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Understanding the Pathophysiology of Atopic Dermatitis: Have We Only Scratched the Surface?

Video | Voiceover for Introduction Slide:
This medical feature, brought to you by Pfizer, is titled "Understanding the Pathophysiology of Atopic Dermatitis: Have We Only Scratched the Surface?"

Joining us today are doctors Eric Simpson and Jonathan Silverberg, two experts in the field of atopic dermatitis, and paid consultants for Pfizer.

Pfizer does not currently have any JAK inhibitors approved for the treatment of atopic dermatitis.

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ERIC SIMPSON, MD, MCR: Welcome everyone. We'll be talking about the mechanisms involved in atopic dermatitis, including skin barrier disruption, inflammation, the pathophysiology of itch, and the role of the JAK/STAT pathway in atopic dermatitis. My name is Eric Simpson. I'm professor of dermatology at Oregon Health & Science University. And I'm very pleased to be joined by Jonathan Silverberg, who I'll let introduce himself.

JONATHAN I. SILVERBERG, MD, PhD, MPH: Hi everyone. I'm Jonathan Silverberg. I'm also a dermatologist. I'm an associate professor of dermatology and director of clinical research and patch testing at the George Washington University School of Medicine & Health Sciences. And I'm looking forward to a wonderful conversation.

ERIC SIMPSON, MD, MCR: Thank you. Well, would you mind starting us off with a case?

JONATHAN I. SILVERBERG, MD, PhD, MPH: Absolutely. This is a black female, age 23 years with atopic dermatitis that started very early in childhood. And the atopic dermatitis had been under pretty good control from the age of about 15 to 18 years. But has really started to worsen with widespread itch and lesions. And the patient's atopic dermatitis is now uncontrolled even with topical corticosteroids, using a substantial amount of mid potency topical steroids on a daily or twice-daily basis. In terms of the presentation, there really were a number of signs of inflammation that were present including erythematous lesions and hyperpigmented papules with follicular prominence, coalescing into larger eczematous plaques and with that really a widespread involvement over greater than 99% body surface area of involvement. Evidence of skin barrier disruption exemplified by flexural lichenification. But it also, some of those accessory signs we see, mild ichthyosis on the anterior shins and the patient also had the presence of eyelid dermatitis and cheilitis as well. Symptomatically, a really severe, chronic itch that was causing notable sleep disturbances. So, this patient presented with really a complex and heterogenous presentation, multiple different types of signs and symptoms that appeared. While we can't really know the exact mechanisms in this particular patient, Eric, can you take us through what we do know about some of that complex and heterogenous pathophysiology of the disease?

ERIC SIMPSON, MD, MCR: Sure. Yeah. What we do know is that underneath the skin, the inflammatory infiltrate is pretty complex and heterogenous just like the clinical picture.

So, we know that inflammatory cytokines are involved, and these include interleukin-4, -5 and -13, so called type 2 cytokines, as well as enzymes, such as phosphodiesterase-4 that are involved in AD related inflammation. Patients with AD can exhibit dysregulated immune responses even in their nonlesional skin. IL-4 and IL-13 are type 2 inflammatory cytokines that play an important role in the regulation of IgE synthesis and they're major drivers of atopic inflammation. Thymic stromal lymphopoietin or TSLP also plays a crucial role in allergic inflammation via activations of Langerhans cells that cause differentiation of T_H-2 cells in lymph nodes. So, Jonathan, in lesional skin, acute and chronic lesions have distinct pathophysiological changes. So, in acute, the acute lesions of your patients—those weepy, very erythematous lesions—IL-4 and IL-13 are very important and they can damage the skin barrier, they bring in inflammatory cells that they recruited, and that can cause the redness and swelling that you see. Now in the more chronic lesions, the more lichenified lesions in your patient, the infiltrate is characterized by more T_H-22, as well as type 2 cytokines, such as IL-13 and -4, for example, that stimulate keratinocyte proliferation. And T_H-22 is the very important one for the proliferation of keratinocytes. Chronic inflammation in general is stimulated by type 2, T_H-22 and T_H-1 cell recruitment and dendritic cell activation of inflammatory cells and production of proinflammatory cytokines. Now in terms of itch, there are four really important cytokines, TSLP, IL-4, IL-13 and IL-31. While itch is a primary complaint of patients with atopic dermatitis, visible or prominent lesions can make patients self conscious or cause them to withdraw from social events.

JONATHAN I. SILVERBERG, MD, PhD, MPH: Thanks Eric for that excellent explanation. You know, it's really interesting that itch has such a complex pathophysiology. That's really clinically relevant because, you know, it leads the patients to avoid socializing because they're, you know, the embarrassment about clothing choices or an inability to go to certain venues because of those different triggers for itch. So, we see that complexity of the disease really manifest in the burden of patients. So, this patient had several signs of skin barrier disruption. And while we can't really know the exact cause of these barrier phenomena in this particular patient, Eric, can you take us through what we do know about barrier disruption in general with atopic dermatitis?

ERIC SIMPSON, MD, MCR: Sure. You know, the pruritic eczematous skin lesions of atopic dermatitis result in part from skin barrier disruption as well as the underlying inflammation due to the immune system regulation. So, both things are playing a role in barrier disruption. So, if there are inherited skin barrier defects, such as filaggrin mutations that can lead to decreased ability to retain moisture in the stratum corneum and are more commonly seen in patients with atopic dermatitis. There is also a reduction in ceramide content, so lipids in the skin, as well as an increased pH disruption of tight junction proteins and altered composition of epidermal lipids and an overexpression of enzymes that are other factors that can contribute to skin barrier disruption in atopic dermatitis.

Now when you have the skin barrier disruption, both irritants and allergens can more readily penetrate the skin and trigger further inflammatory responses. There are other exogenous environmental factors such as dust, soap, cleansers, winter dryness, heat, sweat, even occupational exposures that can all contribute to the barrier disruption that can just exacerbate the underlying condition. Skin barrier disruption can at times manifest in symptoms that cause substantial discomfort and burden to the patient as well. So, you can see, Jonathan, that it's just not inherited genetic defects that cause barrier disruption. The inflammation plays a role and further contributes to barrier disruption. It's driven by various cytokines, like IL-4, -13 and -31, TSLP and IL-22. For example, IL-22 upregulation promotes epidermal hyperplasia. That contributes to skin barrier disruption in chronic lesions and chronic atopic dermatitis.

Interestingly, IL-4 and IL-13 and IL-31 have been shown to downregulate terminal differentiation genes in the epidermis of atopic dermatitis patients as well as tight junction products, further contributing to barrier disruption.

Interestingly, the five key AD cytokines, IL-4, -13, -22, -31 and TSLP, all signal through the JAK/STAT pathway.

JONATHAN I. SILVERBERG, MD, PhD, MPH: It's so interesting that, you know, you have this intersection of the barrier disruption and the immune dysregulation, and, you know, one of the fascinating things that comes up is there's a big discussion about what is the chicken or the egg. You know, does it start at barrier? Does it start at the inflammation? But regardless, you know, these core principles are really relevant in all patients. And we see them conceptually manifest as well, along with some of the clinical presentation, in the sense that we can see more chronic lesions. We can see more acute lesions for those, you know, acute inflammation, acute barrier disruption will manifest more with that, you know, exudative lesions, oozing, crusting, weeping. But when you get into the more chronic stages, you tend to see a lot more of, you know, fissures, lichenification, et cetera. And, in truth, even this distinction in terms of acute and chronic and how long the inflammation plays out in some of these different pathways, really can take its, you know, long-term toll on patients where chronic, more severe disease is associated with sequela like lower self-esteem, sleep loss, reduced productivity. And, you know, in our patient, there really were profound sleep disturbances that occurred over time and patient missed many days of work because of the intense symptoms. And when she was at work, she had difficulty concentrating because of fatigue, et cetera. And, you know, it's really fascinating to see how those skin findings or the pathophysiology can translate into that clinical burden of disease.

ERIC SIMPSON, MD, MCR: Yeah. Absolutely. And I think our therapeutic approach will probably address both the skin barrier and the inflammation for optimal responses.

JONATHAN I. SILVERBERG, MD, PhD, MPH: So, our patient really had a profound burden of itch, sometimes 12 hours or more a day, seven days a week for months on end. And again, while we can't know the exact mechanisms of itch in this individual patient, Eric, can you take us through what we do know in terms of the mechanisms of itch overall in atopic dermatitis?

ERIC SIMPSON, MD, MCR: Sure. In AD skin, pruritogens are released by various cells such as keratinocytes, T cells like T_H-17, T_H-2, or ILC-2 cells, mast cells, macrophages, dendritic cells, eosinophils, as well as even nerve fibers. So multiple cytokines play a role in the AD-related itch. Despite crosstalk with other pruritogens, IL-31 signaling has emerged as a key cytokine in the mechanism of pruritus in the skin. The IL-31 receptor alpha is primarily found on C-fiber sensory nerves. TSLP also promotes itch via activation of sensory neurons. IL-4, -13, and -31 and TSLP are all pruritogenic cytokines that signal through JAK1. The signal induced by pruritogens is transmitted from the skin to the spinal cord through afferent fibers. Direct activation of sensory neurons to propagate chronic itch is mediated through JAK1 and is in part independent of skin inflammation.

Chronic itch associated with atopic dermatitis is induced by histamine-independent neuronal pathways.

JONATHAN I. SILVERBERG, MD, PhD, MPH: Yeah. It's really so interesting to see so many complex mechanisms for the symptom of itch. And, you know, it's obviously such a burdensome symptom to our patients, in general to this particular patient. You know, itch is bad for patients of all severities of atopic dermatitis, but certainly the more severe it gets in those moderate to severe atopic dermatitis patients, I mean it can really be devastating, so debilitating, so impactful on their life, just preventing them from being able to sleep sometimes for years on end. And it's just something that is so relevant in clinical practice.

ERIC SIMPSON, MD, MCR: Yeah. Absolutely. I really find it interesting that those inflammatory cytokines aren't just important for inflammation, but actually bind to neurons and can cause itch through direct mechanisms.

JONATHAN I. SILVERBERG, MD, PhD, MPH: So, this has been an outstanding discussion.

Eric, can you tell us, you know, what are some of the common threads in atopic dermatitis pathophysiology?

ERIC SIMPSON, MD, MCR: Sure. You know, while each component of AD pathophysiology, skin inflammation, skin barrier disruption, and chronic itch likely contribute to the burden of AD and has its own important mediators, there is considerable overlap among all these three components. So chronic itch likely contributes to ongoing skin barrier disruption via the itch-scratch cycle. IL-4, -13, -22, and -31 and TSLP are key cytokines in atopic dermatitis pathophysiology and appear to contribute to the inflammation and chronic itch seen in AD via JAK1 signaling. By inhibiting JAK1, it may be possible to decrease signaling of key cytokines that drive AD inflammation, itch, and skin barrier disruption.

JONATHAN I. SILVERBERG, MD, PhD, MPH: Thanks so much for that wonderful summary. And I'd like to thank the audience for your attention.

I hope we found that this discussion was useful and relevant for your clinical practice. And I'd like to thank my colleague, Eric Simpson, for his time and outstanding presentations. Thank you.

ERIC SIMPSON, MD, MCR: Thank you.

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