Amelanotic melanoma in a patient with Hermansky-Pudlak syndrome

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INTRODUCTION

Hermansky-Pudlak syndrome (HPS) is an autosomal recessive, genetically heterogenous disease resulting from the dysfunction of intracellular lysosomal trafficking.[1,2] HPS is characterized by oculocutaneous albinism (OCA), platelet deficiency and dysfunction, and, in some cases, pathologies of other organ systems such as pulmonary fibrosis, granulomatous colitis, cardiomyopathy, and systemic immunodeficiency.[1,2] Mutations in 11 genes have been identified in the pathogenesis of HPS, and the highest prevalence of HPS is found in Puerto Rico, where it affects 1 out of every 1800 people with a carrier rate of 1:21.[2,3] The most common types of HPS in Puerto Rico are HPS-1 and HPS-3, which present with varying rates of lung and colonic involvement.[3]

Various etiologies of OCA, including HPS, have been associated with an increased risk of UV-induced skin cancers such as basal cell carcinomas (BCCs) and squamous cell carcinomas (SCCs) due to the reduction or absence of protective melanin.[4,5] The incidence and risk of malignant melanoma in patients with OCA is less understood, and melanoma in these patients most frequently presents as amelanotic, often complicating clinical diagnosis and delaying the initiation of adequate treatment.[6,7] Here, we present a case of amelanotic melanoma diagnosed in a patient with HPS.

Abbreviations used:

BCC:	basal cell carcinoma
HPS:	Hermansky-Pudlak syndrome
OCA:	oculocutaneous albinism
SCC:	squamous cell carcinoma

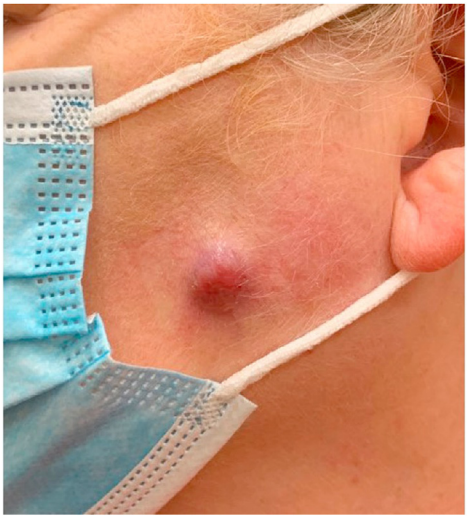

Fig 1. Clinical image of primary melanoma on the left cheek. There is a 1.5-cm *pink-red* nodule on the left cheek. Note pigmentary dilution of skin and hair as characteristic features of Hermansky-Pudlak syndrome.

CASE REPORT

A 51-year-old female, originally from Puerto Rico, with a history of HPS presented to our dermatology clinic with a new lesion of concern on the left cheek. The lesion first appeared 4 months prior to presentation as a small nodule that grew progressively larger over time. The patient endorsed intermittent mild pain and pruritus of the lesion and denied any

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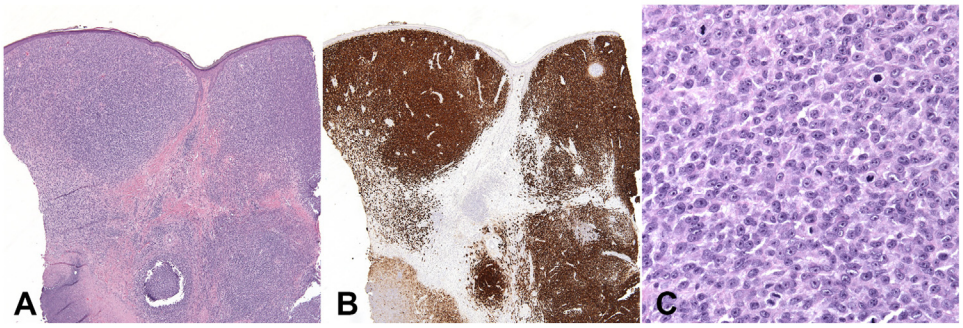

Fig 2. Histological images of amelanotic melanoma. **A**, Hematoxylin & eosin (H&E) staining of melanoma at 40×. **B**, Melan-A staining at 40×. **C**, H&E at 400×. Note lack of pigment and numerous mitoses.

bleeding. She was assessed by her primary care physician 2 months prior to presentation and was prescribed a 10-day course of cephalexin for a potential infectious process, but there was no improvement of the lesion.

The patient denied any fevers, chills, fatigue, weakness, unexplained weight changes, or lymph node swelling. Her previous dermatologic history was notable for peristomal ulcers and vulvar erythema consistent with cutaneous Crohns disease after biopsy confirmation several years prior in the setting of HPS. She has no personal or family history of skin cancer, including melanoma, though has an extensive family history of HPS. Her HPS had not been previously genetically profiled, though was believed to be either HPS-1 or HPS-3 given her history of granulomatous colitis and mild pulmonary fibrosis. Per chart review, she had been previously counseled on the importance of sun protection given her HPS during an appointment with hematology in 2019.

On examination, the patient was well appearing with Fitzpatrick type I skin. On the left cheek, there was a single 1.5-cm pink nodule (Fig 1). There was no appreciable cervical lymphadenopathy. A 4-mm punch biopsy of the lesion was performed and sent to pathology, which identified sheets of atypical tumor cells in the dermis with positive Melan-A and S-100 immunohistochemical stains consistent with the diagnosis of malignant melanoma (Fig 2). The lesion depth extended at least 5.1 mm with involvement of peripheral and deep margins with a mitotic rate of 17 mitoses per mm^2. An additional punch biopsy of the left check lateral to the primary lesion was performed 2 weeks later which identified a satellite lesion.

A whole-body positron emission tomography/computed tomography was performed and revealed possible tumor involvement of the left periparotid lymph nodes. The patient was referred to plastic surgery for wide local excision of the left cheek, partial superficial parotidectomy, and sentinel lymph node biopsy. The sentinel lymph node biopsy of the left neck showed involvement of metastatic tumor cells. Given the patient's history of a known bleeding diathesis, she was pretreated with desmopressin and received platelets immediately prior to the procedure. Despite the preprocedure treatment, she required additional desmopressin, platelets, and Factor VIIa in the days following surgery for continued bleeding. She was discharged from hospital 4 days after the procedure in good condition.

The final pathologic diagnosis after surgical excision showed stage IIIc nodular melanoma with microsatellitosis. According to the 2018 World Health Organization Classification of Skin Tumours, her melanoma qualifies as a High-CSD (cumulative sun damage) melanoma given the primary site on a sun-exposed area.[8] A targeted generation cancer gene panel was performed which revealed somatic variants in PTEN, EGFR, SMCARCA4, RB1, PMS2, and SMAD4 and gene amplifications in FGFR1 and MYC. The patient is undergoing evaluation as a candidate for immunotherapy given her history of HPS.

DISCUSSION

Amelanotic melanomas account for around 8% of all melanomas and are more likely to be diagnosed at a more advanced stage than pigmented melanomas.[9,10] Nonacral amelanotic melanomas are often misdiagnosed as BCC, SCC, or benign skin lesions as they often lack characteristic features or appear atypical.[9]

Although melanoma is much rarer in patients with OCA than BCC or SCC, the typical presentation of melanoma as amelanotic in these patients presents a unique challenge for early identification and treatment of disease, which is crucial for reducing eventual morbidity and mortality. Few cases of amelanotic melanoma in patients with OCA have been previously described, and almost all

involve patients with primary OCA syndromes (OCA1−OCA7).[4,6,7] It is unknown whether patients with HPS are at a greater risk of melanoma than patients with other causes of OCA, though as seen with our case, HPS patients may be subject to delayed diagnosis or misdiagnosis as with other cases of amelanotic melanoma.

Patients with HPS often require regular monitoring and screening of their disease with multiple specialists, including ophthalmologists, hematologists, cardiologists, pulmonologists, and gastroenterologists.[1,2] Due to their increased risk of skin malignancies and propensity to develop amelanotic melanomas, HPS patients should also undergo regular annual skin examinations with dermatologists to help facilitate early detection and treatment, and dermatologists should be aware of the amelanotic presentation of melanoma in these patients.

We would like to thank the patient for sharing her experience.

Conflicts of interest

None disclosed.

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