.

Conclusions: The hair- and skin-lightening phenomena in diffuse alopecia areata may be the result of an overstimulated immune system that targets epidermal and follicular melanocytes. Destruction results in irreversible pigmentary loss of the skin. In a patient with multiple risk factors for anhidrosis, a specific cause may be difficult to determine.

Arch Dermatol. 2012;148(8):931-934

Alopecia Areata is an autoimmune disease characterized by patchy hair loss. Diffuse alopecia areata or canities subita is a rare variant in which hair loss is associated with regrowth of white hairs and possible lightening of the skin. The pathophysiology of alopecia areata is not completely understood; however, preferential loss of pigmented hair in this disorder has led some experts to hypothesize that the autoimmune target in alopecia areata may be related to the melanin pigment system and/or melanocytes. Acquired generalized anhidrosis can be associated with autoimmune disease, cancer, graft-vs-host disease (GVHD), or medications or can be idiopathic. Regardless of the cause, extensive anhidrosis may cause hyperpyrexia on exposure to heat, and protection from overheating is essential. We herein report a case of alopecia areata with diffuse skin and hair whitening and generalized anhidrosis.

Report of a Case

A 38-year-old man with a history of hypothyroidism and idiopathic autoimmune aplastic anemia that became refractory to multiple immunomodulatory medications (antithymocyte globulin, cyclosporine, methylprednisolone sodium succinate, and mycophenolate mofetil hydrochloride) and required frequent blood transfusions underwent an allogeneic hematopoietic stem cell transplant 18 months before presenting for evaluation of diffuse hair whitening and generalized anhidrosis. Eighteen months earlier, he had received chemotherapy with fludarabine phosphate, alemtuzumab, and melphalan hydrochloride as preparation for a matched unrelated-donor stem cell transplant. During and immediately after chemotherapy he had his normal brown hair; 2 weeks later, he experienced hair loss all over his body consistent with anagen effluvium, followed by regrowth of brown hair. Six months later, a bout of patchy loss of pigmented hair occurred on the face, scalp, and body within 24 hours. This shedding was followed by a decreased density and uneven regrowth of completely white hair. Eighteen months after the transplant, the white hairs persisted (Figure 1); he had complete anhidrosis and excessively dry skin. He denied decreased tear or saliva production. His therapeutic course had been previously complicated by mild chronic GVHD with...
an erythematous and pruritic rash, eosinophilia, and loose stools.

On physical examination, depigmented hairs were found on the entire body surface with irregular thinning of the scalp and facial hairs, including eyelashes. Exclamation point hairs were visible on the scalp. Wiry hairs were observed on the extremities and trunk. The skin appeared mildly erythematous, xerotic, and devoid of pigment. Results of a punch biopsy on the right arm showed vacuolization of the basal layer and satellite cell necrosis in the epidermis, which was consistent with a diagnosis of GVHD. Eccrine glands with thick basement membranes and hair follicles surrounded by lymphocytes were also noted (Figure 2A). Immunohistochemical staining with melan A and microphthalmia-associated transcription factor (MITF) staining revealed internal control of mast cells highlighted with brown (original magnification ×200); no melanocytes were noted with MITF and melan-A stain (not shown).

Diffuse alopecia areata followed by white, depigmented hair regrowth has been reported as early as 83 CE during the Babylonian Talmud era. Other names for this disease include Marie Antoinette syndrome, named after the queen whose hair reputedly turned white the night before her guillotine execution during the French revolution; canities subita; and sudden or rapid whitening of the hair. Several case reports of sudden hair whitening from as early as 30 minutes to several weeks after a stressful event or nonautoimmune disease have been described. The pathophysiology is not completely understood, but a 2-step mechanism has been proposed. First, the pilar unit is transformed from one that produces pigmented hair to one that produces nonpigmented hair; the pigmented telogen hairs are rapidly shed, and the new anagen hairs are depigmented. Next, the sudden whitening may be attributed to the retention of preexisting white hairs and abrupt selective shedding of the pigmented hairs. Synchronous lengthening of the white hairs during regrowth provides the final appearance. Therefore, unlike classic alopecia areata, diffuse alopecia areata may not be associated with the typical circular patches of alopecia areata or progression to alopecia totalis or alopecia universalis. However, a rapid loss of pigmented hairs and a general thinning of the scalp and body hairs followed by regrowth of white hairs are observed.

Alopecia areata might be a disease of differentiating cortical keratinocytes, the failure of pigmentation in the regrowing white hair may be a postinflammatory reaction, and the pigmentary mechanisms in the hair bulb might contribute to the pathogenesis. Cases of alopecia areata can demonstrate abnormal melanoblasts and melanogenesis, and pigmented hairs are preferentially targeted, whereas depigmented hairs are preserved within evolving patches. Depigmented hairs may persist. These findings and others suggest that the autoimmune target in alopecia areata may be related to the melanin pigment system and/or the melanocytes.
in mouse models indicate that the induction of T-cell–mediated immunity against hair follicle melanocytes causes alopecia areata and may be accompanied by vitiligo-like coat color change.11 In addition, decreased numbers of follicular melanocytes are documented in patients with alopecia areata.12 The skin-lightening phenomenon may also be a result of the proposed defect or destruction of the melanin pigment system and melanocytes; therefore, diffuse alopecia areata may overlap with or encompass vitiligo in its disease course.

Generalized vitiligo and leukotrichia have been described in patients with GVHD and those undergoing hematopoietic stem cell transplant or donor lymphocyte infusion.14–16 Alopecia areata in the ophiasis pattern was observed in a single patient with vitiligo and GVHD.16 In contrast to the present case, these reports describe a gradual progression of vitiligo with patches of normal pigmentation visible on examination. Consistent with previous reports of diffuse alopecia, our patient’s hair turned white overnight (no progression to leukoderma), with no evidence of normal pigmentation. Total leukoderma has also been described as a rare complication of GVHD and hematopoietic stem cell transplant17; however, associated hair loss was not observed. Our patient had an acute (24-hour) patchy hair loss of pigmented hairs all over his body. Unlike diffuse alopecia areata, vitiligo causes destruction of melanocytes resulting in depigmented patches of skin and leukotrichia, but it is not associated with hair loss. Melanocyte destruction caused by autoimmune reactions triggered by chronic GVHD may have contributed to a diffuse alopecia areata–like phenotype in this patient. A similar pathophysiologic process has been suggested for vitiligo in patients with chronic GVHD and a history of hematopoietic stem cell transplant.18

Chemotherapy has also been associated with alopecia areata or skin and hair depigmentation. Recurring alopecia areata in a patient receiving paclitaxel and carboplatin was presumed to be related to the autoimmune changes instigated by rather than a direct effect of the chemotherapy.17 Inhibitors of c-kit tyrosine kinase are known to cause hair and skin depigmentation that is usually reversible on cessation of the therapy.18–21 In the present case, irreversible skin and hair whitening began after 6 months and occurred within 24 hours; the patient had a history of autoimmune disease and did not have exposure to paclitaxel, carboplatin, or c-kit tyrosine kinase inhibitors. In addition, histopathologic findings demonstrated a complete lack of epidermal and follicular melanocytes, further supporting the theory that melanocytes may be the autoimmune target in alopecia areata.

Acquired generalized anhidrosis has been associated with subclinical Sjögren syndrome, GVHD, or medications or may be idiopathic.22–24 In chronic GVHD, complete sweat gland destruction with fibrosis may be observed and, less frequently, squamous metaplasia and dilation of the sweat glands.25 Drugs that induce hypohidrosis (deficient sweating) include antimuscarinic anticholinergic agents, carbonic anhydrase inhibitors, and tricyclic antidepressants.26 Although a lymphocytic infiltrate surrounding the eccrine glands could be consistent with an autoimmune anhidrosis, a definitive cause of the anhidrosis could not be confirmed in this patient. Patients with anhidrosis should avoid factors that produce thermal stress; if a primary cause is determined, it should be treated.

Finally, adnexal involvement in chronic GVHD, including different types of scarring and nonscarring alopecia and impairment of sweating, is a constant finding in up to 80% of patients with chronic GVHD.27 Therefore, in a patient with a known genetic predisposition, chronic GVHD may act as a triggering factor for the appearance of autoantibodies and autoimmune diseases. Diffuse alopecia areata is an uncommon type of alopecia areata that dermatologists should be able to recognize and diagnose. Although the pathophysiologic basis of alopecia areata and its variants has not been completely elucidated, autoimmune targets such as follicular melanocytes likely play a role. Further studies are necessary to confirm these findings.

Accepted for Publication: January 21, 2012.
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Author Contributions: All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Petronic-Rosic. Acquisition of data: Larson and Petronic-Rosic. Analysis and interpretation of data: Kamińska, Larson, and Petronic-Rosic. Drafting of the manuscript: Kamińska. Critical revision of the manuscript for important intellectual content: Kamińska, Larson, and Petronic-Rosic. Administrative, technical, and material support: Larson. Study supervision: Kamińska, Larson, and Petronic-Rosic.

Financial Disclosure: None reported.


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“Marker” skin lesions on the posterior midline are evident in approximately 80% of individuals with occult spinal dysraphism.1 In a retrospective study of 54 children with congenital midline lumbosacral skin lesions, Guggisberg and colleagues found that 61% (11 of 18) of patients with 2 or more types of cutaneous findings in this location had occult spinal dysraphism compared with 8% (3 of 36) of those with a single skin finding (*P* < .001). Although small numbers of patients precluded risk assessment for specific types of isolated lumbosacral skin lesions, the authors concluded that certain solitary lesions (eg, a lipoma or a dermal sinus) were “high risk.” More recently, a prospective study showed an approximately 35% risk of spinal anomalies in patients with an isolated lumbosacral infantile hemangioma larger than 2.5 cm in diameter,² adding this to the high-risk category. Both Guggisberg and coauthors and Drolet et al² emphasized the need for spinal magnetic resonance imaging in individuals with multiple or high-risk isolated lumbosacral skin lesions, noting only approximately 50% sensitivity for spinal ultrasonography (even if performed at <4-6 months of age).

From October 2010 to August 2011, this article was viewed 2916 times on the *Archives of Dermatology* Web site.

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