Dr. Mariam Hanna
Hello, I'm Dr. Mariam Hanna and this is The Allergist, a show that separates myth from medicine, deciphering allergies and understanding the immune system. In the workup of idiopathic anaphylaxis, a tryptase is not unreasonable.

In the consideration of venom immunotherapy, a tryptase is also not unreasonable. In my patients with strange sounding reactions, a tryptase is never unreasonable. In reality, I've sent off quite a number of tryptases because hey, it's not unreasonable.

And truly, I've only had a few highlight ones that come back markedly elevated. Like this one, a patient had recurrent episodes of anaphylaxis over a two-year period. It had happened three times.

Respiratory symptoms and hives. Precipitated by a viral illness. No other clear triggers of note.

We talked about food, exercise, medications. Really, nothing. I got a tryptase.

It was normal. I asked for an acute tryptase during further episodes. It was abnormal.

This was two years later. So I sent him to hematology, genetics done, and confirmed hereditary alpha tryptosemia. There you go.

I thought I was going to diagnose my patient with mastocytosis. Close, but totally wrong. It's HAT.

I've continued to follow along. Not much to do in this case, but a different story for our actual mastocytosis patients. We actually covered mast cell activation last year, and it was one of our most listened to episodes, really highlighting interest in physicians and the overall community in this really challenging disorder.

It's why I was actually really delighted to have today's guest, who's going to do kind of like a part two, but exploring the intriguing world of mastocytosis. Allow me to introduce today's guest. Dr. Mathieu Picard is an allergist and clinical immunologist. He completed a research fellowship at Brigham Women's and Women's Hospital under Dr. Mariana Castells and acquired an expertise in the management of mast cell disorders, he founded the Division of Clinical Immunology and Allergy at Hôpital Maisonneuve-Rosemont in Montréal, where he continues to practice, working in close collaboration with hematologists and dermatologists. He actually cares for lots of patients with mast cell disorders, ranging really from mast cell activation syndrome to mastocytosis, making him the perfect guest for today's episode. Dr. Picard, merci beaucoup for joining us and welcome to the podcast. Bienvenue.

Dr. Matthieu Picard

Dr. Picard Thank you, Mariam. It's my pleasure to be here.

Dr. Mariam Hanna
Dr. Patrick Picard And I'll stop my French at this point in time and we will switch to English entirely. So I want to start off with level setting in a not fair way. We're going to ask you to do a little bit of an overview of mastocytosis, just so that we know what we're about to delve into with today's discussion.

Dr. Matthieu Picard
Dr. Picard Perfect. So to start off, mastocytosis is a clonal disorder of mast cells, so it's a neoplastic condition, but it's a benign one for the vast majority of patients, meaning that their life expectancy is normal and patients will not die from this condition over their lifetime.

But overall, for the vast majority of patients, it's a benign condition. The clonal mast cells and mastocytosis can be found in many different tissues, most commonly the skin, and then it would be the bone marrow and possibly the GI tract. And in some very rare patients, you can really have it in many organ tissues.

So there's two main subtypes. There's the cutaneous subtypes, that's when the clonal mast cells are only found in the skin.

That's what we call cutaneous mastocytosis. And then we have the systemic mastocytosis, which is defined by the fact of finding clonal mast cells in another organ than the skin, usually it will be the bone marrow. This condition is caused in almost every patient by a gain-of-function mutation in the KIT receptor found in mast cells, usually it will be the KIT D816V mutation, and that causes the mast cells to proliferate and to accumulate in tissue.

The other thing to know is that this is a very rare condition, so it will affect maybe one to three over 10,000 patients. So it's quite uncommon to diagnose mastocytosis. So you will think it is mastocytosis much more often than you'll actually diagnose mastocytosis.

Dr. Mariam Hanna
Fair. Okay.

And let's talk about how it fits into the broader category of our mast cell disorders in general that we're seeing in clinic.

Dr. Matthieu Picard
The key difference is that the burden of clonal mast cells, so the amount of clonal mast cells is much lower in patients with the monoclonal mast cell activation disorder. So it will be much harder to diagnose. It may even require special techniques analyzing the bone marrow to find this very small clonal population.

And the other difference between the two conditions is that, as we'll talk later on, mastocytosis can be associated with other health issues like osteoporosis, which is not the case for the monoclonal mast cell activation disorder. And as of now, we don't think that patients with the monoclonal mast cell activation disorder would progress to systemic mastocytosis. So those are the two primary mast cell activation disorders because the clonal mast cells, they accumulate, but they are also more prone to activate or to degranulate.

It can happen without any identifiable trigger. And it frequently also happens from immunologic things. So that's the two primary disorders.

And then you have the secondary disorders, which are usually IgE-mediated allergies, which could coexist with systemic mastocytosis.

And then there's the idiopathic category where there's no identifiable defect with the mast cells. They don't proliferate, they don't accumulate, and there's no identifiable trigger for the mast cell activation. So that's for the idiopathic category.

Dr. Mariam Hanna
A frustrating but present category in all of our clinics when we are left with this diagnosis, but it does happen.

So let's talk about pediatric presentations and specifically cutaneous mastocytosis, please.

Dr. Matthieu Picard
Yes. So in children, almost all cases of mastocytosis are cutaneous. So their abnormal clonal mast cells are really restricted to the skin.

. So in children, the most common subtype we'll see is what we used to call urticaria pigmentosa. We should call it now maculopapular mastocytosis, because we have macules or papules that are usually reddish to brownish.

They're often in children polymorphic, so that they vary in size and shape from one another. And those lesions, when you scratch them, typically you will provoke a wheel and flare reaction within several minutes. There's a correct way that I learned from all my readings on the subject to do that.

So you need to use a tongue blade and you need to scratch with moderate pressure five times the lesion. And you can also scratch the normal skin surrounding it, which should not. So it's different from dermographism, because the normal skin surrounding the lesion should not have a wheel and flare reaction.

The wheel and flare should be restricted to the lesion that you're scratching. So that's the most common type of cutaneous mastocytosis seen in children. The second type is diffuse cutaneous mastocytosis.

So usually in this subtype, the skin is diffusely erythematous. It can also appear thickened. And again, if you scratch the skin, there will be marked dermographism.

So all the skin there is abnormal. So there's no normal skin to test to compare. And it can even sometimes blister.

And finally, the last subtype in children would be skin mastocytoma. So that's an isolated lesion. Usually that is elevated, yellowish, brownish.

It's a ton of abnormal mast cells. So you need to be really careful scratching it because it could cause systemic symptoms like diffuse flushing or even hypotension. So sometimes it's so typical of a mastocytoma that you don't even need to do the scratching and induce this derriere sign.

So I want to go on to patients that require referral to hematology. So your pediatric patients largely were saying it's a benign condition. It depends on the degree of cutaneous involvement that they have.

But which ones should prompt concern like a systemic disease and referral on to another specialist?

Dr. Matthieu Picard
Yeah. So in most children, these lesions will typically disappear around puberty. If they do not, you need to consider systemic disease and you need to consider the possibility of a referral to get a bone marrow biopsy.

The other things that would be concerning in the children would be if they have an abnormal CBC or they have lymphadenopathy that is not explained or they have a big liver or big spleen. So other signs of a hematologic neoplasm. The other component would be of a higher than normal tryptase, although there are caveats to that.

In some references, they say that you should consider bone marrow only if it's very high, like above 100. Because in some children with especially the diffuse subtype, they can have just skin involvement, but an elevated tryptase because they have so much abnormal mast cells in the skin. So if it's only the tryptase that's concerning, it could be followed over time.

And if there's a downward trend, then it's pretty reassuring. On the contrary, if the trend is upward, then you could consider referral and having them have a bone marrow biopsy.

Dr. Mariam Hanna
Okay. We'll talk about biopsies in just a second, but let's talk about adult-onset mastocytosis. How is this different in terms of pathophysiology, presentation?

Dr. Matthieu Picard

So in adults with mastocytosis, the most common presentation will be again, skin mastocytosis. So they have skin involvement with those lesions. So it will be typically the maculopapular subtype, the Urticaria pigmentosa, those reddish brownish macules or papules, usually on the torso or the extremities.

In adults, it typically spares the face and the derriere sign is not as commonly present as in children. If you have an adult with cutaneous mastocytosis, or what we should call it is mastocytosis in the skin, they have roughly an 80% chance of having a systemic mastocytosis. So that's a pretty high pre-test probability.

So that's the key difference here between children and adults. So in children, they're almost always only cutaneous, whereas in adults, they're almost always systemic. So you need to be very sure that there's no bone marrow involvement because before you call an adult with skin mastocytosis, cutaneous mastocytosis.

So that would be like the first and most common clinical presentation. The second presentation would be patients with severe recurrent anaphylaxis. Or a severe anaphylaxis after an hymenoptera sting.

By severe, we mean with hypotension, with significant hypotension. And the likelihood of finding clonal mast cells will increase if in addition to that, the patient is a male or if he had no skin symptoms associated with anaphylaxis event. So that would be the second consideration.

There are other presentations that are much rarer for systemic mastocytosis in adults. Just to touch briefly on them, I would say because systemic mastocytosis increases the likelihood of a patient developing osteoporosis along the way, especially in male patients or premenopausal women diagnosed with osteoporosis. It's in the big differential of secondary causes of osteoporosis.

And just to finish with that, I would say that most patients that have the aggressive subtype, they present like they have cancer.

So they have weight loss, night sweats, big lymph nodes, a big liver or a big spleen, or abnormal CBC. Usually they don't have the skin involvement and usually they don't have mast cell activation episodes.

Dr. Mariam Hanna
Okay. So the aggressive type presenting with the classic red flags or B symptoms that we think of for malignancy, that's quite helpful. At what point should we be getting tryptase on these patients?

Dr. Matthieu Picard
Always. Always get a tryptase. So the reason for that...

Dr. Mariam Hanna
I love affirmation on this. Okay, yeah, go ahead.

Dr. Matthieu Picard
So the reason for that is that the tryptase is pretty useful because in mastocytosis, it is a reflection of the burden of abnormal mast cells. So it will give you a ballpark idea of is this patient full of abnormal mast cells or it's a tiny clonal population. So if you have a normal tryptase, it does not rule out mastocytosis, but it means that if there are clonal mast cells, there are not many of them.

So you'll need to have sensitive technique to pick them up. On the other hand, if your tryptase is like above 100 or above 200, then you're more concerned because it reflects a huge burden of mast cells. The most common cause for an elevated baseline tryptase is hereditary alpha tryptasemia.

And the fact that you diagnose HAT does not mean that patient cannot have mas tocytosis because the two can coexist.

And there's a clinical correlate to that because patients with both conditions, mastocytosis and HAT, they are more likely to suffer from severe anaphylaxis, especially from venom.

Dr. Mariam Hanna
Now I'm just thinking about my patient. Okay, hold on. The role for bone marrow biopsy.

Okay, so I've been in meetings with a lot of allergists who are quite passionate as to like, why can't we get this biopsy? We really need to get this patient biopsied for their mastocytosis. If I heard you correctly from the pediatric patients, relatively few need a bone marrow biopsy unless they have systemic features, hepatosplenomegaly, lymphadenopathy, trending upwards of tryptase, if I got that right.

But like, what's it like in the adult space?

Dr. Matthieu Picard
So you're correct. In children, it's very rare we should get a bone marrow biopsy, whereas in adults, in theory, you would want to do it in almost all patients in whom you suspect systemic disease. However, my main concern in doing a bone marrow biopsy is getting a false negative result, which I've seen in the past.

So you do the bone marrow biopsy, comes back negative. What do you do next if your suspicion is still high? So you need, the next step is to look at how was the bone marrow biopsy done?

Is it a good quality specimen? Was it diluted with peripheral blood? What did they look for?

Did they do flow cytometry on hundreds of thousands of cells? And they looked for the CD117 marker, the kit marker, and also looked for co-expression of clonality marker, not just CD25, but also CD2 and CD30. Because if that was not done, it's a suboptimal bone marrow biopsy.

All this research and those markers you should be looking for, it's not been in for many years in the literature. So it's not all centers that really know specifically what to look for. I think most all pathologists will look for the mast cell aggregates in the bone marrow biopsy, but those are pretty rare.

Dr. Mariam Hanna
Okay. And if biopsies are not all of equivalent quality and may have some issues with staining, should all our patients be then moving on to genetic testing if your pretest probability was quite high, or should they be going after repeat biopsy, as you mentioned in this case?

Dr. Matthieu Picard
So I think the kit D816V mutation should always be looked for in the blood. But my message here would be that if your suspicion is high, and the kit PCR test that you ran came back negative, you could arrange a send out to a US lab to get this more sensitive PCR, which can also be done on the bone marrow, which will be even more sensitive.

So the kit D816V mutation because it's present in more than 95% of systemic mastocytosis patient is really, I think, a key test to be run in those patients. And if it is positive, it's a systemic mastocytosis, or at least a monoclonal mast cell activation syndrome until proven otherwise.

Dr. Mariam Hanna
Fair, fair.

Let's talk about what are kind of available options in terms of disease control or disease modifying options.

Dr. Matthieu Picard
So the first thing I do with my patients is I try to reassure them that they have a benign condition, and that besides some symptoms they might have following this condition, which we can treat with some symptomatic treatment, they will be fine.

One thing I stress is the risk of anaphylaxis. I try not to stress it too much. I don't want them to be over anxious about it, but I do prescribe them epinephrine auto injectors.

The other thing I do, which can sound a bit shocking, I know I was shocked the first time I heard that, is that because their main risk of anaphylaxis is from hymenoptra sting., I offer screening them to see if they have IgEs against hymenoptra, even though they don't have a history of reaction. I do not do that for any other patients, but that is something that can be considered and that can be discussed with mastocytosis patients. It's been quoted as an expert opinion

recommendation in a past stinging insect allergy practice parameter, so it's a relatively common practice.

The second thing that we're looking for is osteoporosis, so we do DEXA scans, which we can repeat over time depending on the risk factors and the results we get. And the third risk is for them to progress to an aggressive subtype, which is very, very low.

It's less than 3% over the patient's lifetime, but we do a CBC liver function tests and triptase yearly. Then the treatment is really for most patients symptom-based. Typically, their main complaint is skin symptoms, so itchiness, those lesions, they don't like their appearance, but we cannot do much about that.

What we can do is try to make them less sym ptomatic, so the first step would really be antihistamines, second generation antihistamines. We increase the dose up to four times standard dose like we do for chronic spontaneous urticaria. If they're really bothered by the lesions themselves, we can refer them to dermatology for phototherapy.

We can try corticosteroid creams, but the effect of these treatment is usually transient and will come back once they stop. Some patients have GI complaints also, like stomach pain, diarrhea. First off, I always try antihistamines.

If that doesn't work, we can try H2 blockers, we can try PPIs. The other thing that could be tried is nalcrum or sodium chromoglycate, but it's quite cumbersome to take because you have to open up the capsules, mix it in hot water so that it will dissolve, and then they need to take it four times a day.

And finally, for very, I would say, severe symptomatic patients, especially with skin symptoms of hives, I've tried omalizumab, for very minority of patients with mixed results and that's also been found in small trials. It's not that effective in mastocytosis.

Dr. Mariam Hanna
Very interesting and good to know that there's like a variety, a range of symptoms that you need to control and kind of reassess patients periodically. Okay, I already heard you talk about venom allergy and like risk of venom anaphylaxis. What about like any other high-risk scenarios for these patients?

Dr. Matthieu Picard
So not really. I reall y try to adapt my approach to the patient's experience. So for example, it's true that a minority of mastocytosis patients will not tolerate NSAIDs and they will get mast cell activation when they take NSAIDs.

But that's really a minority. I think it's about 5% of patients. So that means 95% are just doing fine.

So if they've been taking NSAIDs, I have no reason to say, oh, you have to stop taking it. It's dangerous for you. Not at all.

Just continue. No problem. And for those patients who are unsure, usually I schedule a challenge for them in the clinic to make sure it's safe.

And usually it is. There are other questions that patients usually they find online that they could go on a low histamine diet will make them better. There's no proof of that.

My question for them when they tell me this is like, have you had any problems with any specific food? And if not, there's no reason for you to change your diet because of this condition. Just go on with your normal life.

But if there are food that recurrently will make you miserable, then sure, you can try and avoid them. But we can also try and different symptomatic treatment to see if that could improve your condition and make you able to eat more stuff. So that's a bit of my approach.

The other thing that frequently comes up is that usually doctors from other fields, they don't know about this condition.

So I find that my main role is just telling doctors and patients, no, there's no issue. You can just give it. There's no problem.

So I just tell them, go and continue your regular meds and everything should be fine.

Dr. Mariam Hanna
Everything should be fine.

All right, time to wrap up and ask today's allergist Dr. Mathieu Picard for his top three key messages to impart to patients and physicians and the online community on today's topic, mastocytosis. Dr. Picard, over to you.

Dr. Matthieu Picard
So my number one key message would be that the most common cause of an elevated baseline tryptase is by far hereditary alpha-tryptosemia, not mastocytosis. The second message is that the investigation for a clonal mast cell disorder should be pursued even in patients with a normal baseline tryptase if you have a high pre-test probability of having a systemic mastocytosis. For example, you have an adult with skin mastocytosis or someone who had a severe anaphylaxis with hypotension either following an Hymenoptera sensitization testing or if it happens recurrently without any identifiable trigger.

And your investigation should not stop at getting a tryptase. You should also be looking for the kit D816V mutation in the blood, ideally with a highly sensitive PCR assay. And the third

message is that patients with indolent systemic mastocytosis should be monitored for three main things.

They have an increased risk of anaphylaxis, so they need to have an epinephrine L2 injector. And you can screen them for Hymenoptera sensitization because if they are sensitized, you can offer them venom immunotherapy. They need to be monitored for osteoporosis.

And finally, they need to be monitored for a very small risk of progression to advance disease with yearly monitoring of the complete blood count, liver function test, and tryptase.

Dr. Mariam Hanna
You took a complicated disorder and you simplified it. I love that. Merci, Dr. Picard, for joining us on today's episode of The Allergist.

Dr. Matthieu Picard
Thank you very much. It was my pleasure.

Dr. Mariam Hanna
This podcast is brought to you by the Canadian Society of Allergy and Clinical Immunology and produced in collaboration with PodCraft Productions.

The opinions shared by our guests are their own and do not necessarily reflect the views of the CSACI. Please remember that this podcast is for informational purposes only and does not provide any individualized medical advice. For show notes and relevant links from today's discussion, please visit www.csaci.ca. While you're there, check out the Find an Allergist tool to connect with a specialist near you. If you enjoyed this episode, we'd love your support. Leave a review and a five-star rating wherever you listen to podcasts. It helps others find the show.

And remember, while screening, remember your tryptase and your tongue depressor and scratch five times. Sincerely, The Allergist.