Itch Related to Prurigo Nodularis
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Shawn Kwatra, MD, FAAD, interviewed by Sabrina Shearer, MD, FAAD

SABRINA SHEARER, MD, FAAD: Welcome back to another episode of *Dialogues in Dermatology*. I'm Sabrina Shearer, Assistant Professor of Dermatology at Duke University and the Durham Veterans Affairs Medical Center. I'm super excited to be joined today by Dr. Shawn Kwatra. Dr. Kwatra serves as Professor and Chair of Dermatology at the University of Maryland School of Medicine. Throughout his career, Dr. Kwatra has been a leader in clinical and translational research in patients with chronic pruritus and prurigo nodularis and in skin of color. He is here today to share his pearls on itch related to prurigo nodularis. Dr. Kwatra, thank you for joining us today.

SHAWN KWATRA, MD, FAAD: Thank you so much for having me today.

SABRINA SHEARER, MD, FAAD: So chronic pruritus can be an incredibly daunting topic for a lot of us. How did you get interested in studying pruritus?

SHAWN KWATRA, MD, FAAD: Practicing dermatology, it's actually our hallmark symptom, itching. So just seeing a lot of patients, it has truly just been fascinating, all of the different manifestations of itch. When you start asking about it, which I ask my patients about it, my friends about it, everybody about it, you start appreciating just how severe chronic itch can be and how significantly it can impact your quality of life.—

--It's, I think, our biggest burden that we have in dermatology is chronic itch in these patients. Work by ourselves and others are trying to reveal just how devastating chronic itch can be to peoples' lives. It can cause you to have terrible sleep loss, anxiety, depression. We did a study about overall quality of life that it appears to be when you compare their medical conditions in

mind with having a stroke or kidney failure, that's the level of seriousness that this condition warrants and deserves.—

--So being attracted to the symptom and almost like a detective looking into all of the different causes and origins and treatments has really captured my attention. It's just I think a fascinating, growing area for research, investigation. But everything is related back to clinical care and having the right tools in the toolbox to manage these patients, which can be really hard.

SABRINA SHEARER, MD, FAAD: You touched a bit on just by their first presentations of chronic pruritus or itching in lots of patients and the many different ways that it affects their lives. What do we know about what causes itching?

SHAWN KWATRA, MD, FAAD: Itch is a neuroimmune process. It is related to dysfunction that can occur from any aspect of the nerves and immune response. One way to start is to think about why do we even itch? Well, we itch because we want to protect ourselves evolutionarily from pathogens. So parasitic infections, other types of infections, fleas, bites, mosquitoes. So we want to be able to remove the stimulus by scratching.—

--So that can go haywire. We have nerves that go all the way up to the outer layer of the skin, the epidermis or dermis. Thinly myelinated A-delta fibers or unmyelinated C-fibers. They go to the dorsal ganglion and spinal cord in the brain and back. You also have immune cells, like eosinophils and basophils and T cells that secrete cytokines that stimulate these nerves. The nerves also secrete neuropeptides and there is an itch/scratch cycle going on that is the forefront and cornerstone of the pathogenesis here of chronic itch. We're trying to stop that cycle any way we can.

SABRINA SHEARER, MD, FAAD: Where does prurigo nodularis fit in?

SHAWN KWATRA, MD, FAAD: Our group recently did the first genetic study of prurigo nodularis. One of the big conclusions we found is that people are genetically predisposed to either itch on normal-appearing skin or to itch with skin lesions, prurigo nodularis. So it can be small bumps or papules, nodules, excoriations. All of that falls into the term prurigo nodularis. So actually that analogy for prurigo nodularis is itching in general or chronic pruritus of unknown origin.—

--The key feature of prurigo nodularis is that you also have these skin lesions that can be heterogeneous but often times very thickened, very fibrotic, very raised lesions, in addition to the chronic itch. So there also seems to be a bigger role for the fibroblast.

SABRINA SHEARER, MD, FAAD: Obviously, you are an expert in itch. I imagine that patients who have been really suffering are seeking you out specifically. Tell me a little bit more about your patients. What has their journey been like up to this point when they see you?

SHAWN KWATRA, MD, FAAD: Oftentimes it's very difficult. They've seen a lot of different doctors or in some cases been on topical steroids for an unusually or abnormally long period of time. And they've been suffering for quite some time, unfortunately. Some people may have told them it's all in their head, so that's another aspect of the burden, dealing with someone telling what you have is artificially generated or made in your head. That's another element of burden of this disease, as well.

SABRINA SHEARER, MD, FAAD: So when you see patients for the first time and you've identified that they have chronic pruritus, they've gone through all of these things already, can you sort of run us through your approach to that initial evaluation?

SHAWN KWATRA, MD, FAAD: The initial evaluation for these patients is if they don't have a rash or they have some skin lesions, prurigo nodularis, we still want to do the similar workup,

which is a complete blood count with differential. And that's really important because we want to be able to make sure there's no hematologic dyscrasias, things like polycythemia vera. So we want to make sure that we're checking out the hemoglobin levels, this is very important.—

--We also want to do a comprehensive metabolic panel and in particular, we want to focus in on the liver and kidney to make sure that there's no issues. We know that chronic liver disease or chronic kidney disease can also be associated with chronic itch. Really cool studies that I was a part of also showing that bile for any chronic liver disease can actually directly stimulate itch on nerve endings, very cool. And we know in uremic pruritus or chronic kidney disease-associated pruritus or itching that you have a bunch (?) of toxins that are circulating that can absolutely activate the nerves, as well.—

--So those are two big conditions. And then finally, diabetes can also stimulate itching because that's the glucose. So I do a CBC, CMP, and then other things, thyroids less frequently associated with chronic itch but it's an easy fix. So I get a CBC, CMP, and a TSH in these patients. And then you can use your clinical judgment about going further. Do you have a concern for infectious diseases based on their travel history, country of origin, risk factors? You can do tuberculosis, you can do hepatitis, HIV testing if that's appropriate.—

--Does someone have a recent history of going to a tropical location? That might be the only situation where I would do a stool investigation for ova and parasites. Otherwise, it's usually not productive. Then what I would say is there are a whole host of investigations you can do, based on different additional risk factors. So timing of the itch is very important. If it's less than a year in particular, that actually increases slightly your risk of having a malignancy. So if somebody has itch for three months to a year, that might be reasonable to get a chest x-ray to rule out a Hodgkin's or non-Hodgkin's lymphoma, or a serum or urine protein electrophoresis.—

--But if someone has had itch more than five or ten years, they're at a normal population risk of these malignancies, so they should be getting their up-to-date age-appropriate screenings but not necessarily needed to do all of these other things, as well.

SABRINA SHEARER, MD, FAAD: It sounds like the biggest red flags for looking for an underlying etiology are if they have had itch for a short period of time, as you mentioned, like months to less than a year. And if you identify, of course, any abnormalities on that initial laboratory workup, which it sounds like you're doing for all of your patients the initial time that you see them?

SHAWN KWATRA, MD, FAAD: Yeah.

SABRINA SHEARER, MD, FAAD: You've also dedicated a lot of your clinical research career and clinical career to skin of color and identifying racial disparities in dermatologic patients. So looking at itch through that lens specifically, what's important for dermatologists to know about prurigo in patients with skin of color?

SHAWN KWATRA, MD, FAAD: I think it's important to be aware of different manifestations of skin disease. So prurigo nodularis patients oftentimes in skin of color have more thickened and fibrotic lesions. That's important that people recognize that, because sometimes it looks different. Atopic dermatitis too, sometimes they can be more bumpy or papular type of lesions, that's important to factor that in. So I think it's more awareness.—

--And then also realizing that you have less erythema or redness, that's also a very important factor, as well. Also because of several health disparities, sometimes the disease can be more severe in these different patient populations.

SABRINA SHEARER, MD, FAAD: So once you've identified a patient with chronic pruritus, you've kind of done your initial laboratory workup, let's say everything is coming back negative.

They've had itch for a long time. You're not seeing any red flags on their labs. What's your initial approach to treatment for these patients?

SHAWN KWATRA, MD, FAAD: So if I do the initial lab and doesn't reveal anything, then what I like to do is I like to treat first with immune-based therapies. I think that's a great way to go, because we do have immune-based therapies. We have world class biologics, new drugs, we have also nonspecific earlier generation immunosuppressants like methotrexate, cyclosporin, azathioprine, and we also have prednisone, steroids, intramuscular steroids, you have options.—

--I think the neurological drugs are not as good. One thing that I oftentimes do if you have an undifferentiated itch patient, to know is this actually immune-generated itch or is this more generalized neuropathic itch which is emanating from the somatosensory nervous system? A way to tease that out is to give a test. We actually recently published about giving intramuscular steroids, say a shot of between 40-80 mg depending on weight, usually in the thigh or butt.—

--And it can last six to eight weeks and works after a few days. Less side effects than oral prednisone because it's metered out in the bloodstream a little less. And you'll have a good sense, does that work. Or even a short course of oral prednisone and JAK inhibitors. You'll get a sense if peoples' itch gets way better fast, then you know this is more immune-generated itch and then you can come up with an appropriate treatment plan, maybe a longer course of methotrexate or off-label any of these great biologics we have: dupilumab, nemolizumab, lebrikizumab, if you can get it. So all reasonable options for our patients.—

--If they don't respond, especially in patients who have disc (?) disease, our group is discovering a new form of chronic pruritus of unknown origin, which has been the reason these clinical trials are so hard to conduct is because it is a little bit more of a heterogeneous population, so we're really at the front line there developing the criterion for these clinical trials and biomarkers like

IgE and eosinophils, which predict a type 2 immune response if present. But if they don't respond to immune-directed therapy, it could be more generalized neuropathic or nociplastic pruritus, which we talk about. And if that's the case, that can be difficult.—

--So we have folks on gabapentin and pregabalin but there's a whole host of other neural therapies. The problem is there's not great data for them. There's not randomized controlled trials, there's not good evidence for all of that stuff, so that's something to factor in.

SABRINA SHEARER, MD, FAAD: I feel like there are very different practice patterns in the use of antihistamines in these patients with nonurticarial itch. What's your take on that? Do you think they work?

SHAWN KWATRA, MD, FAAD: I'm so glad you asked this, because there's a thought of, an idea of what an antihistamine is. The way I think a lot of practitioners actually practice is, "Oh, you're itchy? Here's an antihistamine, here you go." And I don't think they're at fault, because that's what the messaging was. "Oh, your itchy, just take an antihistamine, it will help you." It's actually almost like let's manifest. Let's just give you an antihistamine, you'll get better, let's hope it works. But the science is, other than hives for chronic spontaneous urticaria where it can help a little bit, there's really not a pathogenic mechanism of nonsedating antihistamines.—

--Sedating antihistamines probably work through activating brain mechanisms associated with sedation and itch relief. But really sedating people really heavily, which also has anticholinergic effects, potentially dementia risks long term, so antihistamines have much more limited efficacy. What I will mention is many of our itch clinical trials, one of the impediments has been that there is a dramatic placebo effect in itch patients, because it's both the immune system and the nerves, the neurons.—

--So the dual axis of pathogenesis makes it so that if you think something is working, well there's neurons in your brain that go down to your spinal cord, the dorsal ganglion spinal cord, and your skin. So you can actually have central nervous system changes in processing. They've done studies about mirror neurons. If you see someone else itching and scratching, you start scratching. Even me talking about itching will make you itchy. So I'm sure many people listening to this are itchy right now, because I'm talking about them being itchy.—

--So we can't avoid it, that the nerve system is very important. So I actually think the reason antihistamines are given is because docs may not be aware of this, but we are consciously or subconsciously trying to manifest, and the placebo effect is at work. So when people say, "Well, it seems to work," placebo effect. So at least we should know what's going on when we give these therapeutics. But from a pathophysiology perspective, no, really there's not great evidence outside of just hives or chronic spontaneous urticaria. Somewhat, although we know biologics are dramatically more effective when there's non-histamine-mediated aspects of mast cell direct neurogenic inflammation, too, so even in that situation.—

--I think what we're going to see in the future now is we're already seeing it, is the rise of drugs that are safe, effective. It's amazing, the biologic-type medicines are safer than antihistamines. But that's what we have right now, from looking at all the data. So those medicines, the other medicines in the future, like maybe Bruton and tyrosine kinase inhibitors that block both histamine and non-histamine-derived generation of pruritogenic mediators. It's such a shifting landscape right now, it's so fascinating.

SABRINA SHEARER, MD, FAAD: It sounds like there's lots of exciting things coming down the pipeline for us to be able to use for our patients. Any last pearls for our audience?

SHAWN KWATRA, MD, FAAD: I would just say it's important to not give up on these itch patients. I will share that I was giving a talk recently and I was talking with dermatologists. There

was a patient who was on triamcinolone for a long time, one of our medium potency topical steroids. The patient hadn't had an up-titration of therapy. I've heard many stories like this, of even suicide in itch patients. So I would say let's take it very seriously. Just ask, ask patients, "Hey, what's your worst itch in the last 24 hours at any time, zero is no itch, ten is the worst imaginable," and I just get a number.—

--If it's five, even seven or higher in particular, they need systemic therapy, even probably lower than that. There's some studies even itch above 3 or 4 dramatically affects your quality of life. Take it seriously. When people are really suffering, don't give up on them. We've worked on a lot of experimental therapeutics because of patient need, things like even medical marijuana, ketamine infusions, bupivacaine scalp injections, some other things that we're exploring. It's just been a commitment to the patient that we're going to value the suffering that you're going through and we're not going to stop trying new therapies.—

--So oftentimes I tell patients there's not a lot of great evidence for this when I'm compounding different topical medications or trying new systemic options but I promise them that I won't give up. I think having hope and understanding we're living in a new era, with development of new therapeutics, will help a lot. So I just ask that we do that because within dermatology, this is one of the most profound ways I think that we can truly make an impact on our patients' lives, just by being there and trying, not giving up, thinking outside the box.—

--That would be my hope and call to action for everyone listening. Just ask people about their itch. I ask my friends about their itch, just because I'm curious. So just be a little curious about things. Thank you so much for having me and for everyone's attention.

SABRINA SHEARER, MD, FAAD: Thank you so much. That was very inspirational and I know that we'll be able to take a lot of these back to our practice and help our patients better. So

thank you so much, Dr. Kwatra, for your really impactful work on pruritus, for joining us to share your expertise. And thank you all for tuning in to another episode of *Dialogues in Dermatology*.