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Practical Dermatology Roundtable: Generalized Pustular Psoriasis, Ch. 2

Dr. Neal Bhatia:
Jason, I'll build on something you said about maybe more typical presentations of psoriasis. I mean, you'll hear a lot of our colleagues who will recognize psoriasis, but they may be dealing with GPP. Yet they may say some of the response to traditional therapies have worked for them, or at least maybe put out the fire. Do you think there's some value to that and maybe bridge into some of the IL-36 pathway behind that?

Dr. Jason Hawkes:
Yeah, I mean, it's interesting when you look back at the history, because pretty much everything we learned about psoriasis started in the skin. We were collecting biopsies, they were starting to tease out some of the traditional pathways. Even the way we taught psoriasis as a spectrum started with the skin. I'm sure both of you learned the same, where patients get plaque psoriasis, then five to seven years later, they get psoriatic arthritis. So, we're talking about how everything kind of started with the skin. I think we built the framework that way.

We know that it's not entirely true. It's true for most patients, but we start to see sort of this distinct presentation that didn't really necessarily start with the skin. Well, in the same concept, we have this idea that maybe these variants are different. We assume they must be the same because patients with plaque psoriasis, we figured, oh, it's IL-23, IL-17 pathway predominant. So, all of these other variants must also be the same way. And many of them are. We see inverse and localized disease, guttate psoriasis. These tend to respond to some of the same therapies.

But what's interesting is we see these other variants, which appear to be much more recalcitrant or resistant to these traditional therapies, which work really well. So we see things like palmar plantar pustulosis, or even palmar plantar disease. Erythrodermic patients can respond really well, but the GPP patients didn't. And so, we're starting to then tease out that not everything looks like plaque psoriasis, and even has the same underlying biology.

And I think this was really highlighted when the New England Journal of Medicine paper came out with the Tunisia patients, showing that they had these inborn defects of the IL-36 signaling pathway. So, now we have something that's completely different. We're talking about the adaptive immune response with IL-23 and 17. Now, we're really talking about the innate immune response. So totally different, even though it occurred in patients who could have plaque psoriasis.

So I think carrying through that idea that everything started in the skin, practitioners just assumed that if I use the same therapies that worked really well in plaque psoriasis, maybe they'll work for this. And particularly in those patients who do have both. But from our experience, we find that sometimes it can keep some features of the disease down. But it wasn't highly effective at really controlling disease. And that was what we saw really different from the clinical trials where IL-36 we learned was from both the mutations, but also molecular studies that IL-36 dysregulation was the predominant driver of GPP as opposed to IL-23, 17. And it's actually a great translational science story where you say, here's this new signal that we didn't attribute as being really a key factor in plaques psoriasis. And yet targeting could clear patients and the majority of patients in one week after therapy. So, I think it really highlights just how different GPP is.

So these patients typically have either higher levels of IL-36 or they have a defect in their IL-36 receptor antagonist, which shuts off that signaling of that pathway. And I think this has been a nice full circle proof of concept, that bench to bedside, where now we have a therapy that can shut down this predominant signaling driving this variant, which is quite different from plaques psoriasis.

Dr. Neal Bhatia:
Yeah. And you hit on the big pathway there being not 17 driven, but 36 driven. And again, you mentioning about some of those neurotransmitters like MyD88 and NF-kappa beta that have a lot of role on lymphocyte stimulus and such. But Laura, we know a little bit more about neutrophils. Where do you think the role of neutrophils fits in? And then where does that translate back to the overall process?

Dr. Laura Ferris:
So neutrophils, we know, are just key for GPP. While we can't see neutrophils in the skin, if we look histologically at plaque type psoriasis, we know that that is really the main cell type that we see histologically in GPP. And so, we also know how important IL-36 is in driving neutrophil activation and homing to the skin. And so, it really does kind of drive home that we have a targeted therapy that actually gets at the pathogenesis of this disease. It's unlike plaque psoriasis where we have multiple different cytokine pathways that we can think about being involved. This really is one where we can kind of hone down to a single cytokine, IL-36.

I think to Jason's points, if we look at the patients who have inborn errors in the IL-36 pathway, so mutations specifically in the receptor antagonists, or even some mutations that drive sort of accumulation of IL-36 and reduction of the breakdown of IL-36, we really know that we've got one cytokine. And we really know that that is a key cytokine for neutrophils in the skin. And so it really makes sense that this is, in some ways, a little bit more of a simple immunologically simple disease compared to plaque type psoriasis.

Dr. Neal Bhatia:
And a lot of that ties into the visceral symptoms and some of the other components that go along with the presentation. I mean, intense pain in the skin, a lot of the desquamation that, like you said, lakes and pusses is really good descriptor of the presentation. But it also kind of points back to the differential. When you think about AGEP, you know the pusses are a little bit different in their distribution. Obviously, a little bit of history will go a long way with the differential of AGEP if you know the medication history started within a couple of days, there's a big pointer in that direction.

And then of course, standard folliculitis, which gets overdiagnosed unfortunately to the untrained eye, but also to many of the trained eye, when they're not going in under the hood. And that kind of points also to the rule of neutrophils, the way that standard folliculitis can also look. But without, again, that intensity of erythema, that really deep, dark, ruddy erythema that goes along with the plaques as well as just the intense symptom profile that a lot of the patients go through.