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. There are diseases in medicine with nonspecific presentations that challenge the patient, the physician, and everyone to come to the right diagnosis. Months and years of unexplained issues, traditional and holistic medicine, getting involved with different theories, and finally an answer. Not knowing is the hardest part. Our patient today had episodes of flushing, hives, and occasional dizziness. She had initially brushed these off as “minor reactions”. Over time, her symptoms had escalated. She started experiencing abdominal pain after meals, palpitations, maybe brain fog, and intense fatigue. She visited multiple doctors, each offering a different explanation—IBS, stress, anxiety—and a variety of treatments, each without response. She was trapped in her own body with no clear understanding of what was going on. As an allergist, I too struggle with what's going on—when is it real, and when is it really a constellation of unrelated symptoms in a person that's really just dealing with something else in life?

In today's episode, we're going to learn how sometimes a complex array of symptoms can fit neatly into a puzzling condition and when to consider mast cell activation syndrome. It's my distinct pleasure to introduce to you a colleague of mine, Dr. Olynych. He's an allergist and clinical immunologist currently working in Ottawa, Ontario, in both the community and hospital setting. Dr. Olynych trained in internal medicine at Dalhousie University in Halifax, Nova Scotia, and did his clinical immunology and allergy at McMaster in Hamilton, Ontario. He's a lecturer at the University of Ottawa, and he runs a high-risk drug allergy clinic at the Ottawa Hospital for drug challenges and sees patients with a myriad of allergic issues. Dr. Olynych wouldn’t tell you, but he did his PhD in mast cells, and that's why he's the perfect guy to talk to about this condition. So with that, Dr. Olynych, welcome to the podcast.

Dr. Timothy Olynych:
Thanks for inviting me. It's a pleasure.

Dr. Mariam Hanna:
Okay, so we're going to start with the basics. Let's start with the definition. What is mast cell activation syndrome?

Dr. Timothy Olynych:
Yeah, so it's difficult. By definition, it's a syndrome, which means it's a constellation of symptoms. So there's not a clear pathognomonic sort of feature that's going to say, "Ah, this is what I'm dealing with. This is mast cell activation syndrome." And there's been various classifications, but basically we're looking for patients who have what we'd call symptoms of mast cell mediator release, meaning their mast cells have been activated. These would be your typical allergic sort of symptoms, right? So hives, itch, flushing, nausea, vomiting, diarrhea, wheeze, rhinitis. And these symptoms may always be present a little bit under the surface. And classically, they have flares of symptoms, and these might be recognized as idiopathic anaphylactic sort of events where it seems like anaphylaxis with no obvious trigger. And so symptoms that are related to mast cell activation—so release of histamine, leukotrienes, things

like that. And then the second part is responding to treatments that target those mediators. So if somebody has this constellation of symptoms and we're thinking maybe this is mast cell activation syndrome and we're not thinking it's just isolated allergic disease, then you might trial these medications—so antihistamines, H1, H2 blockers, those sorts of things. And if they get significantly better, then that is supportive of the diagnosis but not diagnostic. And then the final piece that is quite important, but people would argue about, is a tryptase level. So by definition, MCAS has a normal serum tryptase at baseline. So when they're well or normal, their tryptase is in the normal range, and there's a significant increase in their baseline tryptase when they have a flare of symptoms. So if they have one of these events where all of a sudden all their symptoms flare up and are more significant, if you can get a tryptase level measured during one of those flares, it doesn't need to go up to 20 or 30, which would be considered to be significantly elevated and more in keeping with an anaphylactic reaction. But they use this equation: 1.2 times their baseline plus two is a significant increase. So if their baseline was three and they went up to seven or eight, we would say, well, that's not a high tryptase. We wouldn't really get worried about a tryptase, usually classically until it's above 11.4, but that's a significant increase above their baseline. So maybe there's evidence of mast cell activation. And so we want all those component parts, but getting them all together is difficult.

Dr. Mariam Hanna:
So the most common symptoms of mast cell activation are kind of symptoms that we would expect to see with mast cell conditions, allergic conditions. So those are ruled out as the first step, is that correct?

Dr. Timothy Olynych:
Yeah, so I guess you get the constellation of symptoms, and if they're complaining of rhinitis symptoms, yeah, we'll test them for environmental allergies. If they have reactions to foods that sound like it could be a food allergy, we test them for food allergies. If they have wheeze or shortness of breath episodes, we'll test them for asthma. So we still look for those primary allergic type two inflammatory conditions, but sometimes they might not have any allergies that you can identify. They're having these allergic sort of symptoms, and then you start to think, well, they have multiple systems involved. It seems like it's related to histamine release or mast cell activation sort of mediators. And then you start to think, well, maybe this is that sort of process.

Dr. Mariam Hanna:
Okay. How common would you say mast cell activation syndrome is in the general population? Do we kind of have a sense for that?

Dr. Timothy Olynych:
So I think that's very difficult to put a number on. There's a lot of patients self-diagnosing because they have a random constellation of symptoms and they go online and they believe they have mast cell activation syndrome or they have some other disorders that have been associated with mast cell activation syndrome, but they don't necessarily have any symptoms of mast cell activation. So I think there's a lot of people either being diagnosed or self-diagnosing, I

would say somewhat inappropriately, without any actual evidence of mast cell activation. We're seeing it more and more commonly, I don't know why.

Dr. Mariam Hanna:
Let's talk about associated comorbidities with mast cell activation syndrome. We said sometimes that helps with the unifying diagnosis, but are there common comorbidities that occur with MCAS?

Dr. Timothy Olynych:
I'd say the operative word in that question is *common*, right? Certainly there was a report a few years back associating MCAS with POTS, or postural orthostatic tachycardic syndrome, and Ehlers-Danlos syndrome, or some forms of hypermobility. And in that report, it suggested that these things are fairly tightly linked, and that has, I think, caused some issues. So I think now...

Dr. Mariam Hanna:
Hold on. They're fairly tightly linked because they had a genetic common origin or physiologic, or they just occurred commonly in the same person?

Dr. Timothy Olynych:
I think they occurred commonly in the same people. There was no pathologic or diagnostic test or something that would link them or any reason why they would be associated. But in this paper, they had seen a few patients who seemed to have these three disorders in conjunction and said, well, maybe these go together. And then that's kind of taken off to the point where now if somebody is diagnosed with POTS or has hypermobility, there's some clinics that are telling people, well, go get screened for mast cell activation syndrome, even though they may not have any active symptoms or any evidence of mast cell activation. So I would say it would be the exception to the rule that if you have Ehlers-Danlos syndrome or hypermobility or POTS, that you have all three. These are relatively common diagnoses, and the vast majority of these people do not have mast cell activation syndrome. That being said, we do see people with mast cell activation syndrome who have hypermobility and POTS. But again, I would say that's the exception to the rule rather than the rule.

Dr. Mariam Hanna:
This is always a pearl in medicine: don't go looking for trouble where there isn't trouble. When should a patient be suspected of having this syndrome?

Dr. Timothy Olynych:
Yeah, I think it's one of those things where you have to have a high level of suspicion, but it's not something you necessarily need to be screening everybody for. And so again, just like the case you presented, you have somebody who keeps coming back with various constellations of symptoms. Some of them sound allergic in nature, nothing's really adding up, there doesn't seem to be a consistent trigger for anything. It's not unreasonable to get a tryptase in that case.

Dr. Mariam Hanna:
It's not unreasonable to get a tryptase. It's not unreasonable to get a tryptase. Okay, continue.

Dr. Timothy Olynych:
And so it can be actually pretty helpful. If you get a tryptase and it's normal, then a) you've ruled out mastocytosis basically. Again, there are some caveats to that, but for the most part, you've ruled out mastocytosis—fantastic, great job. And then referring to an allergist, or if you're the allergist, then great, I have a baseline to start with. And then you can try to get a tryptase level in the face of a flare of symptoms. So I think even if you have somebody with chronic spontaneous urticaria, for example—and we see a lot of chronic urticaria, I get five to ten new referrals per week for chronic urticaria—some of these patients have systemic symptoms. So they get hives flaring with that, they get abdominal upset, and maybe a bit of tightness in the chest.

Is that typical of chronic spontaneous urticaria? No, not typically. Do they have a mast cell disorder? Maybe. What's the treatment? The treatment is going to be the same; you're going to approach it similarly, and they're going to respond to antihistamines, likely. But in that situation, well, this is something we see often, but there are some atypical features. It's probably reasonable to get a tryptase and look for that and rule it out. I feel like the tryptase test has been pushed to the side. I don't know how other people's medical facilities work, but a lot of the hospitals will cancel the test unless you call the lab and specifically request that they process it because they're like, "What's the point?" And so I get referrals for random anaphylaxis, and it would be really nice to know if the tryptase was elevated in those situations or not. So I'd say if somebody has symptoms that seem like a common sort of allergic problem but there are some things that don't quite add up, you have to have that high level of suspicion to go looking for it.

Dr. Mariam Hanna:
What other investigations do you typically pursue in these patients? I get it. Tryptase is my D-dimer, so I get that.

Dr. Timothy Olynych:
You're going to send the pheo. I've sent a bunch of those, and I always joke that this is one of those tests that you do and you look for your whole career, and you'll maybe never find one, but you definitely won't find one if you don't do the test. So typical sort of workup: CBC, liver and kidney studies, obviously the tryptase baseline in the context of a flare. And again, some of the other stuff is going to be directed towards the symptoms they're presenting with. I may do an ANA and immunoglobulin levels, and then the 24-hour urine for metanephrines and 5-HIAA. So that would be a kind of typical approach off the top. But again, if they're having weirder symptoms that make me think, "Wow, this sounds a little bit more of an autoimmune picture," I'm going to go more down that road, and it might modify my tests somewhat.

Dr. Mariam Hanna:
Why is MCAS currently over-diagnosed or a top hit on people's Google search when they go searching with their symptoms?

Dr. Timothy Olynych:
That's a fantastic question. I would like to know why. I think, again, it goes back to that unifying diagnosis. People want to find a unifying diagnosis. It has every symptom is listed on the MCAS websites, and they say, "I have those," or "I have five of these 45 symptoms that are listed on this website, so maybe that's what I have." And the problem is nobody else has given me a better answer. Sometimes they're presenting with these symptoms that seem unrelated; the patient relates them, but it doesn't really make sense to people. So they're like, "I don't know, I can't help you, go see the next doctor." And so they bounce around, and then they find this online. I don't know why it's so high on the Google search algorithm.

Dr. Mariam Hanna:
People's algorithms are just different. I don't know. I want to talk about the role of mast cells in the autonomic nervous system. It's something that we don't do a lot of or touch on much in training, and I think it's important for its potential roles in this syndrome or others. Can we go through that? What is the role of mast cells in the autonomic nervous system?

Dr. Timothy Olynych:
Yeah, I think we're starting to figure that out more, or at least we're paying more attention to it. I remember—I don't know if you remember if you were there during our fellowship together—I did a grand rounds on mast cells and why they were the most important cell in the body.

Dr. Mariam Hanna:
That's why you asked for today's episode as well. Yes, I do remember.

Dr. Timothy Olynych:
It's paying dividends. Yes, that was a great talk. And so I put a slide up, and the number of receptors on the mast cell and the number of mediators it's able to produce are greater than, I think, any other cell in the body. The mast cells are typically located near blood vessels, near interfaces with the external environment, and they're tightly located with nerve endings. They can produce neurotransmitters, they have neurotransmitter receptors, they have vasoactive mediators and receptors for vasoactive substances. And so they can act on nerve cells, and they can respond to nerve cell activity. There are many studies—basic science studies, all kinds of studies—showing that there is this interaction. And I think there's growing recognition of these subjective symptoms in MCAS of brain fog, fatigue, and muscle aches and pains.

When they look at that, and they look at the mast cell and the mast cell's ability to interact with the nervous system, they say, "Wow, there's a possible link here. There's a possible explanation." The mast cell could hypothetically be acting on the neurons and resulting in this sort of feedback mechanism, manifesting these symptoms. That's a great hypothesis. Obviously, chronic illness in general will cause those symptoms too, but is the mast cell specifically, is mast cell activation causing these more subjective symptoms in MCAS? I'm not totally convinced, and I'm not sure. But I think there are two camps. There's a camp that says this is all related to mast cell activation, and it's our bag and we should take it on. And there are some good articles in the recent *JACI* and *JACI: In Practice* about using antidepressants to help with fatigue and using stimulants to help with the brain fog—so ADHD medications—and there's some success there. That's great. It's nice to have treatments for those symptoms, but does that determine or does that mean that it's caused by the activation of the mast cell? I think the jury is still out. And certainly, using H1, H2 blockers, anti-leukotriene receptor antagonists, and mast cell stabilizers do not help with those subjective symptoms. So either we're not targeting the right pathway, or it's not mast cell-related. But certainly, the potential is there for the mast cells to interact with the nervous system and vice versa. We're still in the early stages of unlocking that relationship, I think.

Dr. Mariam Hanna:
And that's exciting that we're still learning even about this potential role or what might be there. Now, let's talk about what currently is there in terms of treatment options for this syndrome.

Dr. Timothy Olynych:
So I have a kind of way of thinking about this disorder. And so again, I say there's two camps. There's the camp of people who recognize which symptoms are likely related to mast cell activation, and then there's all these other associated disorders like POTS, Ehlers-Danlos syndrome, chronic fatigue, brain fog—all these other things that may or may not be related. If you think they're all part of it, then your treatment toolbox is going to be larger. But I'm going to talk mostly about the mast cell-specific symptoms, so all of the allergic sort of stuff. And I approach it similarly to treating chronic spontaneous urticaria.

In my mind, I actually think of MCAS as being basically chronic spontaneous urticaria with systemic symptoms or potentially chronic urticaria acting on non-cutaneous mast cells. It never really made sense to me why chronic urticaria only affected skin mast cells when there are mast cells everywhere. If the mechanism is you have autoreactive IgE to self-proteins in chronic urticaria, why does that not affect the mast cells in the gut, or in the lungs, or elsewhere? And so perhaps—and this is all hypothetical—MCAS is a systemic form of CSU, and so the treatment approach is very similar.

You're going to use predominantly H1 blockers and push that up to fourfold doses, just like we do in chronic spontaneous urticaria. If they're having abdominal issues, the H2 blockers like famotidine or ranitidine can be effective, and sometimes they can be more effective than the proton pump inhibitors for their reflux sort of symptoms. Adding montelukast—if they're having a lot of abdominal issues—I will use cromolyn, so sodium cromoglicate. And I don't know who told me this trick, but opening the capsules into warm water, dissolving it, and then drinking it rather than swallowing the capsules whole, because the cromolyn doesn't really get absorbed into the body very well. It just works where it contacts, and if you swallow a capsule, it's going to bypass the upper GI tract. So if you drink it in a slurry, then maybe you get some extra benefit in the upper GI tract.

You can use ketotifen, although it's one of the last ones that I throw on. I haven't seen dramatic improvements with ketotifen, but certainly, it's marketed as a mast cell stabilizer. And then, if they're still having issues with chronic spontaneous urticaria or angioedema, and you think, "Well, this is chronic spontaneous urticaria," then you can get Xolair on board, and that can help a lot with any mast cell-mediated symptoms. But I would say in the MCAS group of patients, I think it's rare to get patients back to 100%, feeling a hundred percent well, whereas in chronic urticaria, we can often be completely symptom-free. Hopefully, you can minimize the degree or severity of the flares and decrease the symptom burden day-to-day. But it's not common, in my experience, to get people to be a hundred percent and back to normal, unfortunately.

Dr. Mariam Hanna:
That's a sad ending. Wait, is there a cure? Is there a cure for this condition?

Dr. Timothy Olynych:
I think we're probably grouping 10 or 15 different disorders under the umbrella of mast cell activation syndrome. It's possible there are multiple different presentations of this same problem, but I think more likely there are multiple different disorders being put in here. And I think dysautonomia in general is a big problem that currently, again, doesn't have simple diagnostic tests, and it's hard to rule it in or out. And there aren't great treatments for it. And so it's getting lumped in with these other things that don't have diagnostic tests and don't have great treatments for. And the hope is that, "Oh, if it's all MCAS and we treat MCAS, this will all get better." But I think some symptoms will get better, and I think some are perhaps unrelated, or we haven't identified the mediator we need to target just yet.

Dr. Mariam Hanna:
Is this syndrome time-limited like chronic urticaria, or will it improve, or will it worsen over time?

Dr. Timothy Olynych:
It's a great question. I think I can think of two patients off the top of my head that have gotten better and improved, like chronic spontaneous urticaria patients. And they had systemic stuff—a lot of it. I think they had legit MCAS, and they did improve and have been able to decrease their meds. They were on Xolair, and now they're off, and they're on low doses of antihistamines, and they're pretty happy with their degree of symptom control. And so I'm hopeful that maybe more of my patients will follow that trend. By and large, it's been more of a long-term grind. I'm trying not to be negative—it's honesty, but I think it's a long-term thing. But we can certainly improve the quality of life and reduce the degree of symptom burden.

Dr. Mariam Hanna:
Okay. What would you say are the big milestones that have happened over this past decade?

Dr. Timothy Olynych:
There's not a ton of milestones. I think there's been a lot of recent interest in exploring this neuro-immune axis and the relation of the disautonomic features, and breaking down these associated disorders. Again, there was a good article in *JACI: In Practice* a couple of months ago that kind of breaks down each individual disorder—everything from neuralgia, fibromyalgia, brain fog, fatigue—and is like, "These are reasonable treatments that anybody should feel comfortable starting in patients with these sorts of symptoms." And so I'm hopeful that there's more awareness of the disorder, but also perhaps people who see these patients will embrace the fact that there are these associated issues, and we can feel empowered to start low doses of antihistamines or low doses of stimulants to help with some of these issues if other doctors

aren't going to be willing to see them. But ideally, this is a multidisciplinary team, and I think the main important part for allergists is to get involved early.

Dr. Mariam Hanna:
I feel like that was a positive note—more awareness and more looking towards the future. Alright, time to wrap up and ask today's allergist, Dr. Tim Olynych, on his top three key messages to impart to patients and physicians on today's topic, mast cell activation syndrome.

Dr. Timothy Olynych:
Alright, so I'd say number one is, like I just said, we need to be proactive. So getting involved in the patient's care early, determining what is and isn't going on, and making sure that we're addressing their concerns and answering their questions before they go online. If they do have it, then the treatments we have do pretty dramatically improve their quality of life. So we have a fair number of drugs we can try, and we can up-dose, and we can significantly improve the quality of life. So it's important to get involved early and help treat. And then just being part of a multidisciplinary team, working together to help other healthcare professionals understand what this disorder is, and highlighting each individual's role in the process. Maybe the family doctor is more comfortable prescribing the antidepressants and stimulants than the allergist is, so working together to make sure we're optimizing the patient's care.

Dr. Mariam Hanna:
Thank you, Dr. Olynych, for joining us on today's episode of *The Allergist*.

Dr. Timothy Olynych:
Thanks for having me. It's my pleasure.

Dr. Mariam Hanna:
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