TRANSCRIPT

S1.E9. Urticara

Dr. Tom Kovi: Hello and welcome to Spot Diagnosis, a podcast about all things dermatological, brought to you by the Skin Health Institute in Melbourne, Australia. I am Dr. Tom Kovi.

Associate Professor Alvin Chong: I'm Associate Professor Alvin Chong.

Tom: We are your co-hosts. This episode, we'll be talking about urticaria which is otherwise known as hives, it's a common condition that affects about 25% of the population at some point in their lives, it's a condition that can be quite confusing to some people. Today, we have Dr. Katherine Armour who will shed some light on this topic. She is a Melbourne-based Kiwi Dermatologist at the Alfred Hospital here at the Skin Health Institute, as well as private practice in South Yarra. She doesn't only have a sub-specialty interest in urticaria but can also speak from a personal experience as a patient of chronic urticaria herself. Welcome and thank you for sharing your time with us today, Dr. Armour.

Dr. Katherine Armour: Thanks for having me.

Tom: Firstly, what is urticaria?

Katherine: Urticaria, which is also known as hives, is a common skin condition in which we see transient, smooth, raised, and very itchy areas of skin. Often you see small lumps in the skin, often the size of a mosquito bite, but they can actually be much larger and hives can sometimes group together and form large areas of swelling in the skin known as giant urticaria. I should also mention that most hives will appear skin-coloured but they may also have a red ring around the outside or they may just look like a pink or a red lump as well, just depending on what stage they're at in their development. They usually last from between 20 minutes to up to 24 or even 48 hours before they resolve.

Alvin: Urticaria is often mentioned at the same time as angioedema. Can you explain the difference?

Katherine: Angioedema is actually the exact same process as urticaria, but it's swelling that occurs much deeper in the skin and the subcutaneous layers. Often the skin itself will still look skin-color. You'll just have a large smooth lump. Angioedema, because there's so much more swelling, tends to take longer to resolve. It may take up to 72 hours to resolve, and it's commonly seen in the eye area. It can also involve the lips, the tongue, the uvula, in the throat, or even the larynx itself. It also commonly affects the hands and feet.

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Tom: Why does urticaria happen?

Katherine: Urticaria occurs due to the release of chemical mediators including histamine and bradykinins from mast cells, and these are released into the skin and the mucous membranes. Histamine stimulates sensory nerves in the skin causing severe itch, but it also makes the small blood vessels leaky and this leads to the associated swelling.

Alvin: What do patients actually experience?

Katherine: Classically, the hives or the wheels of urticaria are intensely itchy, but they can also be burning in nature. They tend to be worse when the body heats up. People complain that these symptoms are particularly bad at night when they're hot in bed or after a hot shower and so much so that the itch often interferes with people's sleep. Angioedema can also be extremely itchy, but patients will also report that it can be burning and painful in nature and pain from angioedema often occurs if the skin is significantly stressed.

That's particularly on the soles of the feet and on the hands. One really important thing I think people need to be aware of is that urticaria is a really unpredictable condition because it can often involve the face and lead to significant disfigurement. It can be really socially quite embarrassing. The unpredictable nature of this can cause a lot of stress to patients. You can imagine it would be terrible waking up and having to go to work or an interview and having one of your eyes closed up.

Tom: How do you classify urticaria?

Katherine: We talk about urticaria as being acute, when an episode will last less than six weeks or chronic when it continues for more than six weeks. Acute urticaria is far more common and in their lifetime will affect one in five individuals in the population. Acute urticaria may resolve in hours or days.

Tom: What are some of the triggers?

Katherine: The classical triggers that we see in acute urticaria are particularly bacterial or viral infections. The common cold is one that we see a lot. Also stinging and biting insects, allergies to foods or medications, and rarely vaccinations. You can also sometimes see urticaria occurring as a drug pseudo-allergy. In this instance, urticaria is not due to an immune reaction. We often see this with radiocontrast media or aspirin, non-steroidals, or opiates.

Tom: Can you always find a trigger?

Katherine: Often no trigger is found.

Alvin: Katherine, can you tell us what causes chronic urticaria?

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Katherine: In chronic urticaria, which by definition has continued for more than six weeks in duration, recent studies have shown that more than half of the cases are actually due to circulating autoantibodies. This means in a given patient, their B cells are making antibodies against either IgE or the IgE receptor which lives on the mast cells. What these autoantibodies do is causes activation and what we call degranulation of mast cells. So, I tell patients that this means their mast cells release their packets of itch-producing chemicals.

Chronic urticaria can be either spontaneous, which is most of these patients who have autoimmunity or inducible in nature. Inducible urticarias are physical urticarias that can be triggered by quite a long list of different physical stimuli such as pressure, cold, heat, or sweat. Sometimes, these can actually overlap with chronic spontaneous urticaria.

Alvin: Do you routinely investigate urticaria?

Katherine: My practice in this regard has changed a lot over the last four or five years. I now do very limited investigations on patients with chronic urticaria. I would routinely now check a full blood count and a CRP and an ESR. That's mostly to tell me if there's an infective or chronic inflammatory process at play, which might be driving the autoimmunity. Other investigations would only be done based on history, so I might check autoantibodies if there is a history to suggest that or if patients have traveled overseas, and I'm worried about an unusual infection like Strongyloidiasis, I may investigate that, but that's also based on now international recommended guidelines.

Tom: Is there a place for allergy testing in urticaria?

Katherine: Very rarely. Nowadays, we would only recommend allergy testing, in particular skin prick testing in the setting of contact urticaria.

Tom: A common situation that doctors are faced with is someone who develops an acute widespread urticaria rash. How do you treat acute urticaria?

Katherine: Firstly, just general things like I'd suggest they avoid any known triggers. For certain patients with acute urticaria, it might be a medication such as codeine or an anti-inflammatory, foods like in a contact urticaria or even alcohol, but usually, it's about general measures, so trying to avoid overheating such as excessive bed clothes and lukewarm showers and doing things like applying cold compresses to the area or having cold showers.

Really, the mainstay of treatment in acute urticaria is second-generation non-sedating antihistamines. That's medications such as loratadine or cetirizine, which I'd suggest patients take 10 milligrams daily, desloratadine at a dose of 5 milligrams daily or fexofenadine 180 milligrams daily. I'd usually recommend that they take those doses for

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approximately a week. If that had no benefit from that, I then recommend they actually quadruple that dose.

Tom: If one doesn't work, is there any role in switching to another type of non-sedating second-generation antihistamine?

Katherine: Sometimes, we do see a better response with changing second-generation antihistamines. Unfortunately, there aren't really any guidelines or studies to help tell us which ones will work better for an individual patient, but we do sometimes see a better result. In particular, there's a little bit of evidence that cetirizine may be slightly more potent than the other non-sedating antihistamines.

Tom: Sometimes I see doctors using prednisolone. Do you think that there's any role in that?

Katherine: Sometimes we do, sort of have an emergency-type situation when patients either have very severe facial angioedema or they're very debilitated from lack of sleep, I think there's definitely a role for a short rescue course of prednisolone. Ideally, between 5 and 10 days maximum. I think there's definitely a role for that. Again, guidelines do recommend that. There is no role for using prednisolone chronically to treat urticaria.

Tom: What sort of doses are we looking about?

Katherine: My experience is that using a higher dose will lead to better control ultimately, so I would usually in most adults use 50 milligrams for about five days and then drop down to 25 milligrams for a further five days and then stop. I find that if you just go in with 25 milligrams, you don't get complete control and they rebound back quite quickly.

Tom: What about intramuscular adrenaline?

Katherine: Certainly, there can be a role for that if patients have airway compromise such as wheeze or laryngeal edema. They obviously need to be taught how to administer that. That's usually given either via an EpiPen or via a medical practitioner. Just interestingly, when I developed CSU when I was 17, I was given a six-month course of oral steroids just to get me started, a vial and a syringe, and told if I couldn't get on top of my hives with prednisolone, I should just give myself intramuscular adrenaline. That's pretty much what I did all the way through medical school [laughs]. It should be used very judiciously.

Alvin: Katherine, we have patients who get urticaria, but it keeps going for months even with no obvious causes. What's happening there?

Katherine: Alvin, in more than half of these patients, we're actually looking at an autoimmune basis for their disease. Here, we see these patients are making antibodies to

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either the IgE receptor on the mast cells or to IgE itself. What's really interesting is that this is actually not an allergic condition even though IgE is involved. These autoantibodies cause mast cells to degranulate and then hence set off the urticarial cascade.

Alvin: How do you actually manage chronic idiopathic urticaria?

Katherine: It's now pretty straightforward. The first line of therapy should be remove obviously any known triggers, treat any relevant infections. Second-generation antihistamines at the standard dose of one tablet daily should be tried for at least a week. International guidelines suggest trying this for two to four weeks, but I think if you have acute urticaria, you wouldn't put up with that first four weeks before you up-dosed. So, I'd say one to two weeks at the standard dose of antihistamines. If there's an inadequate response, you would then quadruple the dose. So, four times the standard dose of a standard antihistamine such as cetirizine daily.

It's worth trialing that for between two and four weeks as a second-line therapy before you move on to third-line therapy, which in Australia now is omalizumab and that is the same as all of the international guidelines.

Tom: Just before we talk about the newer therapy, are there any particular side effects we need to watch out for especially when we are giving the high doses of antihistamines?

Katherine: Second-generation non-sedating antihistamines are actually really safe and that's thankfully now really well-established in clinical trials, so not really, not with the second-generation antihistamines. However, with the first generation antihistamines which unfortunately we do still see prescribed more than as ideal, there are lots of side effects. That's your promethazines and cyproheptadine, etc, which are used to try and help patients sleep at night, but they have lots of side effects.

They often cause significant sedation the following day. They have anticholinergic side effects such as a dry mouth and dizziness. They impair learning the day after they've been taken and they interact with alcohol and quite a lot of other medications. Basically, all international expert guidelines regarding treatment of acute and chronic urticaria recommend against ever using first-generation antihistamines. So, we should always go to the second generation.

Alvin: Is there a role for the H2 blockers and other drugs like doxepin and montelukast?

Katherine: The evidence for their effectiveness in urticaria is actually very poor. But in Australia, we are still required to trial either H2 blockers or montelukast or doxepin in addition to a second-generation non-sedating antihistamine for at least two weeks before we can access third-line therapy. There's really hardly any evidence that montelukast is useful in non-steroidal-induced urticaria. Doxepin is of course far more potent in its action

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compared to other antihistamines, but the sedating side effects are really dose-limiting, and generally, it's nice to avoid it. I'd use them merely as a mechanism to get patients onto effective therapy.

Tom: Let's talk about biological therapy. Can you tell us about this?

Katherine: We are now very lucky to have in Australia access to the first-ever biologic therapy to treat chronic spontaneous urticaria, which is omalizumab which also goes by the name of Xolair. This is an injectable treatment which is given subcutaneously into the fat layer of the skin once every four weeks to treat chronic spontaneous urticaria. Omalizumab works by blocking both IgE and the IgE receptor on mast cells, but it probably also has far more complex actions such as working on the coagulation cascade and decreasing the number of receptors on mast cells that we're still only learning about, so this needs to be studied a lot more.

Omalizumab is a highly effective therapy, which really is a game-changer in a therapeutic area, which really was an orphan disease and we never previously had any particularly good treatments for. Omalizumab decreases both itch and the number of hives that develop in 75% or 80% of patients within the first three months of therapy. Many patients have significant improvement in their symptoms within a week of their first injection, but there are some that take longer, say, up to three or even six months to get good control of the disease.

Tom: Is it one of those medications that needs to be taken for life or can you take it for a little while and then stop?

Katherine: We're really still learning about this with omalizumab. What we do know is that it is not curative. This is sort of a disease-controlling therapy rather than a cure. Certainly, studies show that after ceasing omalizumab, a lot of patients will relapse within approximately four months, if not earlier. Certainly, I aim, once patients are well-controlled, you'd perhaps try a taper of therapy, but a lot of patients would need to be retreated. Like a lot of other autoimmune diseases, urticaria will often burn itself out, but the time that it might take is very variable.

Alvin: That's excellent. Now, when should patient be referred for specialist treatment?

Katherine: In my humble opinion, it should be if they're failing to respond to a quadruple dose of antihistamines, so I think it should be relatively quickly. The reason for that is patients become highly distressed from severe itch and lack of sleep. Then there's often a tendency to seek emergency care and then be prescribed prolonged courses of oral steroids. So, we want to avoid that and get patients onto safe disease-controlling therapies sooner rather than later.

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Tom: I understand that you're on the omalizumab yourself. How did you find it?

Katherine: It's changed my life, to be honest, Tom. If you can name any medication or treatment possible for urticaria, I have tried it and with very variable effects, and it's the first time in my life that I've gone for months and months at a time without having any urticaria or angioedema. It's safe, the injections are really tolerable and I've had no side effects whatsoever, so I feel very blessed.

Tom: That's amazing to hear. We should also just touch on about, are there any particular side effects that we should be watching out for?

Katherine: With omalizumab, overall, all the clinical trials and post-marketing data show that omalizumab in the urticaria population is a very, very safe treatment. There are no what we call organ toxicities with this drug. We don't see any problem with the kidneys or the liver. The main thing to worry about is the very rare incidence of anaphylaxis with omalizumab.

This has been reported far fewer than a 100 times worldwide and this is not in urticaria patients. This is actually in the allergic asthma population. So, omalizumab was actually first developed to treat allergic asthma, and by definition, those patients unfortunately have quite a high inherent risk of anaphylaxis. That's why omalizumab must be given at a medical facility with monitoring at the moment because there is still an incredibly small risk of anaphylaxis even in CSU patients. That's the main thing people need to be aware of.

Tom: Are there any resources that you can recommend for our patients to learn more about urticaria?

Katherine: The DermNet NZ website is a fabulous resource and has a really great section on both acute and chronic urticaria. Survive Hives is another really fabulous website with a lot of good written information and photos.

Tom: That's fantastic. That's the end of our episode on urticaria. Thank you very much, Dr. Katherine Armour, for joining us. We would like to acknowledge our production team, Joanne Coughlin for podcast editing and Peter Monaghan for podcast support. Thank you for listening to another episode of Spot Diagnosis. We hope it's been educational for you. Stay tuned for our next episode.

Alvin: We hope you have enjoyed this podcast. Remember, these podcasts are not meant to replace medical advice. If you have a skin condition that requires attention, we strongly encourage you to see your medical practitioner.

Tom: For those who would like to access some further information of this subject, we have placed a transcript, together with some further education and information resources for

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you on our website. I also want to do a shout out for the GP education events that we run at the Skin Health Institute. Just go to spotdiagnosis.org.au.

Alvin: Please share spot diagnosis with your friends and colleagues. Rate and review us. Let us know what you think. We would really appreciate your feedback and any suggestions. Thank you for listening.

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More information, and other dermatology education resources, can be found on our website at

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