Hair Repigmentation With Anti-PD-1 and Anti-PD-L1 Immunotherapy: A Novel Hypothesis

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To the Editor

The article by Rivera et al[1] is the first report of a previously undescribed side effect of checkpoint inhibitors: hair repigmentation (HR). In this significant case series of 14 patients, all patients received an anti-programmed cell death 1 (PD-1) and anti-programmed cell death 1 ligand 1 (PD-L1) an-tibody for the treatment of a lung cancer.

We report an additional case illustrating that HR follow-ing PD-1 blockade is not limited to patients with lung cancer. A man in his 70s was diagnosed with Hodgkin lymphoma. Two years after treatment with chemotherapy, he experienced a re-lapse and was also diagnosed with metastatic colorectal can-cer associated with microsatellite instability (CRC-MSI). Both cancers were treated in parallel but progressed within 3 years to involve the liver, lungs, spleen, and lymph nodes. Given the high sensitivity of Hodgkin lymphomas and CRC-MSI to anti-PD-1 antibodies, it was decided to treat the patient with nivolumab (3 mg/kg every 2 weeks).[2] The patient experi-enced a mixed response, with tumor regression at most tumor sites except for a liver metastasis, which was treated with local radiotherapy. The patient remained on nivolumab treatment for a year with acceptable toxic effects (grade 2 fatigue, grade 3 hepatitis, grade 2 hypothyroidism). One month after nivolumab treatment initiation, the patient reported HR of his whole body although he had harbored white hair for the last 25 years.

Hair and skin pigmentation is linked to immunity.[3] As men-tioned by Rivera et al,[1] other drugs can induce HR. Interest-ingly, most of them have immunomodulatory properties. It is also striking to notice that 14 of the 15 reported cases (includ-ing ours) are men. Although some biases may partly explain this sex imbalance (increased incidence of lung cancer in men, underdiagnosis of HR in women owing to hair dye), we make the hypothesis that these observations might highlight a patho-physiological substrate. Indeed, many immune genes are X-linked, some of which are involved in pigmentation disorders

(eg, *IKBKG*, *POLA1*).[4] One of them, *FOXP3*, the critical driver of regulatory T cells (T-regs), is of peculiar interest because of increasing evidence regarding the role of T-regs in hair biology.[5] Thus, immune modulation induced by PD-1/PD-L1 antibod-ies in patients with an X-linked gene polymorphism (eg, affecting T-regs) may explain both HR and the increased an-titumor efficacy observed in almost all of these patients. Fur-ther studies are warranted to assess this hypothesis.

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