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Letters to Blood

TO THE EDITOR:

Incidence of skin hyperpigmentation in Black patients receiving treatment with immunomodulatory drugs

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Immunomodulatory drugs (IMiDs) are a cornerstone of multiple myeloma treatment. IMiDs, particularly lenalidomide, are associated with adverse skin reactions. These reactions are most commonly rash, xeroderma, and pruritus.[1-3] Although multiple myeloma disproportionately affects Black patients, <2% of patients were Black in a pivotal clinical trial used for registration of these medications.[4,5] The incidence and severity of skin pigment changes in Black patients are not well described. This retrospective study seeks to describe the incidence and natural history of skin changes observed in Black patients receiving IMiD therapy.

Boston Medical Center is a large safety-net hospital in New England. More than 70% of patients treated at this institution are underserved minorities. This retrospective study evaluated all patients treated at Boston Medical Center with thalidomide, lenalidomide, or pomalidomide from January 2013 to March 2020. An internally developed survey consisting of 14 questions was mailed to all patients identified through prescriptions written in the electronic medical record. The survey questions included ethnicity and race identification and whether skin changes occurred during treatment. For those patients with skin changes, follow-up questions asked about the nature of the skin change, including pattern, location, and duration. Distress related to skin changes was reported on a scale of 1 to 10, with 1 being minimal distress and 10 being maximal distress. The distress score used was an original internally developed survey that had not been previously validated. Photographs were obtained of the skin changes after IMiD therapy. The research team reviewed all surveys received. Patients who did not return a survey were called at their primary phone number, and the survey answers were verbally obtained. This study was approved by the institutional review board at Boston University Medical Center.

Over the period of interest, there were a total of 214 patients prescribed thalidomide (n = 4; 1.9%), lenalidomide (n = 204; 95.3%), or pomalidomide (n = 81; 37.9%). Completed surveys were received from 106 (49.5%) of these patients. Of the 108 patients (50.5%) who did not respond to the survey, 57 did not answer after 2 attempts, 21 had died, 16 declined to participate, 6 had phone numbers that were not in service, 5 did not recall IMiD therapy, 1 was hospitalized, 1 was unable to consent to participate in the survey, and 1 returned the survey blank.

In the completed surveys, 49 patients (46.2%) identified as Black and 57 (53.8%) identified as non-Black (Asian, Hispanic or Latino, American Indian/Alaskan Native, White, Native Hawaiian/Other Pacific Islander, or other). Skin changes were reported by 27 patients (25.5%) who completed surveys.

Table 1. Skin changes in patients receiving IMiD therapy

	n (%)
Total surveys	106
No skin changes reported	79 (74.5)
Skin changes reported	27 (25.5)
Description of skin changes	27
Pigmentation	
Darkening (hyperpigmentation)	22 (81.5)
Lightening	2 (7.4)
Distribution	
Spotty	9 (33.3)
Generalized	2 (7.4)
Other	6 (22.2)
Location of hyperpigmentation	22
Palms/soles	15 (68.2)
Forearms	7 (31.8)
Face	6 (27.2)
Shins	3 (13.6)
Thighs	3 (13.6)
Chest	3 (13.6)
Everywhere	3 (13.6)
Other (back, abdomen, nails, fingers/toes, groin)	5 (22.7)
Time to onset of hyperpigmentation, mo	22
<3	10 (45.5)
3-6	4 (18.2)
>6	6 (27.3)
Unsure	2 (9.1)
Resolution of hyperpigmentation after IMiD discontinuation	11
Not better	2 (18.2)
Partially better	5 (45.5)
Fully resolved	4 (36.6)
Score (1-10 scale) of distress caused by hyperpigmentation	22
More bothersome (7-10 of 10)	7 (31.8)
Less bothersome (1-6 of 10)	15 (68.2)
Range	1-9

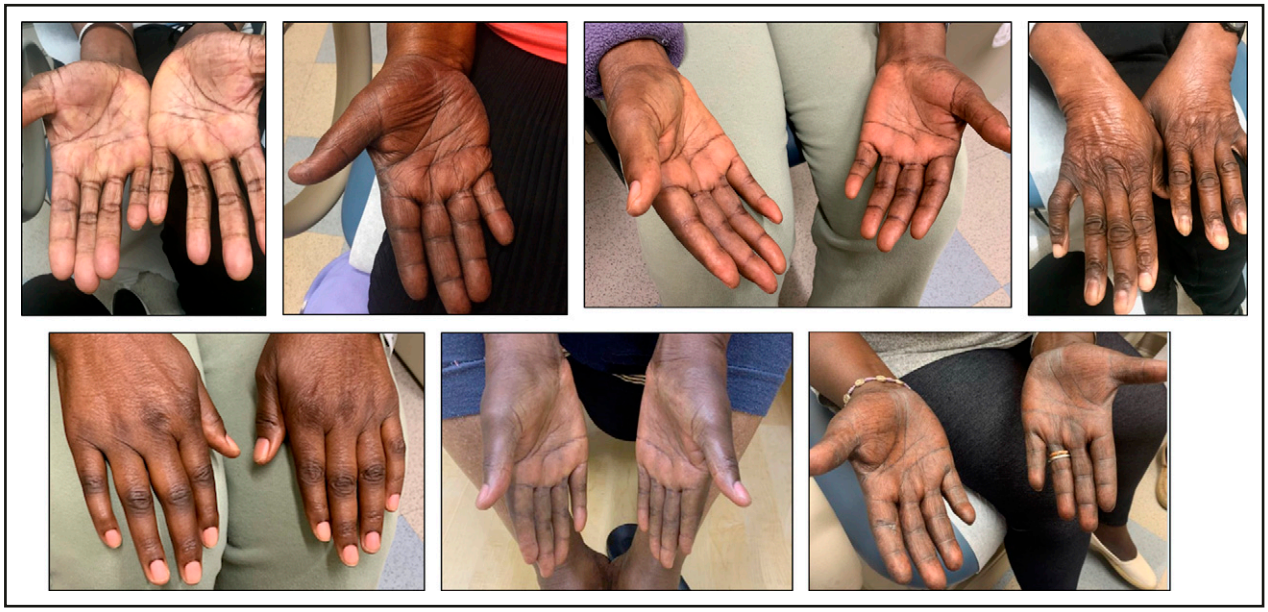

Figure 1. Photographs of typical hyperpigmentation of palms and backs of hands associated with IMiDs.

Hyperpigmentation (skin darkening) was reported by 20 Black patients (40.8%) and 2 non-Black patients (3.5%). The most commonly reported locations of hyperpigmentation were on the palms and soles (n = 15; 68.2%), forearms (n = 7; 31.8%), and face (n = 6; 27.3%). Onset began within 3 months of starting therapy in 10 (45.5%) of these patients. Using the distress score, the changes were very bothersome (7-10 of 10) in 7 patients (31.8%) and less bothersome (1-6 of 10) in 15 patients (68.2%). Of the 11 patients who were no longer receiving IMiD therapy, 4 (36.6%) had full resolution of skin changes, 5 (45.5%) noted partial resolution, and 2 (18.2%) had no improvement. Description of the skin changes and associated distress can be found in Table 1. Photographs of typical skin hyperpigmentation are included in Figure 1. All responses are included in the supplemental Data, available on the *Blood* Web site.

The mechanism for hyperpigmentation resulting from IMiD therapy is not clear. Potential mechanisms for IMiD hyperpigmentation include melanocyte stimulation, impaired degradation of melanin, or direct pigmentation from the drug itself. Further research is required to elucidate the mechanisms responsible for the pigment changes.

The limitations of this research include the subjective nature of distress and recall bias. A prospective study using a validated distress instrument should be considered for future research.

This is the first study to describe skin hyperpigmentation resulting from IMiDs, an adverse effect that disproportionately affects Black patients. Specifically, hyperpigmentation is common in Black patients and is 11.6 times more likely to occur in Black patients than in patients of all other races. In these patients, hyperpigmentation is most noticeable on the palms, face, and soles of the feet. These changes typically occur early in the course of therapy and do not completely reverse, even long after drug cessation. It is important for providers to counsel patients about the risk of potentially irreversible skin changes when using IMiDs in this patient population.

Authorship

Contribution: C.J.M. performed research, collected data, contributed analytical tools, analyzed and interpreted data, performed statistical analysis, and contributed to the manuscript; F.B., D.H., and J.M.S. designed research, collected data, and contributed to the manuscript; and A.L., S.S., and V.S. contributed to the manuscript.

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Footnotes

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For original data, please e-mail the corresponding author.

The online version of this article contains a data supplement.

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TO THE EDITOR:

Markers of complement activation in plasma during quiescent phases in patients with catastrophic antiphospholipid syndrome

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Complement activation has been implicated in the pathogenesis of catastrophic antiphospholipid syndrome (CAPS), a rare life-threatening disease.[1-5] Low C3 and C4 levels that have been identified in patients during acute or relapsing CAPS have, in fact, been considered signs of complement activation and consumption.[1-3] Likewise, complement activation products and high levels of C5b-9 terminal complex have been detected in the plasma of patients with acute CAPS.[2,4] Studies by Chaturvedi et al have further broadened our understanding of the complement system's role in the pathogenesis of CAPS thrombotic storm by demonstrating that sera from acute phase patients induced complement-dependent cell killing and cell-surface deposition of C5b-9 on *PIGA*null TF-1 cells.[5] No signs of complement activation during quiescent CAPS phases, that is, long before its onset or after its remission, have ever been reported. High C5b-9 levels (1657 U; normal value <200) were recently identified in a patient with CAPS that had severe cardiac involvement immediately before treatment was begun.[4] She was refractory to the so-called triple therapy (anticoagulation + steroids + plasma exchange/IV immunoglobulins)[6] and was successfully treated with eculizumab. Unexpectedly, 5 months after a complete recovery (eculizumab had been suspended 3 months earlier), the patient's C5b-9 plasma levels were found to be similar (1804 U) to those registered during the acute phase.[4] In the current study, plasma levels of C5b-9 terminal complex and C5a anaphylatoxin during the quiescent phases of CAPS were investigated, compared with control populations, and discussed.

The plasma of 7 patients who had suffered from CAPS between 2009 and 2017 was collected during the quiescent CAPS phases, 3 before (median, 57 months; interquartile range [IQR], 26) and 4 after (median, 38 months; IQR, 24.2) the acute CAPS episode. The samples were stored at −80°C. Plasma concentrations of C5b-9 and C5a were assessed using the MicroVue C5b-9 Plus EIA and the MicroVue C5a Plus EIA, respectively (QUIDEL, San Diego, CA). There were 6 women and 1 man with a median age of 44 years (IQR, 20). Because histological studies were performed only in 2 cases, 2 patients had definite, and 5 had probable CAPS, according to Asherson et al classification criteria.[7] Eight patients with antiphospholipid syndrome (APS) who had experienced a thrombosis over the preceding year and 8 healthy subjects sex and age matched with the quiescent patients with CAPS were used as the control populations. The median follow-up of the APS patients was 15 years (IQR, 9.2). The study was approved by the regional ethics committee and was carried out in accordance with the 1964 Declaration of Helsinki. Written informed consent was obtained from all the participants.

The patients' demographic and clinical characteristics along with the time to recovery and antiphospholipid antibody profile at time of diagnosis are outlined in Table 1. All were successfully treated using conventional triple therapy, and none required therapeutic complement inhibition. The results of C5b-9 and C5a analyses during the quiescent phases in the patients with CAPS and in the controls are outlined in Figure 1. The C5b-9 levels in the quiescent CAPS were significantly higher than those in the thrombotic patients with APS (median, 330.2 ng/mL; IQR, 86.6; vs median, 189.7 ng/mL; IQR, 138.9) and in the healthy controls (median, 330.2 ng/mL; IQR, 86.6; vs median, 120.9 ng/mL; IQR, 83.7). Similarly, the C5a levels were significantly higher in the quiescent patients with CAPS with respect to the thrombotic patients with APS (median, 27.6 ng/mL; IQR, 58.4; vs median, 8.9 ng/mL; IQR, 8.3) and the healthy controls (median, 27.6 ng/mL; IQR, 58.4; vs median, 4.9 ng/mL; IQR, 4.9).

There are some investigations in the literature reporting elevated plasma levels of C5b-9[2,4,8,9] and C5a[9] in the active phase of CAPS[2,4] or thrombotic APS.[8,9] The current study demonstrates for the first time the finding of significantly high C5b-9 and C5a plasma levels during the quiescent phases long before the onset of the acute phase and after CAPS remission. Excessive delivery of complement activation products in the plasma of quiescent patients with CAPS both before and after an acute episode