Hair repigmentation associated with the use of brentuximab

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INTRODUCTION
Brentuximab vedotin is an antibody-drug conjugate that is approved by the US Food and Drug Administration to treat refractory Hodgkin lymphoma and systemic anaplastic large cell lymphoma. Numerous clinical trials are currently evaluating the efficacy of brentuximab for other conditions, including T-cell lymphoma and steroid refractory graft-versus-host disease. Although brentuximab has been associated with various adverse effects, such as neutropenia, peripheral sensory neuropathy, fatigue, nausea, anemia, upper respiratory tract infection, diarrhea, pyrexia, rash, thrombocytopenia, cough, and vomiting, no reports exist to date of changes in hair pigmentation related to brentuximab. We report herein the first case, to our knowledge, of hair repigmentation associated with the use of brentuximab.

CASE REPORT
A 72-year-old man was admitted to Massachusetts General Hospital in August 2014 for 2 months of increasing fatigue, fevers, and dyspnea. The patient was found to be pancytopenic, which led to a bone marrow biopsy and diagnosis of acute myeloid leukemia. In October 2014, he underwent an allogeneic hematopoietic stem cell transplant preceded by reduced intensity conditioning with busulfan and fludarabine. In August 2014, he began chemotherapy with cytarabine and idarubicin. During his reduced intensity conditioning treatment, the patient lost all his hair. Ultimately, his blood counts began to recover, and he was discharged in late September 2014. At that time, a repeat bone marrow biopsy found complete remission of his acute myeloid leukemia. By January 2015, the patient’s hair grew back completely white (Fig 1). The patient reported having a full head of all white hair long before the current illness, since his late 50s. He denied a personal or family history of premature hair graying.

In April 2015, the patient had oral and cutaneous chronic graft-versus-host disease (cGVHD). Despite initiation of prednisone, he continued to have progressive cGVHD. In May 2015, he enrolled in a study protocol for his refractory mucocutaneous cGVHD receiving brentuximab, 1.8 mg/kg every 3 weeks through October 2015. The patient had a good response to treatment and tolerated the medication well, apart from some mild neuropathy. He started taking prednisone in January 2016 for presumed liver GVHD, but otherwise was not on any other new medications. By March 2016, the patient’s hair began to partially repigment, growing in a dark gray color, a striking contrast from his previously white hair. His hair color has remained this way to date (>1 year; Fig 2).

DISCUSSION
Hair graying is one of the first and most common signs of aging in humans, and yet its mechanism remains incompletely understood. The process is usually progressive and permanent, but rare reports of hair repigmentation exist. Gray hair follicles

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exhibit a reduced number of differentiated, functional melanocytes in the hair bulbs, unlike white hair follicles. Recent studies yielded possible mechanisms and factors that contribute to the senile (age-related) hair graying process. Melanocyte stem cells reside within the bulge region of the hair follicle. Defective self-maintenance of these melanocyte stem cells plays a key role in age-related graying. In both aging C57Bl6 mice and in human populations of increasing age, the number of bulge melanocyte stem cells appears to progressively diminish. This diminishment is accompanied by the formation of rare ectopically pigmented bulge melanocytes that are likely destined to undergo apoptosis and may thus represent a means of melanocyte stem cell depletion. Additional studies suggest that genomic damage (stochastic or triggered by specific injuries such as ionizing radiation of chemotherapeutic agents) contribute to this melanocyte stem cell attrition. Certain hypomorphic mutations in Mitf, the melanocyte transcriptional regulator, may enhance this stem cell aging process. However, the current observation and other reports of hair repigmentation suggest that hair graying may occur through mechanisms other than melanocyte stem cell depletion (ie, maintenance of some residual/functional stem cells) or that repigmentation might occur through repopulation of new stem cells.

Brentuximab vedotin is an antibody-drug conjugate that is used to treat CD30+ lymphomas. This conjugate binds to antigen CD30 on the surface of CD30-expressing cells. The resultant complex is taken up by the cell, and monomethyl auristatin E is subsequently released via proteolytic cleavage. Monomethyl auristatin E binds tubulin, disrupting microtubule activity and resulting in cell cycle arrest and apoptosis. The use of brentuximab in patients with Hodgkin lymphoma and certain types of non-Hodgkin lymphomas resulted in significant improvement in patient outcomes. Although the mechanism of action against tumor cells is well known, its effects relating to hair pigmentation remain less clear. Here we explore potential ways in which brentuximab may contribute to the reversal of hair depigmentation.

Reports of hair repigmentation are rare, but there are a limited number of cases associated with drugs such as thalidomide, lenalidomide, etretinate, erlotinib, and adalimumab, among others. Interestingly, the latency period between drug initiation and hair repigmentation reported with these medications ranges from 3 months to 3 years, similar to that in the current case, with hair darkening noted 10 months after the start of brentuximab. The reason for this lag between initial drug exposure and hair repigmentation is unclear, but one explanation may be the long duration of the anagen phase of the hair follicle cycle. Approximately 90% of scalp hair follicles are in anagen at any given time, and this growth phase lasts several years. Because follicular melanogenesis occurs during late anagen, medication-related hair repigmentation would not be expected immediately.

Fig 1. Patient with white hair in January 2015 before brentuximab therapy. Hair is completely white.

Fig 2. Patient with gray hair in June 2016, 8 months after completing brentuximab therapy. Hair is a salt and pepper color.
The mechanism by which these medications cause hair repigmentation is also uncertain. Many reports of medication-induced hair repigmentation concur that these drugs inhibit negative regulators of melanogenesis, such as proinflammatory cytokines tumor necrosis factor (TNF)-α, transforming growth factor-β, interleukin (IL)-1, and IL-6.\(^5\) As discussed, CD30 is the key target of brentuximab. CD30 is a member of the TNF receptor family, and it exhibits pleiotropic biologic functions. Antibodies like brentuximab that target CD30 have both agonistic and antagonistic signaling functions.\(^1\) CD30 signaling leads to activation of the nuclear factor-κB pathway, which promotes production of proinflammatory cytokines, including IL-6 and TNF-α.\(^1\) Specifically, through nuclear factor-κB activation, TNF-α down-regulates tyrosinase gene expression, which diminishes the pigmentation pathway in vitro.\(^1\) Although tyrosinase expression is not reported to modulate hair graying and might alternatively modulate pigmentation switching between pheomelanin and eumelanin, it is possible that this might contribute to the hair repigmentation seen in individual patients, as described here.

Further study is needed to carefully understand the clinical scenarios in which hair repigmentation occurs and to elucidate the pathogenesis of medication-induced hair repigmentation and the role of CD30 on hair follicle melanogenesis specifically.

REFERENCES