INTRODUCTION

Polymyxins belong to 5 classes of polypeptide antibiotics, including polymyxins A, B, C, D, and E, with only polymyxins B (PMB) and E, also known as colistin, being used in clinical settings. Polymyxins are composed of a peptide structure acting as a cationic molecule that binds to and destabilizes the negatively charged outer membrane of gram-negative bacteria. Clinical use of PMB decreased in the 1970s following reports of nephrotoxicity, neurotoxicity, and hypersensitivity reactions. PMB is a therapeutic option for the management of infections caused by multi-drug-resistant (MDR) bacteria and used in combination with other antibiotics when options are limited. Here, we report the development of generalized skin hyperpigmentation in an adult treated with PMB.

CASE PRESENTATION

A 30-year-old woman with a history of gastroparesis and short-gut syndrome after extensive bowel resection due to internal volvulus received a multi-visceral transplant (stomach/duodenum/liver/pancreas/small and large intestine) and a kidney transplant for end-stage renal disease. Following the multi-visceral transplant, the patient developed diffuse skin darkening after initiation of intravenous PMB for treatment of MDR Pseudomonas aeruginosa. Her skin hyperpigmentation was most prominent on her face and forearms. Hyperpigmentation peaked at around 2 weeks following PMB initiation and was discontinued after 3 weeks when the possibility of PMB hyperpigmentation was raised and other causes were ruled out. Skin biopsy showed hypermelanosis of the basal layer and melanin deposition in the dermis. Overall clinical picture was consistent with PMB-induced hyperpigmentation. The patient demonstrated some improvement in discoloration within 4 weeks of PMB discontinuation.
12 hours) were initiated based on susceptibilities. Four days following PMB initiation, patient noticed diffuse brown-gray hyperpigmentation on her face, neck, arms, and hands, which peaked 2 weeks later (Figure 1). Dermoscopy demonstrated diffuse muddy-brown hyperpigmentation with perifollicular prominence, annular brown or gray circles (Figure 2). A skin biopsy taken from her forehead showed hypermelanosis of the basal layer and minute particle deposition in dermis (Figure 3). Immunohistochemistry (IHC) staining for CD1a failed to show increase in Langerhans cells. Staining for S100 demonstrated a normal number of melanocytes in the basal layer of the epidermis as well as normal dermal nerve fibers. C-kit staining did not demonstrate increased number of mast cells. PMB was identified as the culprit for her hyperpigmentation and was stopped 20 days following initiation. Patient observed some improvement in discoloration 1 month post-PMB cessation.

**3 | DISCUSSION**

Medication-induced hyperpigmentation is a common dermatologic complaint that not only adversely affects the patient’s appearance but also quality of life. Skin darkening can occur via several different mechanisms, including hypermelanosis, hyperchromia, and deposition of exogenous materials in the dermis (ie, iron, metals,
hemosiderin). Hypermelanosis in the epidermis is associated with increased melanin in the basal or suprabasal layers with either a normal or increased number of melanocytes. Dermal hypermelanosis is often due to pigment incontinence or the transfer of melanin from epidermis to dermis. It can also result from deposition of endogenous (ie, iron, hemosiderin, or homogentisic acid) or exogenous pigments (ie, silver or mercury). Medications account for 10%-20% of acquired hyperpigmentation. Usually, the onset is insidious and worsens over months or years of medication use. Establishment of chronology between medication initiation and onset of hyperpigmentation is critical in identifying the culprit, albeit challenging. Common culprits of hyperpigmentation include antibiotics (minocycline, rifampin), anticonvulsants (carbamazepine, lamotrigine, phenytoin), psychoactive agents (chlorpromazine), anti-malarials (chloroquine, hydroxychloroquine), anti-neoplastic agents (cyclophosphamide, 5-fluorouracil, bleomycin), heavy metals (silver, gold salts), and amiodarone.

PMB-iH has been reported in the pediatric population, likely due to slower renal-drug clearance rate in younger patients, which results in higher drug levels. Presumably, patients who have renal-insufficiency would be at more risk of developing PMB0-iH. However, this is unlikely an exacerbating factor of PMB-iH in our patient due to her normal renal function post-transplant. The incidence of PMB-iH varies from 8% to 15%. More men and darker-skinned patients (Fitzpatrick scale IV as opposed to I-III) are affected (Table 1). Although some patients developed diffuse hyperpigmentation, others had limited skin discoloration to photo-exposed areas such as the face and neck. According to a recent cohort study of 60 patients with gram-negative infection who received 14-day course of PMB, hyperpigmentation was observed by the 3rd day of treatment and improved gradually upon medication discontinuation. In contrast, zidovudine-induced skin hyperpigmentation, which is also more prevalent in dark-skinned individuals, tends to occur weeks to months following drug initiation and tends to affect the oral mucosa, nails (longitudinal melanonychia), and occasionally the palms and soles in addition to skin of the head, neck, dorsal hands, and feet. Zidovudine-induced hyperpigmentation seems to be dose-dependent and reversible.

Several potential mechanisms of PMB-iH have been proposed. PMB leads to histamine release as part of the inflammatory response.
response, which could activate the H<sub>2</sub> receptor on melanocytes and upregulate tyrosinase and protein kinase A, thus increasing melanogenesis. In addition, there are more melanocytes in the head and neck areas, which could explain the propensity for PMB-iH to occur in these areas. Another hypothesis is that PMH-iH can be considered as the endpoint of PMB-incited inflammatory response in the skin. Indeed, Langerhans cells, which are important in chronic inflammatory skin conditions, are noted to be increased in skin biopsies of some PMB-iH patients. Lastly, IL-6, a known suppressor of melanogenesis, was found to be lower in PMB-iH patients, suggesting a potential role of IL-6 in PMB-iH. In our patient, IHC staining failed to show increase in Langerhans cells, mast cells, or nerve fibers, suggesting that the underlying mechanism of PMB-iH in our patient is likely unrelated to increase in histamine or Langerhans cells. Sunlight may contribute to worsening of hyperpigmentation, but our patient remained in the intensive care unit throughout her hospitalization, making it a less likely culprit. Routine overhead fluorescent lighting was used and may have exacerbated her hyperpigmentation.

There is no clear treatment for PMB-iH. Reports suggest that skin hyperpigmentation tends to resolve in 3-6 months post-PMB cessation. Therefore, it is crucial to identify PMB as the culprit drug in a timely manner and replace it with a suitable candidate. Avoidance of unnecessary light sources may prevent further hyperpigmentation. Additionally, hydroquinone or laser therapy may help.

Although multiple medications were being administered concurrently, PMB was the only medication with the appropriate chronology, clinical picture, and pathological correlation to be identified as the cause of hyperpigmentation. Dermoscopy findings of diffuse muddy-brown pigmentation with increased perifollicular brown or gray circles are also consistent with previous reports.

In conclusion, we report here a case of PMB-iH along with clinical course, dermoscopy findings, and histological findings. Given the resurgence in PMB usage to treat MDR bacteria, clinicians should be aware of this potentially long-lasting adverse reaction.

**AUTHOR CONTRIBUTIONS**

All authors made substantial contributions to the conception or design of the work, or the acquisition, analysis, or interpretation of data for the work; drafted the work and revised it critically for important intellectual content; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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| Presumed Risk Factors | Location of Skin Change | Time to Notice Skin Change | Time to Peak | Follow-up | Treatment | Reversibility |
|----------------------|-------------------------|---------------------------|--------------|-----------|-----------|---------------|
| NR                   | Head, neck, and upper chest | Before 14 d               | -14 d        | NR        | Stopped after 14 d | Partially improved |
| DM, ESRD             | Face                     | 32 d                      | NR           | 5 mo      | Stopped after 30 d | Partially improved |
| ESRD s/p transplant, hypertension | Head and neck          | Before 14 d               | NR           | 3 mo      | Stopped after 14 d | Not improved |
| NR                   | Head and neck            | 3 d                       | NR           | NR        | NR        | NR            |
| COPD                 | Head and neck            | 4 d                       | NR           | 14 d      | Stopped after 14 d | NR            |
| NR                   | Head and neck            | 3 d                       | 7 d          | NR        | NR        | NR            |
| Renal impairment     | Head and neck            | 3 d                       | 7 d          | NR        | NR        | NR            |
| Renal impairment     | Head and neck > trunk, limbs | 5 d            | NR           | 7 d        | NR        | NR            |
| None                 | Head and neck            | 7 d                       | 12 d         | 48 d      | 10-d suspension | Partially improved |
| ESRD                 | Head and neck            | 8 d                       | NR           | 4 mo      | Stopped after 14 d | Not improved |

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