Diagnosing Atopic Dermatitis in Skin of Color

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KEYWORDS

• Atopic dermatitis • Skin of color • Diagnosis • Erythema • African American • Asian • Itch • Eczema

KEY POINTS

- Skin of color patients are disproportionately affected by atopic dermatitis (AD) and carry a heightened disease burden with greater disease severity and health care utilization.
- Unique features of AD in skin of color patients include greater papular and extensor involvement in African Americans and greater psoriasiform presentations in Asian AD patients.
- Erythema in dark skin can appear violaceous and brown; scoring tools reliant on erythema may delay diagnosis and underpredict severity of AD.
- Dyspigmentation is a common sequalae of AD in skin of color patients that carries a significant disease burden.

INTRODUCTION

Atopic Dermatitis (AD) is an extremely pruritic inflammatory skin disease that has a worldwide prevalence of approximately 2.69%, with significant variability by country.[1] In the United States, AD affects approximately 10% to 12% of children and 7% to 8% of adults.[2–4] Stratifying by age, AD is most prevalent among African American children and Asian adults.[5,6] As a chronic disease characterized by recurrent pruritus, AD adversely affects quality of life and is associated with sleep disturbance, many systemic disease comorbidities, and increased health care utilization.[7–11] AD disproportionately impacts Black patients, who incur greater disease severity and AD-related medical expenses compared with non-Black patients.[12–14] Given the disproportionate prevalence and burden placed on skin of color patients, it is important that clinicians are able to diagnose and treat AD in patients of all skin types to help reduce disparities in care. Here we highlight important differences in the pathogenesis, clinical presentation, and treatment options for AD in skin of color patients.

PATHOGENESIS

AD has a complex pathogenesis that involves interactions between the innate and adaptive immune system with various cell types in the skin and sensory nerves.[15] Early steps in the disease process involve dysfunction of the skin barrier, allowing entry of allergens and microbes, and initiating an abnormal innate immune response (**Fig. 1**).[16] Aberrant adaptive immune pathways are activated leading to degradation of the skin barrier, followed by immune activation and sensitization of sensory neurons (see **Fig. 1**).[15,17] Subsequent scratching further damages the skin, allowing for additional susceptibility to microbes, creating a positive feedback loop (**Fig. 2**). The degree of cutaneous immune activation can vary between patients, creating distinct AD endotypes.[13]

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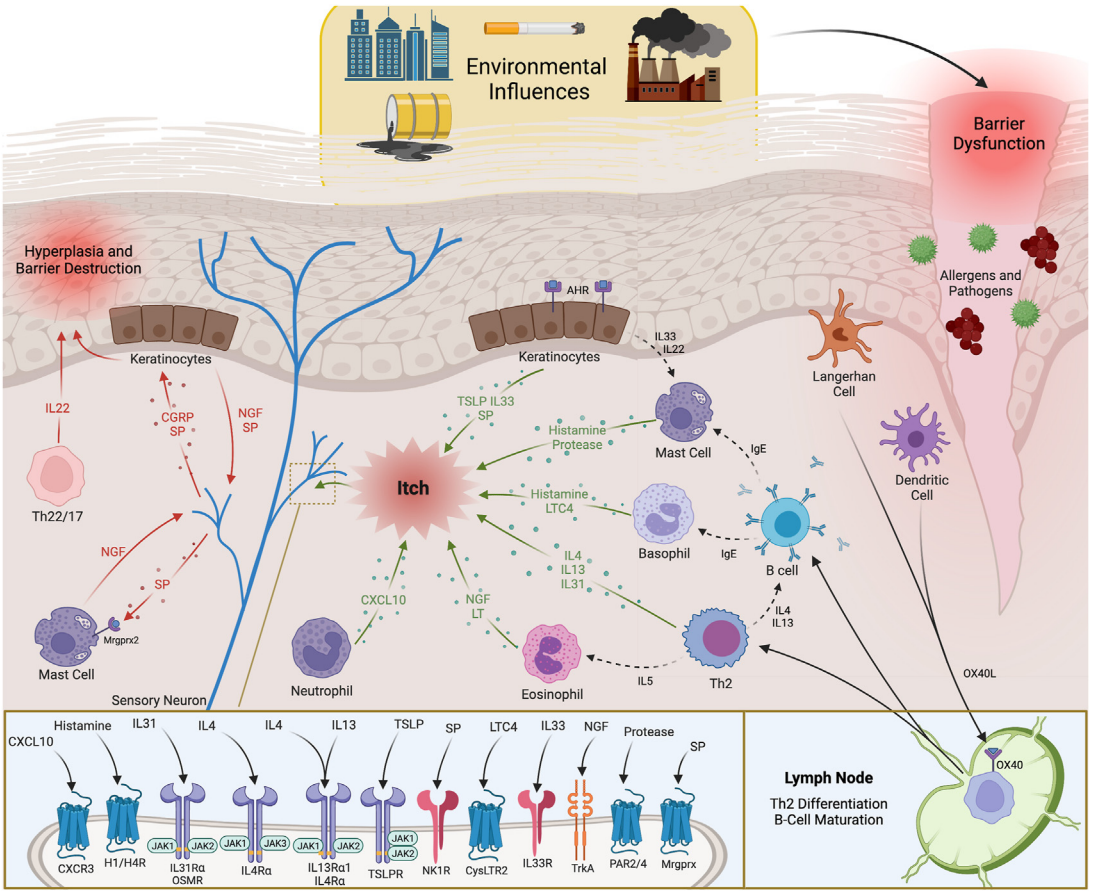

Fig. 1. Atopic dermatitis pathogenesis. AHR, aryl hydrocarbon receptor; CGRP, calcitonin gene-related peptide; CXCL10, CXC Motif Chemokine Ligand 10; CXCR3, CXC Motif Chemokine receptor; CysLTR2, cysteinyl leukotriene receptor 2; H1/4R, histamine receptor types 1 and 4; IgE, immunoglobulin E; IL13, interleukin 13; IL22, interleukin 22; IL31, interleukin 31; IL31R, interleukin 31 receptor; IL33, interleukin 33; IL4, interleukin 4; IL4R, interleukin 4 receptor; IL5, interleukin 5; LTC4, leukotriene C4; Mrgprx, mas-related G protein-coupled receptor; NGF, nerve growth factor; NK1R, neurokinin 1 receptor; OSMR, Oncostatin M Receptor; SP, substance P; Th17, Type 17 helper T-cell; Th2, Type 2 helper T-cell; Th22, Type 22 helper T-cell; TSLP, thymic stromal lymphopoietin; TSLPR, thymic stromal lymphopoietin receptor.

Skin Barrier Dysfunction

Skin barrier dysfunction is a hallmark component of AD. In AD-affected skin, stratum corneum barrier impairment is correlated with lower levels of ceramides and increased transepidermal water loss (TEWL) (see **Fig. 2**).[18,19] At baseline, normal African American skin has been found to have lower levels of ceramide, lower pH in the stratum corneum, and higher TEWL compared with normal Caucasian skin (see **Fig. 2**).[20] These findings likely contribute to the increased degree of xerosis experienced by Black patients.

The strongest genetic risk factor for barrier dysfunction in AD is a loss-of-function mutation in filaggrin (FLG), a stratum corneum structural protein. Patients with mutations in FLG are more likely to have an earlier onset and greater severity of AD, compared with those without the mutation.[21] Interestingly, FLG mutations are observed significantly less frequently in African Americans with AD than in Caucasians with AD.[22] However, low levels of FLG2, a protein important for epidermal differentiation, are correlated with active skin inflammation in AD.[23] FLG2 mutations are associated with more persistent AD in African American children.[24] No association has been reported with FLG2 mutations in Europeans with AD.[23,24] Claudin 1, a tight junction gene, is also associated with barrier dysfunction and early-onset AD in Ethiopian patients.[25]

Immune Dysregulation

Dysregulation of the innate and adaptive immune response plays a crucial role in the development

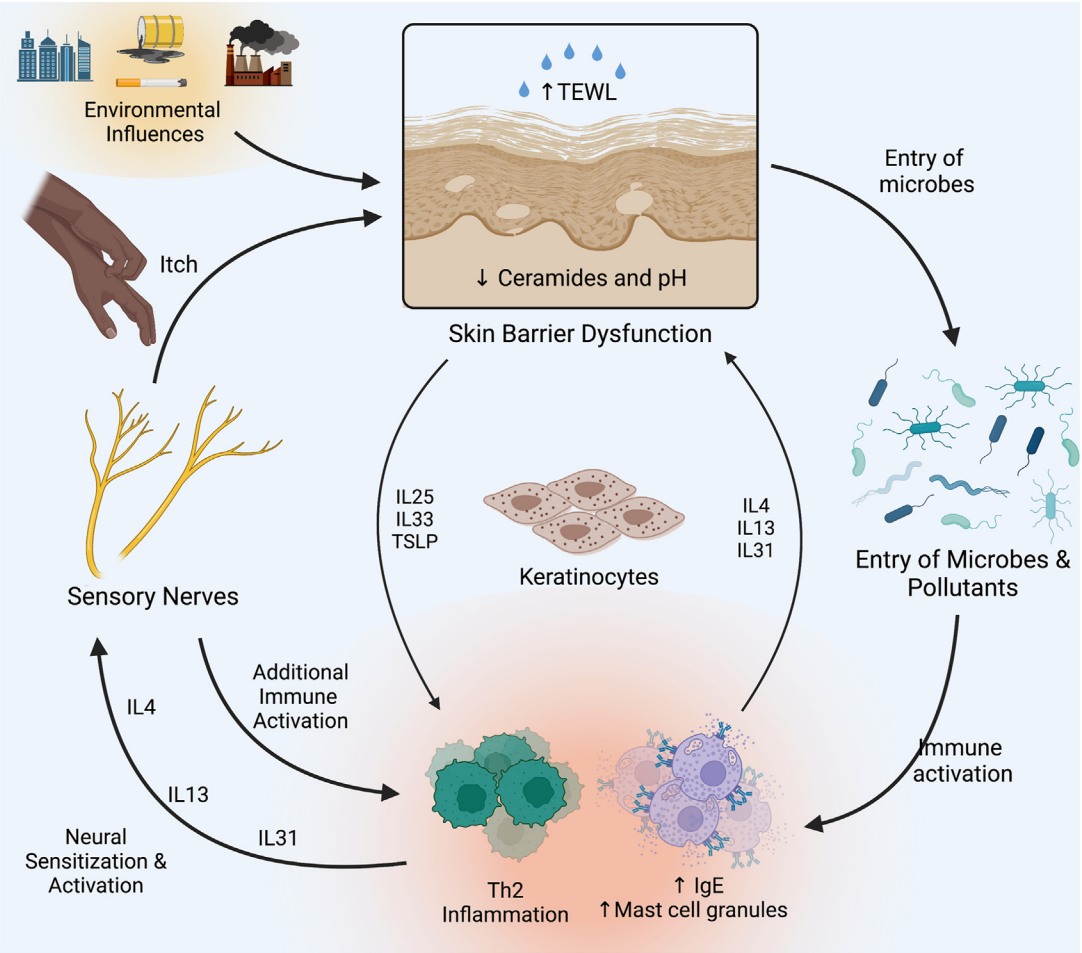

Fig. 2. Inflammatory cycle of AD. IL13, interleukin 13; IL25, interleukin 25; IL31, interleukin 31; IL33, interleukin 33; IL4, interleukin 4; Th2, Type 2 helper T-cell; TSLP, thymic stromal lymphopoietin; TWEL, transepidermal water loss.

of AD. Deficiencies in the immune system increase susceptibility to infection and trigger the inflammatory response. When activated, keratinocytes secrete cytokines that recruit mast cells, T-cells, dendritic cells, and eosinophils, several of which demonstrate racial differences.[26] Mast cells in African American skin contain larger granules, with variation in enzymes and cell structure.[27] In addition, African American AD lesions have greater infiltration of dendritic cells marked by high-affinity immunoglobulin E (IgE) receptors compared with European AD lesions.[28] African Americans also have higher serum IgE levels.[29]

AD is primarily driven by Th2 inflammation. Mutations in interleukin (IL) 4, IL13, IL31, and their appropriate receptors (IL4Rα, IL13Rα, and IL31Rα) are significantly associated with AD. IL4 and IL4Rα in particular are associated with an increased risk of AD in Egyptian children.[30] Recent advances indicate there are various AD disease subtypes, partially attributed to the modulation of different immune pathways.[31] African Americans, for example, have broad immune pathway activation with increases in Th2-related and Th22-related pathways.[13] Increased expression of Th1 and Th17 cytokines has also been observed in sub-Saharan Africans compared with Central Europeans with AD.[32]

Environmental Triggers

The etiology of racial disparities in AD prevalence and severity reaches beyond genetics, highlighting the importance of environmental influence. Living in a metropolitan area is associated with a high risk of AD, likely due to environmental pollution and exposure to infectious diseases (see **Fig. 1**).[33] Urban living is also associated with alterations to the skin microbiome, with increased pathogenic microorganisms such as *Staphylococcal aureus*.[34]

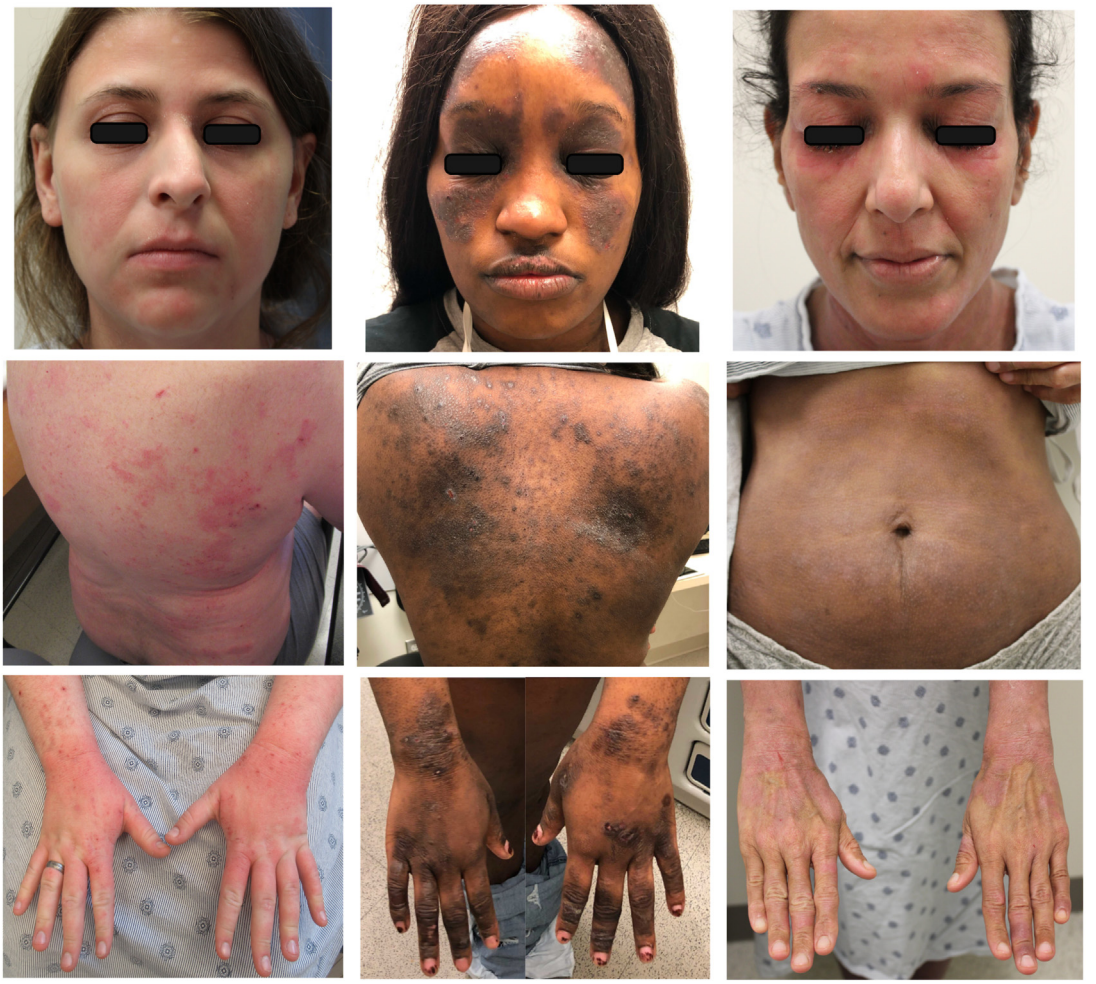

Fig. 3. AD in Caucasian (*left*), African American (*middle*), and Asian (*right*) skin.

Because African Americans are more likely than Caucasians to live in densely populated areas, they may have an increased risk for AD.[35]

Additionally, Black children have increased odds of being exposed to tobacco smoke and traffic-related air pollution, having a caregiver with lower educational attainment, and coming from a lower-income family (<$30,000/year).[36,37] Longitudinal exposure to the aforementioned environmental pollution is associated with the development of asthma and AD, particularly among Black children.[37]

CLINICAL PRESENTATION

Classically, AD presents as recurrent pruritic, inflammatory, and excoriated papules and plaques, classically in flexural areas. However, defining AD only by this classical clinical presentation is not adequate for diverse patient populations, as there are numerous racial and ethnic differences in AD morphology, distributions, texture, and pigmentation that make diagnosing AD challenging across skin types (**Fig. 3**).

Morphology

In skin of color patients, AD can have a heterogenous distribution and morphology compared with traditional, classical criteria for AD. For example, in both the Hanifin and Rajka and the UK Working Party, flexural involvement is listed as a major criterion for diagnosing AD.[38] Although exceedingly common in Caucasians, African Americans also often present with lesions on the extensor or truncal surfaces (**Fig. 4**).[39,40] Additionally skin lesions in skin of color patients commonly present with lichenification (**Figs. 5** and **6**) and with greater papular involvement of lesions with perifollicular accentuation (see **Fig. 4**; **Fig. 7**).[41,42] Psoriasiform thickening and scaling often manifest in Asian patients with AD (see **Fig. 5**E). Severe xerosis and concurrent prurigo

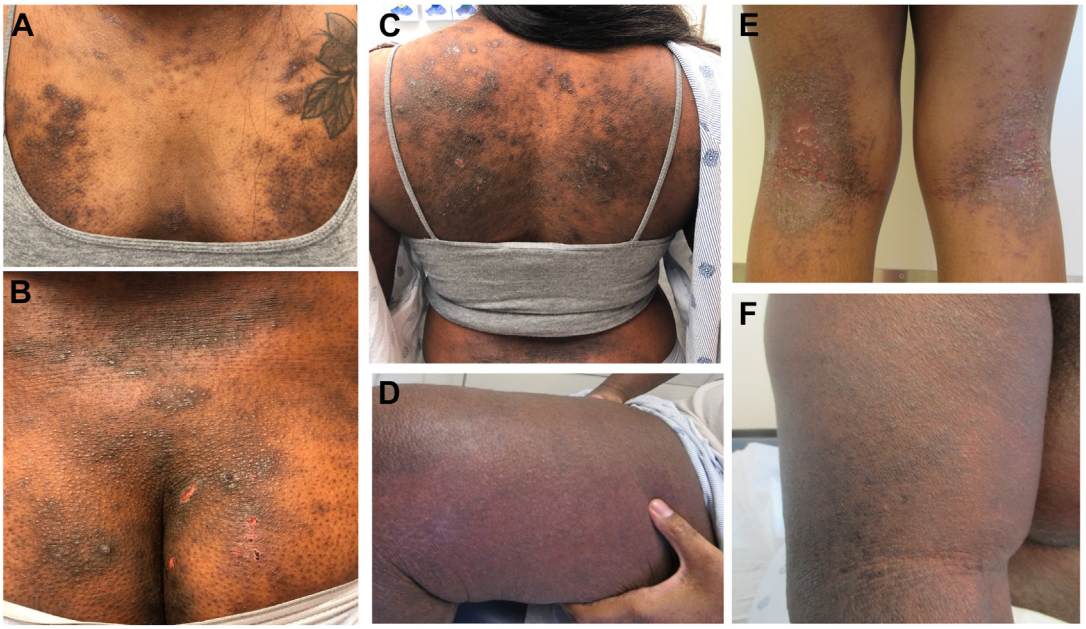

Fig. 4. AD in Black patients. Hyperpigmented perifollicular accentuation coalescing into plaques on the chest (*A*) and buttocks (*B*), with nodular development on the back (*C*). Erythema on the extensor lower extremity (*D*). Flexural plaques with skin fissuring on the popliteal fossa (*E*). Erythema and papules on the upper extremity (*F*).

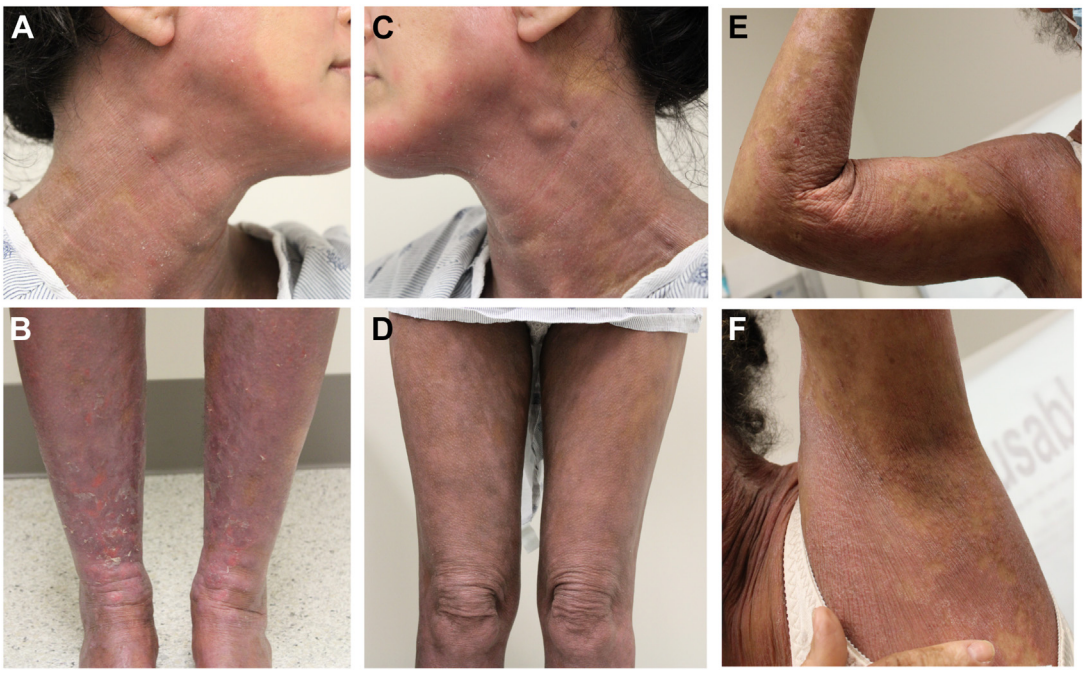

Fig. 5. AD in Asian patients. Gross erythema with lichenification on the neck (*A, C*). Erythema of the lower extremities with exfoliation (*B, D*). Erythematous papules and plaques in addition to psoriasiform scaling on the upper extremity (*E, F*).

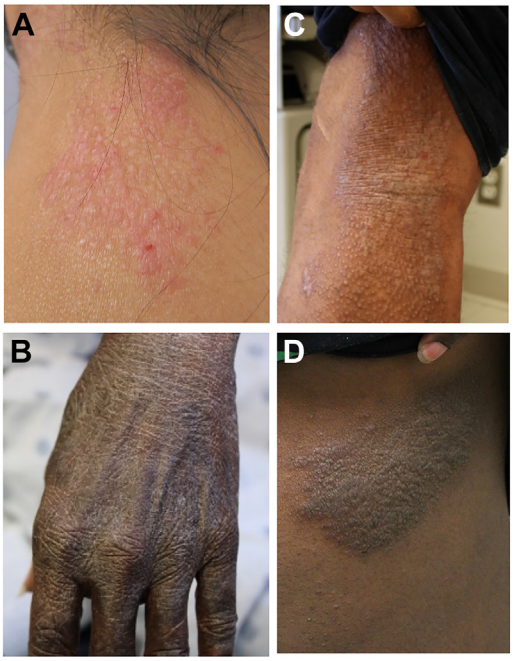

Fig. 6. Lichenification in skin of color patients. Lichenification of the forearm (*A*) and popliteal fossa (*C*) on an Asian patient with AD. Lichenification and xerosis of the extensor wrist (*B*) and trunk (*D*) on a Black patient with AD.

nodules in addition to eczematous lesions are also observed more often in Black patients (see **Fig. 6**; **Fig. 8**).[13] Finally, African Americans also have increased lichenification of lesions.[43]

Erythema

Erythema is a common skin finding in AD and is incorporated into several AD clinical scoring tools. Because of baseline differences in pigmentation, erythema can appear violaceous and brown in skin of color, thus it is harder to distinguish in darker skin tones (see **Figs. 4** and **5**; **Fig. 9**). For this reason, erythema is easily underappreciated in skin of color patients and using scoring tools reliant on erythema, such as scoring atopic dermatitis (SCORAD) and the eczema area and scoring index (EASI), may delay diagnosis and treatment.[44]

Dyspigmentation

Post-inflammatory dyspigmentation is a complication of AD that is more common in skin of color patients.[45] It most often presents as hypopigmentation, which persists after resolution of the disease. This can pose a significant burden as hypopigmentation contrasts more in darker skin tones (**Fig. 10**).[46] Dyspigmentation can also occur with longer-term topical corticosteroid utilization, highlighting the importance of non-steroidal treatment options in skin of color patients.

Disease Severity

Skin of color patients are more likely to present with greater disease severity compared with other patients, both within adult and pediatric populations.[42,44] Significant health care disparities that impact health status and access to care are likely related to decreased socioeconomic status, systemic racism, and several additional contributing factors.[35,47] Black patients with poorly controlled AD are less likely to visit a dermatologist, while more likely to visit primary care or an emergency department compared with white patients.[48] Black children are also 1.5 times more likely to miss school because of AD compared with their White peers.[49]

DIAGNOSIS

The wide range of dermatological manifestations and variability across various races and ethnicities make AD challenging to diagnose. There are a few sets of validated diagnostic criteria that clinicians use when diagnosing AD; however, these may not account for the heterogeneity of AD in skin of color patients. Updates to diagnostic tools are needed to account for the differences in AD clinical presentation between races. We provide an example with an adopted Hanifin and Rajka criteria for AD in skin of color populations (**Fig. 11**)[50]; expanding it to include "extensor papular involvement, lichenification, or psoriasiform thickening of skin in skin of color" as a major criterion, and including "Dyspigmentation (post-inflammatory hypopigmentation and hyperpigmentation)", "Psoriasiform scaling", and "Secondary papular involvement/prurigo nodule formation" as minor criteria. By broadening the criteria to diagnose AD, clinicians can be better equipped to diagnose AD in a variety of patient populations.

There are many limitations with current diagnostic criteria and clinical bedside tools to accurately assess disease severity in skin of color patients with AD. When assessing disease severity in skin of color patients with AD, a patient's self-reported itch severity is a helpful adjunctive assessment as a surrogate marker of disease severity. Monitoring the itch numeric rating scale, from 0 to 10, and worst itch rating scale or peak pruritus scale, in skin of color patients is a real-time indicator of disease progression and treatment response.

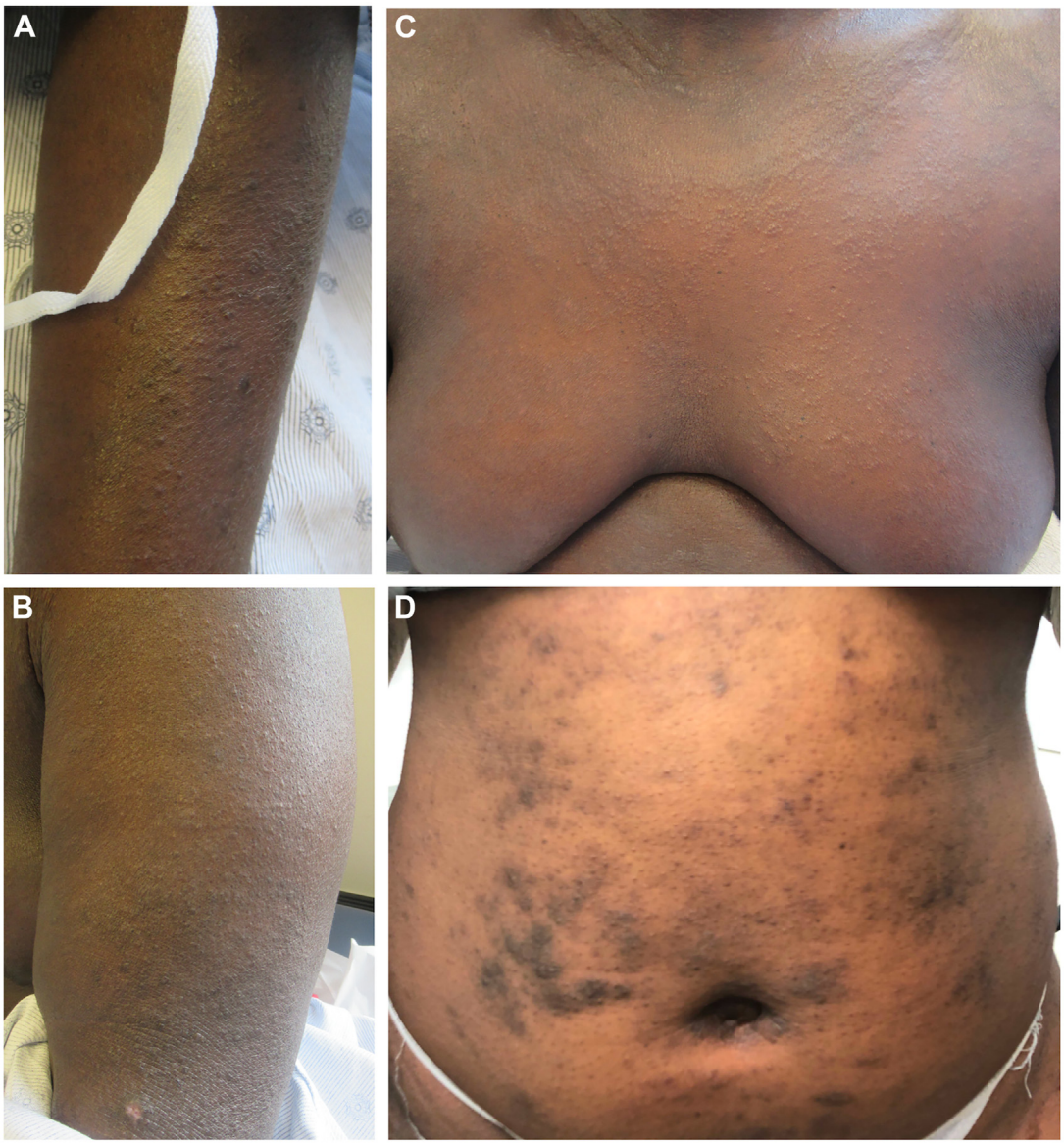

Fig. 7. Perifollicular accentuation on the lower extremity (*A*), upper extremity (*B*), chest (*C*), and trunk (*D*) in Black patients with AD.

DIFFERENTIAL DIAGNOSIS

The diagnosis of AD is made based on clinical presentation and patient history. Important differential diagnoses include seborrheic dermatitis, lichen planus, contact dermatitis, psoriasis, and cutaneous T-cell lymphoma. Especially in Asian patients, AD may present similar to psoriasis, with scaling lesions on extensor surfaces. Lichen planus appears violaceous and papular, which can be difficult to distinguish from erythema in Black patients. Mycosis fungoides, which also suffers from significant racial disparities in its clinical presentation and prognosis, also may mimic AD, often featuring a hypopigmented variant in Black patients.[51] Prurigo nodularis (PN) is another disease in the differential diagnosis for AD.[52] In skin of color patients, AD often has secondary prurigo nodules as well as papular variants.[53] As long as eczematous lesions are also present, this is still the chief diagnosis.[54] PN that is not associated with AD often develops in middle age and can be associated with type 2 diabetes, chronic kidney disease, and HIV.[55–58] Of note, PN disproportionately affects skin of color patients and is associated with several health disparities.[59–62]

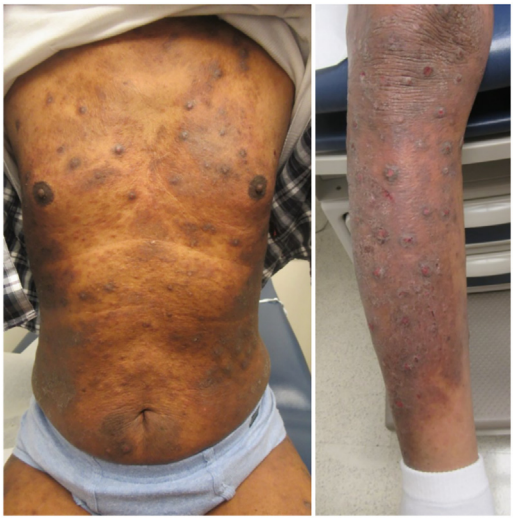

Fig. 8. Concurrent AD and PN. These represent secondary prurigo nodules appearing in the midst of areas of eczema.

TREATMENT

Across all races and ethnic groups, the treatment goals of AD include the prevention of flares to help decrease pain and itch and the repair and maintenance of a functional skin barrier. Initial management begins with moisturizers, the avoidance of irritants, and a variety of topical therapies. Topical agents include topical steroids, calcineurin inhibitors, phosphodiesterase-4 inhibitors, janus kinase (JAK)-signal transducer and activator of transcription (STAT) inhibitors, and wet wrap therapy. In recalcitrant AD, phototherapy and systemic options that target key cytokines can offer more effective control of symptoms.

Despite the numerous treatment options available and the greater disease severity affecting patients of color, skin of color patients are less likely to receive novel therapies for AD than White patients.[63] Even when prescribed, the efficacy of common therapies in non-White ethnic groups is often unknown. This is likely due to the underrepresentation of non-White races in clinical trials, as only 59.5% of studies between 2000 and 2009 included race and ethnicity within the demographic information.[64] Additionally, only 10% of studies commented on race or ethnicity when interpreting results, making it difficult to extrapolate the results to other racial groups. The inclusion of race and ethnicity in future clinical trials is necessary to determine the best treatment regimen for all racial groups.

Topical Treatment Options

Until recently, initial therapy for AD relied greatly on emollients, non-specific topical anti-inflammatory agents, including topical corticosteroids and calcineurin inhibitors. For skin of color patients, colloidal oatmeal can protect the skin barrier and increase skin pH.[20] Long-term use of potent topical corticosteroids can cause hypopigmentation in darker skin tones that may persist after the resolution of AD. Non-steroidal agents are therefore of increased importance in skin of color patients with AD. Of the therapeutic studies that stratified treatment outcomes by race, pimecrolimus 1% cream showed similar efficacy between all racial groups.[65] Crisaborole, a PDE-4 inhibitor,

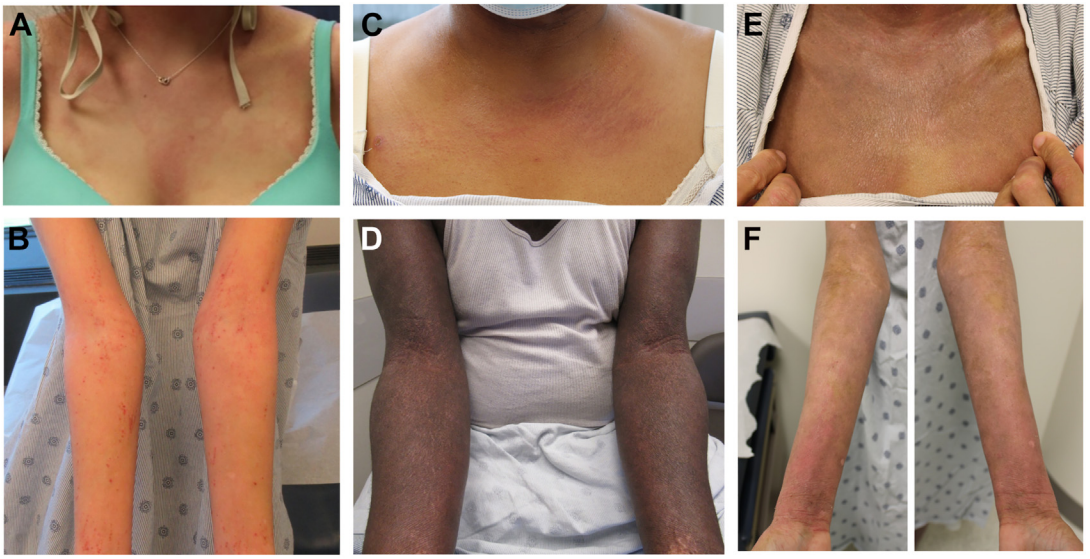

Fig. 9. AD on the chest and forearms of White (*A, B*), Black (*C, D*), and Asian (*E, F*) patients.

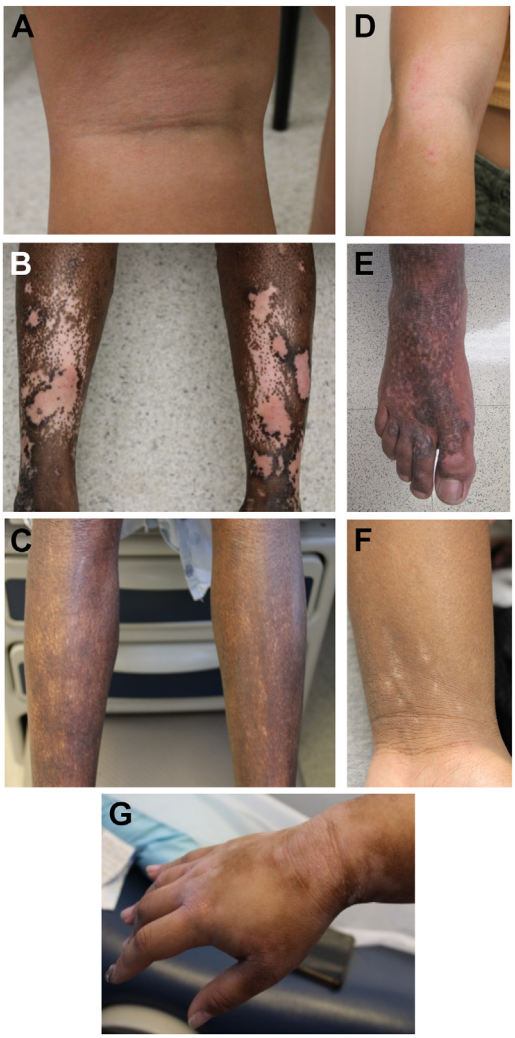

Fig. 10. Post-inflammatory hypopigmentation on Caucasian, Asian, and Black skin. Post-inflammatory hypopigmentation of the popliteal fossa (*A*) and lateral forearm (*D*) on a Caucasian patient. Asian patient with severe depigmentation of the shin (*B*) and dorsal foot (*E*). Black patient with hypopigmentation of the shin (*C*), distal forearm (*F*), and hand and wrist (*G*).

also demonstrated similar treatment outcomes across racial groups.[66] The topical JAK inhibitor roxulitinib, approved for the treatment of mild-to-moderate AD, significantly improves itch, sleep, and quality of life across various races and ethnicities in AD patients.[67] Roxulitinib provides greater itch reduction than triamcinolone, while not having the associated risk of hypopigmentation.[68] Several emerging topical therapies for AD such as the phosphodiesterase-4 (PDE-4) inhibitor, roflumilast, an aryl hydrocarbon receptor modulator, tapinarof, and a pan-JAK inhibitor, delgocitinib, have also shown promising outcomes in clinical trials.[69–71]

Systemic Treatment Options

Currently, there are four systemic agents available for the treatment of AD: dupilumab, tralokinumab, upadacitinib, and abrocitinib. Dupilumab, a monoclonal antibody targeting IL-4Rα, provides significant improvement in the molecular signature of barrier-related genes, inflammatory mediators, and cytokines.[72] This correlates with the clinical improvements in EASI, peak pruritus numerical ratinc score (NRS), and dermatology dife quality index (DLQI) observed in patients, with post hoc analysis showing similar efficacy across all racial subgroups.[73] Tralokinumab, a monoclonal antibody targeting IL-13, reduces investigator global assessment (IGA) scores and EASI-75, and provides patients with improvements in pruritus, sleep interference, and quality of life.[74] Upadacitinib and abrocitinib are both oral JAK1 inhibitors recently approved for the treatment of AD. Clinical trials of both biologics showed significant improvements in EASI-75 and vIGA in patients with moderate to severe AD.[75–78] Patient populations included White, Black, Asian, and Hispanic patients.

Cultural Considerations

Patients in African, Asian, and Hispanic cultures frequently employ complementary and alternative medicine techniques to treat skin conditions before seeking care from a dermatologist. For example, among Koreans, bath therapy and oriental medicine (use of herbs, acupuncture, and cupping) are commonly used to treat AD.[79] However, relapses, short-term alleviation, incomplete resolution, and post-inflammatory hyperpigmentation were all reasons for subsequently seeking medical treatment.

CLINICAL OUTCOMES

Clinical outcomes are difficult to measure in skin of color patients, as existing tools to assess AD are heavily reliant on erythema.[80] An alternative option is to use patient symptoms, including itch intensity, as markers of disease severity and treatment response in patients. Updates to diagnostic tools are needed to assist clinicians in early diagnosis and intervention of AD. We provide an adopted Hanifin and Rajka criteria for AD in skin of color populations (see **Fig. 11**), encompassing the various presentations of AD among a variety of races and ethnicities. This can assist clinicians in earlier diagnosis, thereby, creating opportunities to improve outcomes in skin of color patients.

Major Criteria (3 or more required)	Minor Criteria (3 or more required)

• Pruritus
• Typical morphology and distribution
  ○ Flexural lichenification
  ○ **Extensor papular involvement, lichenification, or psoriasiform thickening of skin in skin of color patients**
  ○ Extensor eruptions in infants and children
• Chronic or chronically relapsing dermatitis
• Personal or family history of atopy (asthma, allergic rhinitis, or atopic dermatitis)
	• **Dyspigmentation (postinflammatory hypopigmentation and hyperpigmentation)**
	• **Psoriasiform scaling**
	• **Perifollicular accentuation**
	• **Secondary papular involvement / prurigo nodule formation**
	• Xerosis
	• Ichthyosis, palmar hyper linearity, or keratosis pilaris
	• Immediate (type 1) skin test reactivity
	• Raised serum IgE
	• Early age of onset
	• Tendency toward cutaneous infections (especially S. aureus and herpes simplex) or impaired cell-mediated immunity
	• Tendency toward non-specific hand or foot dermatitis
	• Nipple eczema
	• Cheilitis
	• Recurrent conjunctivitis
	• Dennis-Morgan infraorbital fold
	• Keratoconus
	• Anterior subscapular cataracts
	• Orbital darkening
	• Facial pallor or facial erythema
	• Pityriasis alba
	• Anterior neck folds
	• Itch when sweating
	• Intolerance to wool and lipid solvents
	• Food intolerance
	• Course influenced by environment or emotional factors
	• White dermographism or delayed blanch

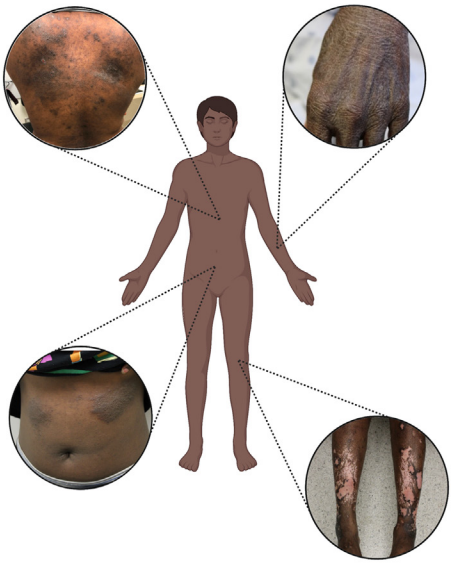

Fig. 11. Hanifin and Rajka Criteria for AD in skin of color.

CLINICS CARE POINTS

- Skin of color patients are disproportionately affected by atopic dermatitis and suffer a greater disease burden, often presenting later in the disease process.
- Clinical manifestations of atopic dermatitis can vary in skin of color patients, often times with greater extensor and papular involvement in African Americans and psoriasiform scaling in Asian patients.
- Assessing itch intensity is a useful bedside tool to objectively assess disease severity in skin of color patients.

DICLOSURE

Dr Kwatra is an advisory board member/consultant for AbbVie, Aslan Pharmaceuticals, Arcutis Biotherapeutics, Castle Biosciences, Celldex Therapeutics, Galderma, Genzada Pharmaceuticals, Incyte Corporation, Johnson & Johnson, Leo Pharma, Novartis Pharmaceuticals Corporation, Pfizer, Regeneron Pharmaceuticals, and Sanofi, an Investigator for Galderma, Incyte, Pfizer, and Sanofi, as well as on the Board of Directors for the Skin of Color Society. Dr Kwatra is also supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health under Award Number K23AR077073. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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