OSS8.2: Inflammatory and Autoimmune Diseases of the Skin Due to Air Pollution and PM Exposure

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FACILITATOR GUIDE

Goal:
Describe the mechanism by which air pollutants including particulate matter exacerbate atopic dermatitis and other inflammatory and autoimmune diseases of the skin (e.g. acne, psoriasis,).

Climate related learning objectives:

1. Describe the mechanism by which air pollutants and particulate matter exacerbate atopic dermatitis and other inflammatory and autoimmune diseases of the skin
2. Discuss the impact that environmental inequities may have on exposure to air pollution and the risk of dermatologic conditions such as atopic dermatitis

Clinical Vignette

JD is a 27-year-old male (he/him) who is seeing a dermatologist because of a rash behind both of his knees. As the medical student on your dermatology rotation, you enter the room to take his medical history..

JD reports that he has experienced episodes of inflamed, dry skin since he was a child. Usually, his rashes clear in 2-3 weeks. However, he notes that it has been especially bad since June of this year. It is currently September. Initially, he noticed the development of a red, very itchy and scaly rash behind his knees bilaterally. He constantly scratches at these areas, and now the skin has become discolored. Recently, he also reports increased discomfort from the rash and new areas of rash have developed on his arms and hands

Patient Review of Systems

JD notes increased itching, redness, and dryness behind his knees. He notes that the itching is worse at night, which makes it difficult to sleep as he is constantly scratching the rash. He does not note blistering but sometimes bleeds after scratching his skin.

Medical History

Food allergies to peanuts and milk
Seasonal allergies
Childhood asthma

Social and Environmental History

JD drinks socially with friends and family on weekends. He reports having smoked cigarettes only a handful of times socially. He denies recreational drug use and exposure to asbestos, industrial chemicals, household pets, or mold. JD works as a park ranger at Golden Gate Park, so he is "always outside," and during warmer months dons a uniform consisting of shorts and a short-sleeved shirt. He loves nature but reports declining enjoyment in his work due to trouble breathing from the increased smoke from the recent Northern California wildfires. He has lived in California for his entire life and lives with his wife. For leisure, he spends ample time outside jogging.

Family History

Mother (50s) and sister (22 yo) have a history of eczema. His sister also had childhood asthma. There is no family history of autoimmune disorders.

Physical Exam

Temp: 98.7F BP: 124/78 Pulse: 81 Pulse ox: 99% on RA

General: Well-appearing male, AOx3, in no acute distress.

Head & Neck exam: Thyroid normal in size, without enlargement or nodules, no other neck masses. No lymphadenopathy.

Pulmonary: No increased work of breathing. Lungs clear to auscultation bilaterally.

Cardiology: Regular rate and rhythm with normal S1 and S2. No murmurs, gallops, or rubs.

Abdomen: Soft, non-tender, and without organomegaly.

Extremities: Warm, well-perfused, and without edema. No cyanosis or clubbing. Pulses are full and symmetric.

Skin: Lichenified, ill-defined, erythematous, eczematous plaques with scale are noted in the bilateral popliteal fossae. Scattered crusted excoriations are noted within the plaques and surrounding hyperpigmentation is appreciated. Pink scaly patches are also observed on the dorsal hands and bilateral antecubital fossae. No vesicles, pustules, purpura, wheals, or burrows are noted on exam. Mucous membranes are spared. Nails are normal appearing.

Lymphatics: No palpable inguinal or axillary lymphadenopathy.

Assessment and Plan
You leave the patient room to discuss your findings with your attending, Dr. Hauld. Dr. Hauld asks you to describe the morphology, size, color, and distribution of the patient's eruption. He then asks for a differential diagnosis, considering the types of skin conditions that present in a manner similar to this patient. ***[Facilitator, review the dermatologic exam for this patient's presentation and brainstorm potential differential diagnosis]***

Based on your conversation with JD, his past medical history, and physical exam findings, you believe he has atopic dermatitis. ***[Facilitator, consider how history of childhood asthma relates to atopic dermatitis and how findings support diagnosis of atopic dermatitis].*** However, JD has noted that this has never occurred before to this severity and with such prolonged duration, noting the newly discolored skin he has now developed. ***[Facilitator, consider how this subacute presentation of atopic dermatitis differs from acute].*** He explains that he has not used any new medications nor changed his diet or bathing habits. When raising this concern with Dr. Hauld, he asks you what environmental factors might contribute to the exacerbation of his atopic dermatitis and the mechanism explaining the severity of the skin rash currently. ***[Facilitator, consider discussing LO1. See the "Answers to LOs" section below.]***

Dr. Hauld asks you about the pharmacologic treatment options for atopic dermatitis and steps that JD can take to prevent exacerbations of his atopic dermatitis in the future. ***[Facilitator, discuss traditional treatments of atopic dermatitis and preventative measures that can be taken.]***

When discussing preventative measures that JD can take to minimize his risk of future exacerbations, you advise limiting exposure to air pollution. JD explains that it is difficult for him to take time off from his work, even if it represents an occupational hazard to his health. He explains that his park ranger job is the only income that supports his family and they have trouble making ends meet as it is. ***[Facilitator, consider discussing LO2. See the "Answers to LOs" section below.]*** During the wildfires, even when he had a hard time breathing on the job, he continued to go into work each day. His current respiratory symptoms and history of childhood asthma raise concern that he has active, atopic-associated reactive airway disease. It is important to alert his PCP and suggest that he wear an effective mask (eg N95) during days with poor air quality.. You can further advise him to download a free cell phone app that allows him to monitor local air quality.

Dr. Hauld prescribes an ultra-potent topical corticosteroid ointment to apply twice daily for 2 to 3 weeks to alleviate his current flare to be followed by topical tacrolimus ointment to be used thereafter for maintenance. Daily oral antihistamines are recommended to manage the symptoms of pruritus and gentle skin care measures along with use of bland emollient creams are reviewed as key measures to maintain skin barrier function. He also encourages JD to avoid potential triggers for his atopic dermatitis and to use UPF-rated, long-sleeved protective shirts and long pants while at work and to bathe nightly to remove contaminants and pollution residue from his skin. JD will follow up in 3 weeks should his atopic dermatitis not improve with topical steroids.

Mini case
JD is a married, 27-year-old Hispanic male working as a park ranger who presents with a rash behind both his knees with increasing redness, itching, flaking, and discolored skin. The itching has significantly impaired the patient's QOL preventing him from sleeping well. He also reports difficulty breathing while working outside due to the recent wildfires. The patient has a history of seasonal allergies and childhood asthma and family history of eczema and asthma. He is a recreational drinker and smoker but has no exposure to asbestos or other chemicals.

Answers to LOs
LO 1: Describe the mechanism by which air pollutants and particulate matter exacerbate inflammatory and autoimmune dermatologic conditions (e.g. atopic dermatitis).

Atopic dermatitis (AD) is an extremely common inflammatory skin condition globally, affecting 20% of US children and often persisting into adulthood. AD frequently occurs in individuals or families with concomitant asthma and allergic rhinitis/seasonal allergies. The pathogenesis of AD is characterized by aberrant keratinocyte differentiation, elevated surface (or stratum corneum) pH, barrier dysfunction, increased transepidermal water loss (TEWL), and subclinical Th2/Th17 inflammation. While pathophysiological models for understanding AD have historically centered around a type 1 hypersensitivity-mediated immune response classically associated with atopic disease (IgE-mediated and T-helper 2 activation), as well as skin barrier defects, recent models have further integrated other key contributors to AD-related immune dysregulation including varied degrees of epidermal

disruption, neuro-immune interactions, alteration in skin microbiota, lipid imbalances, and oxidative stress.

AD develops early in patients' lives and is a heterogeneous disease characterized clinically by recurring eczematous skin lesions that appear poorly circumscribed, erythematous and scaly. The lesions initially form with exudative patches and progress to lichenified plaques accompanied by severe itching and discomfort. However, even patients with AD presenting with normal-appearing skin still show signs of an impaired skin barrier with epidermal hyperplasia and xerosis.

Air pollution, specifically exposure to particulate matter less than 2.5 microns in diameter (PM 2.5), is inherently linked to climate change as both are derivative of fossil fuel combustion. Moreover, climate-driven drought and wildfires increase the contribution of pollution from natural sources, while increasing heat in the presence of ultraviolet light drives conversion of primary pollutants into ground-level ozone production. Although the mechanisms for AD pathophysiology are still being explored, there is mounting evidence that exposomal influences, including air pollution, contribute to triggering and/or exacerbating AD and that reducing exposure to pollution improves symptoms of this disease. In particular, the inflammatory cascades typical of AD can be triggered by exposure to air pollutants, specifically particulate matter, which is demonstrated to activate the cutaneous inflammasome via the production of reactive oxygen substances (ROS) and activation of key transcription factors.

<u>Pathogenesis of Particulate Matter and Other Air Pollutants in Atopic Dermatitis</u>

Skin Barrier Dysfunction
The skin is the body's primary mechanical, chemical, and immunological barrier against environmental insults. As the primary mechanical barrier, the skin is frequently exposed to particulate matter and air pollutants such as polycyclic aromatic hydrocarbons (PAH), volatile organic compounds (VOCs), nitrogen oxides (NOx), particulate matter (PM), and heavy metals that can degrade its protective function, depending upon the nature and mode of entry of these pollutants. As a result of human activity (population growth, industrialization, urbanization) and our continued reliance of the combustion of fossil fuels for energy generation, harmful pollutants are continuously added to the atmosphere.

The pollutant of greatest consequence is particulate matter (PM), aerosolized collections of tiny solid and liquid aggregates to which polycyclic aromatic hydrocarbons (PAHs) and heavy metals adhere. Because these lipophilic compounds penetrate deeply into epithelial tissues (lungs, GI tract, skin) and enter the systemic circulation, PM and other pollutants contribute to the growing global disease burden. The effects of PM are often discussed in relation to respiratory and cardiovascular health but are increasingly implicated in cutaneous inflammatory diseases.

Outside of anthropogenic sources, PM2.5 (particles less than 2.5 microns in diameter) also represents a major component of wildfire smoke. These particles may travel thousands of miles, affecting air quality at sites distant from the fire. Importantly, short-term exposure to air pollution from wildfires increases dermatologic clinic visits for atopic dermatitis and pruritus in both children and adults. Furthermore, the majority of adult patients seen for itch during the 2018 Camp Fire in California did not carry a prior diagnosis of AD, and an

association between smoke exposure and need for systemic medications was observed in adult patients.

Pollutants may enter and breach the skin through direct penetration of the stratum corneum, absorption through hair follicles and sweat ducts, and/or dermal translocation from the systemic circulation. Chemical agents, such as VOCs, can degrade the keratinized surface of the skin's epidermal or outer layer. such that early studies demonstrate that VOCs, formaldehyde, and NO2 damage the integrity of the skin barrier in patients with AD, increasing TEWL which is linked to hypersensitization to aeroallergens and exacerbation of inflammatory processes typical of AD. The filaggrin gene, which encodes for the filament aggregating protein (FLG), is a key contributor to the structural integrity of the epidermal barrier. Research supports inhibition of FLG expression in keratinocyte cultures, organotypic skin cultures, and the skin of the animals exposed in vivo to PM2.5, providing a key mechanism by which air pollution degrades the skin barrier.

Neuroimmune Interactions / Aryl Hydrocarbon and Pregnane X Receptors
Reduced skin barrier integrity increases penetration of air pollution and contributes to inflammatory skin pathology in diseases such as AD. The pregnane X receptor (PXR) and the aryl hydrocarbon receptor (AHR) are ligand-activated nuclear transcription factors modulating xenobiotic metabolism. Activation of PXR favors a Th-2/Th-17 immune response leading to pro-inflammatory cytokine production (thymic stromal lymphopoietin, IL-6, IL-13, IL-17 , lymphocytic infiltration, and granulocytosis. AHR is also shown to downregulate antioxidant gene expression, induce ROS generation, and trigger antimicrobial peptide production which may impact the skin's microbiome accounting for the differences in microbiota observed between AD and non-AD populations..

Toxic environmental agents, particularly PAH, upregulate PXR and AHR activation and play a role in AD exacerbation.. Mouse models have demonstrated upregulation of Th2 cytokine production and increased itch due to PAH activation of AHR. Moreover, urinary PAH metabolite levels in humans are shown to correlate with atopic disease symptoms, stratified by age and body mass. In particular, the metabolite 2-hydroxyphenanthrene is associated with chronic pruritus in overweight individuals while 3-hydroxyphenanthrene, and 1-hydroxypyrene urinary metabolites correlate with chronic pruritus in the elderly.

Oxidative Stress
Skin cells produce ROS in response to inflammatory signals, air pollutants, UV radiation, and other physiologic and environmental stimuli. ROS upregulate cell survival and proliferative signals, and disrupt cellular lipid membranes, collagen structures, and mitochondrial function when not balanced by enzymatic antioxidant defenses (glutathione peroxidase, glutathione reductase, superoxide dismutase, and catalase) and nonenzymatic (vitamin E, vitamin C, and glutathione) antioxidants.

Air pollutants, such as ground-level ozone, can cause oxidative damage to the skin. As previously noted, activation of transcription factors by air pollution such as AHR increase ROS generation and deplete antioxidant capacity. ROS and free radicals interact with lipid membranes triggering a lipid peroxidation cascade that incites proteolytic activity by matrix metalloproteinases resulting in tissue damage and compromise of skin barrier function integrity. ROS also perpetuate inflammation by stimulating proinflammatory mediators that recruit phagocytic cells which, in turn, generate more free radicals. Consequently,

accumulated oxidative stress adds to the inflammatory state seen in AD and other autoinflammatory cutaneous disease by causing direct tissue damage and stimulating proinflammatory mediators via complex signaling pathways.

Traffic-related Air Pollution (TRAP)
Research indicates that increasing levels of traffic-related air pollution increase the incidence and severity of atopic dermatitis, particularly for infants and children. A greater incidence of infantile atopic dermatitis is noted with increasing average levels of seven major outdoor air pollutants, including carbon monoxide, nitrogen dioxide, formaldehyde, and lead. Similarly, studies have demonstrated an increased risk of developing AD in children living less than 50 meters from a main road. Moreover, maternal exposure to TRAP during the prenatal period triggers epigenetic modification, shifting the immune response toward a Th2 phenotype in utero and is associated with a greater risk of AD in early childhood. Collectively, this suggests that the wide variety of pollutants constituting TRAP impacts the development of AD.

While AD represents the prototypical climate-sensitive cutaneous autoinflammatory disease, emerging evidence is also increasingly supporting the role of air pollution and wildfire smoke in exacerbations of psoriasis, acne vulgaris, and pemphigus with exposure linked to increased clinic visits for psoriasis and acne and increased rates of hospitalization with pemphigus, respectively.

LO 2: Discuss the impact that environmental inequities such as air pollution may have on dermatologic conditions including atopic dermatitis.

The health burden resulting from climate change does not fall equally. Rather, environmental issues disproportionately impact certain vulnerable and marginalized groups such as racial minorities and children. Discussion regarding these environmental inequities is vital in the diagnosis and treatment of cutaneous conditions, many of which are exacerbated by the impacts of climate change.

Strongly attributed to premature death, air pollution is known to predispose to a wide array of health ramifications. In addition to its health impacts on the lungs, brain, and cardiovascular system, air pollution is increasingly attributed to the incidence, severity, and exacerbation of inflammatory dermatoses such as atopic dermatitis, psoriasis, acne vulgaris, and pemphigus. Given air pollution's impacts on autoinflammatory skin diseases, the inequitable exposure to air pollution is especially concerning for vulnerable populations. Children, in particular those living in low-income or underserved regions, suffer a greater dermatologic burden from the effects of air pollution.

The disproportionate impact of environmental inequities is rooted in structural racism and primarily shouldered by racial minorities, those of lower socioeconomic status (SES), and Indigenous Peoples. The results of such injustice, reflected at various levels such as healthcare, economics, education, public policy, and more, leads to inequities in the social and physical environments of these marginalized populations. Particularly, structural racism has contributed to modern-day residential segregation, incarceration, and socioeconomic positioning, resulting in greater exposure to environmental pollutants and heat, diminished housing quality, limited access to medical care, and higher rates of comorbid disease. Research suggests Black children are more likely to live in houses that are in low-income

communities that have greater exposure to pollutants. Compounding these inequities, many communities of color are disproportionately exposed to other sources of air pollution like wildfires; considering many minority communities are located in regions with low adaptive capacity to address the impacts of wildfires, Hispanic, Black, and Indigenous communities have a 50% increased vulnerability to wildfires.

Furthermore, although communities of color or those in lower socioeconomic groups generate significantly less air pollution, they have disproportionate exposure, because these neighborhoodsare more likely to be located near sources of anthropogenic pollution, such as highways, industrial and toxic waste sites, and other high pollution-producing sources. In addition, historical housing policies generated racially segregated neighborhoods such that formerly redlined communities are now urban heat islands, with fewer green spaces and trees and more concrete... Since minority groups and those of lower SES are more likely to live within these urban heat islands and in proximity of major sources of pollution, the impacts of air pollution are often further compounded by heat-inducedozone formation, leading to greater health harms. Given these exposures and inequities, not surprisingly Black children in the U.S. display greater severity of atopic dermatitis than their white counterparts. As such, disproportionate environmental exposures have critical relevance to dermatologists and primary care providers caring for the skin health of residents in at-risk communities.

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