Understanding Mast Cell Activation with Dr Larry Afrin Transcript

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Introduction to Mast Cell Activation

Good afternoon. This is another edition of Mycotoxins and chronic illness. And today, we have a treat. It's a chance to discuss with Doctor Larry Afrin all things MSL.

Doctor Afrin. I think the most is is a hematologist oncologist. He went to the University of South Carolina, for his training. But what he has done, what makes doctor and, I think, a very special, physician is that he was a hematologist oncologist, but he never stopped thinking that something else could be happening with his patients when things didn't make sense.

He didn't decide that the patient was, you know, anxious and depressed or confused or more importantly, had ten different, unrelated illnesses. And, doctor friend, wrote the book, never bet against Occam, which, I think everyone should read, especially anyone with a chronic illness.

I, I can tell you I, was had some idea that mast cells were a problem because I had a patient who actually had some mild medical psychosis. But until I read Doctor After, after Doctor Ephron's book, I didn't get it.

I didn't see all the connections. You know, I was still looking for rashes and maybe a little girl. So, so over the years, a doctor has, taught the doctors, but most importantly, as we're going to see, he's taught to patients because, it's hard to get doctors to think about new things.

So, Doctor Everett, can you just briefly. I mean, like, I think it's really important for people to understand, you know, how you actually got into this?

I mean, what made you say, oh, maybe this lowly mast cell is doing something else than, just causing allergies and an a rare cancer. Okay, well, I got into this, well, that probably starts with chapter one of the book, and, then chapter two and three, but, to to summarize, I was, confronted in early 2008 by a patient with a, curious hematologic abnormality that had been diagnosed by another hematologist in a particular way.

But she and she had received quite a bit of, standard treatment for that diagnosis at the hands of that other, doctor. But she wasn't getting any better infection.

It was only getting worse. And, she came to suspect something was being missed and so she went looking about for another opinion. And, long story short, landed in my, my clinic, and it was immediately apparent to me she didn't have the diagnosis that she had been given because I know that disease and her her illness wasn't behaving anything like how that disease is supposed to behave.

So then the question became, well, what do you have that can not only bring about the features that lead to that kind of superficial appearance that she might have that that other diagnosis, but also have the 573 other problems that, she had been developing in her and which her other doctors had either been discounting or ignoring, and it took nearly a year to work it out.

And in the end, all I knew to, label it as, because the term mast cell activation syndrome had not really emerged to that point. But so I wound up calling it an atypical master's psychosis.

And, and, with treatment, which is a whole nother story itself. She actually, came back, in just a month and was remarkably better and has actually continue doing very well for about a dozen years.

Now.

How the First Patient Led to the Diagnosis

But, from all that I have learned in trying to figure out what was going on in her, I began to realize that a number of the other, mystery patients that I had seen over, the years of my career to that point, that at least some of them might also harbor this atypical mast of psychosis, just just manifesting in very different fashions.

And the more I began looking for it, now that I had learned how to say it, the more I began looking for it, the more I began finding it, and the more I began finding it, the more I began treating it.

And lo and behold, these poor people who had been, unwell in so many different ways for years, often decades, sometimes even had almost the entire lives, and obviously, quite often had come to be dismissed as, psychosomatic and, and the like, even if they had been sick for decades, once we made the right diagnosis and started applying the treatments that are appropriate for that diagnosis, it was amazing how much better they got.

And with patient after patient after patient. Actually, it was only about, gosh, the second and third patient. And by that point, the term mass cell activation syndrome was just coming into the literature.

And I began realizing, yeah, that that that fits this much better, because this absolutely was not master psychosis by any of the criteria that we know that disease by.

But it absolutely was a mass cell activation syndrome. When I began realizing that in polar contrast to the rarity of mass psychosis and mass actually is exceedingly common.

Yes, the challenges are it's just, the biology of it is such that it's guaranteed to present with an extraordinary, heterogeneity that can make it very difficult to recognize it at the superficial level, because superficially, one patient can look very differently from the next and the next, but eventually you learn there are patterns to it, and eventually you learn how to recognize them. But, I'll be the first to admit it.

It's challenging. Yeah, well, you know, there's two things. One, I think we're going to get to let's we're going to talk a little bit maybe about the depth of the biology, but just how important it is to realize, the different manifestations of, histamine or other or, and not just histamine, obviously, or other chemicals that mast cells can release in different tissues.

So we're going to we're going to definitely dive a little bit into that. But one of the things I like to make clear to the people listening is just how doctors think, because they think, you know, I, I know I don't think I know that that has been the great frustration of many patients, and they're often angry with physicians.

And I, I always like to have a little compassion is that there are very few doctors, very few people going to medicine wanting to ignore people. It's just kind of how we're taught, in the concept of, you know, especially now that they constrain the time when it's when people are seeing people for 7 minutes or 10 minutes is very much like a very old Groucho Marx joke that only people my age and probably people's parents and grandparents remember.

But, you'd say the magic word and the duck would drop down and you get $100. Well, that's how people practice medicine. You say the magic phrase, the symptom, you know, that fits a diagnosis.

And that's what you got. Now, the fact that you've got all these other symptoms that don't fit the diagnosis in 5 or 10 minutes is is ignored because it's noise.

And here's here's your diagnosis and here's your prescription. And what a good boy am I. And next. So anyway so that's what's happened to medicine. But it's not because doctors are inherently don't want to help you.

It's just that we have to train them in this model of like, you know, X equals you're, you're, you're diagnosis. And people are much more complex than that.

You know, it works again for my favorite story is broken Legs. You know, you get the x ray. You see the thing. It's clear cut. We know what to do. But with chronic illness, and especially when you involve an illness, that's a rate that is being magnified by a cell that I'm going to let you talk about.

That's everywhere. Not it's lots of places in your body. It it can't begin to cover the possible symptoms that can lead you to this diagnosis. So, on on that note, let's talk a little.

I mean, and I just want to say, I really think the, I know you like to do a lot of it, a lot of testing because you feel like, you know, you are the expert, and it's really important that you prove the point.

Okay. But other than the testing. But I like people to think about and we'll talk about that a bit. Is, is, is the the protein symptom symptomatology that this illness, can cause?

I mean, can you just run through really quickly, maybe just head to toe, you know, like where are you? Big? I know you can't do everything, but, you know, running through head to toe.

Yeah. All the possible symptoms will probably take the rest of the hour, I'm sure. But, I mean, just just hit, hit, hit some of these, maybe the high points in the morning.

It's probably best. Yeah. To to look at it from what the general themes are and the, the universal concept. First of all, let me back up just a little bit about the biology.

It's very important to understand the doctors go through their roughly ten years of training and, and all that training all time. They by and large, get taught that the mast cell and they really aren't even taught where the mast cells are in the body.

But but they're taught that the mast cell produces, two mediators, and triptans and histamine. And that's the be all and end all of it. And that's really all the time there is to teach them about what the mast cell does.

Because out of ten years of training, one minute is spent on teaching about the biology and the diseases of the mast cell. And that makes sense when you understand that the only, disease of the mast cell that previously was recognized was the very rare disease of master psychosis, that most doctors, after ten years of training, they'll go out into practice for the next 30, 40 years.

And most doctors will never see a case of it.

Why Mast Cell Disease Is So Hard to Recognize

So if it's so rare disease, I can understand why the medical schools wouldn't invest more time in teaching the students about the biology and the diseases.

So when a cell is thought to produce only, couple of outputs at, a couple of mediators, anybody could be forgiven for a failure to be able to imagine that any significant range of troubles could, come about from disorders of that cell.

But here's the thing. The actual known biology of the mast cell. Turns out that the mast cell is known now to produce and release more than a thousand mediators.

Okay, we've come up for each of which has a huge range of effects throughout the body. Direct effects, indirect effects, local effects, remote effects, acute effects, delayed effects, chronic effects, and, the mast cell also is now, you know, it used to be that the only receptor we were taught in our training about mast cells is that the mast cell and the receptor for, the IGI class of antibodies.

And that's true. But, turns out that the mast cell actually is now known to have more than 250 different receptors. So that's an extraordinary range. Or scope, within which the mast cell has potential to interact with other cells and organs and systems in the body in an extraordinary, number of fashions. So, when, when you try, when you look at such a broad array of mediator output and you try to understand, in spite of all the different things, different specific effects that each mediators having, if you try to divine.

What are the themes of what's going on? Actually, three specific themes do emerge. The first theme, and this is the universal constant of mast cell activation, disease.

All mast cell activation patients feature this in one fashion or another to one degree or another. And that's inflammation chronic multi-system inflammation.

Each of those words is important. The chronic because it's there all the time. Yes, from time to time there are flares to heightened levels of inflammation.

Sometimes even, the disease can sort of, transform in a fashion and escalate permanently to a whole new baseline level of chronic inflammation. But it's inflammation. And you, you know, you, you know, that the manners, the specific manners in which inflammation manifests in different areas of the body leads to very different symptoms.

That's happening on which organ, which tissue, which system is inflamed. And this is a large part of the heterogeneity, the superficial heterogeneity of the disease.

So chronic is important. Multi-system is important. Yes. Every system in the body has potential to be affected by this disease. That doesn't mean that every system will be affected.

But every system has potentially affected. And the fact is there are no mast cell patients who are being affected in just one system in their body. All mast cell patients are being affected by at least a few systems.

And then inflammation. Well, yeah, that is the universal concern of this. But then beyond all the different ways that inflammation can manifest in the body, there are a couple of other themes, but they're not constants.

So I like to say plus or minus allergic type. And so it's chronic multi-system inflammation plus minus allergic type phenomena which can range anywhere from simple allergies to flagrant to anaphylaxis to, urticaria is and angioedema is and and so on and so forth.

And I say plus minus because there are plenty of mast cell activation patients who honestly do not have a speck of allergic type issues to them. And then at the opposite end of that vast spectrum, there are those unfortunate souls, thankfully not too many of them, who are literally in 24 by seven, anaphylaxis, if you can even imagine such misery.

And everybody else with mast cell activation is somewhere between those polar opposite ends of the allergy spectrum. And then there's another plus minus plus minus abnormalities in growth and development and potentially any tissue in the body.

And how is, how does that come about? It's because a number of the mast cell mediators actually are integrally involved in guiding growth and development processes in all the different tissues in the body.

So you can imagine that if you had chronic abnormal output of these growth influencing mediators, then depending on which mediators are being expressed inappropriately, in which amounts, at which times and over which durations and at which points in the body, you can imagine a vast array of abnormalities in growth and development.

What we, really call dystrophy isms. There's a vast array of just trophies and those that can emerge. And again, depending on the tissue that you're talking about, the symptoms just can be vastly different, from one organ to the, to the next.

And so those are the general themes of this. So if you see a patient who's, you know, got a problem list of 57 different diagnoses, and you just take 15 seconds to step back and look at the big picture of what's going on.

And if you see that item after item after item after item on the problem list is itis itis itis itis inflammation inflammation inflammation inflammation.

You have to stop and ask yourself at some point whether it's 20 diagnoses on the problem list or 40 or or 60, you have to stop and ask yourself, what's more likely is this patient so uniquely unlucky as to have coincidentally acquired so many different diseases, all of them developing independently of one another?

Or do they have one thing going on that is actually biologically capable of causing, directly or indirectly, most or all, probably all of what's long been afflicting them?

And the obvious answer in the universe we live in is that it's more likely they've got just one thing going on, and the question all along has been, what disease is it?

Is there a disease that is actually capable of causing all those different problems and now, in just the last dozen years or so, we're beginning just beginning to understand, yes, there really is a disease that can cause such a vast array of generally inflammatory and allergic and dystrophy problems.

Now, let me make it clear, that I am not saying that every chronically multi, systemically, mysteriously unwell person, necessarily has a man cell activation syndrome at the root, of their many problems.

Mast Cell Biology and Where Cells Live

What I'm saying is we're now understanding that mast cell activation syndrome, in contrast to the rare disease of massive psychosis, massive activation syndrome around cats is a very prevalent illness.

And so when the doctor now sees a patient with these general things about them, it becomes very reasonable to consider amicus in the differential diagnosis, at which point the doctor needs to vet that diagnostic, possibility, just like he is going to vet the other diagnostic possibilities in the differential diagnosis.

And when in the end, it turns out that it really is a mast cell activation syndrome that can better account for all of what's been going on in the patient.

And then if you can find, ideally, if you can find at least some laboratory evidence, demonstrating mast cell activation, then at that point, likely a mast cell activation syndrome is, the principal, the root diagnosis in that patient.

And this set about trying to treat the patient accordingly. Well, what I, I love what you know, how you laid that out. I mean, I guess what I would kind of from my worldview is that I look at, you know, mast cells as another one of those regulators of the terrain, you know, and, yeah, there are people who, how do you say it's the sometimes, you know, people, many people have minimal hints that the mast cells are a little, quick to fire, you know, people who have allergies since they were kids.

I mean, those are the easy ones, you know? But then when they, as they get older and they develop either exposure to other toxins or illnesses, then the regulate, we lose regulation of the system and the mast cells start to make noise all over and depending on, on the individual that that's the point.

Because what we see people with, a handful that I've seen with severe, for instance, the CCI, the cranial cervical instability with terrible mass, I mean, Marcel is and it's a circle.

The the mast cell is what's the, the histamine and other chemical release is what's tenderizing their ligaments, you know, so that's what makes it worse.

And when you can control their mast cells, the other symptoms may an often will improve quite a bit. But also when the few the handful that have had surgery which and stable because they were so severe they need I mean it's not something you would do unless you were like, you know, bedbound and like didn't exist.

But the mast cell stuff doesn't disappear, not sometimes disappears, but dissipates remarkably because, you know, the beauty of the the body is that we're all one big soup.

And the when you keep your brainstem, inflamed, it sends a signal. Or you're claiming that inflamed but irritated, it signals danger to the whole body and your mast cells.

And that's what I love to hear you, from my understanding, is like one of the more primitive, immune cells that we have, and it's going to be set off.

So, you know, so again, there can be circles. The but and if you can, so many people, if you control the mast cell, the symptoms go away. And the body kind of can restores homeostasis.

But sometimes we have to you know, and I said we've had this discussion over the years. And I think you I think you're now agreeing that, you know, occasionally there are chronic infections that can also, be triggers because that's been our experience, is that in the old days, when we had a lot of the old days, lots of times when we had people that we think have, a chronic infection, but we can't treat them because as soon as we treat them, they would flare.

And people often called those hoaxes. I think I always thought that was a foolish name for these things, but still. And it's really mast cells in most of them.

And if you treat the mast cells, a whole lot of stuff gets better, you know? So that's just my but you know, again, I think it's like where you cut the circle, you know, whether you and, and but you, you know, and it's, you know, but you get to see the people who the mast cell when you fix the mast cell, the system definitely returns to more normal.

So, so just, just can you just give us a little a little story about mast cells? We're going to come back to some of the symptoms I know we never got to there, but I'll we'll circle back.

But I just really want to hear just a little bit of, you know, mast cells where they come from and where they and where they generally live in the body, you know, other you know, you actually set up the answer to this question quite well with your use.

Just a couple minutes ago of the word primitive. But there is no more primitive defense cell in the human body than the mast cell. This has actually been worked out by the paleo geneticists and past.

Who knew there were such people, but, the, the, the, the ancestral lineages of the different types of cells in the body have largely been worked out. And it turns out that back around the time that eukaryotic organisms are multicellular organisms were first arising.

It actually was the, the mast cell or an ancestral version of the mast cell that was the host defense system in the earliest eukaryotic organisms that began arising somewhere, oh, 500 to 750 million years ago.

And for millions and tens of millions of years, they were the only defense cells that eukaryotic organisms had. And they obviously had a keep the multicellular organism alive in the face of an astonishing array of, of threats and stressors.

So the mast cells, necessarily, from an evolutionary perspective, acquired an extraordinary array. Defense mechanisms, not not just defense, but sensing mechanisms to be able to sense threats in the environment and then defense mechanisms to respond and to help the multicellular organism.

Resist and recover from the threats visited upon the multicellular organism. Well, over time, other host defense cells with more specialized, defense mechanisms began appearing on the scene.

Like the other types of granulocytes, the neutrophils, the eosinophilia, the baser of the monocytes, the macrophages, the lymphocytes, plasma cells, and so on and so forth.

And each of those defense cells clearly does a better job than the mast cell does at the specific range of tasks that

that cell has evolved to address.

But the mast cell is still there and it still remembers all of its old tricks. And as long as it keeps all of its defense mechanisms, properly controlled, you know, with, with a normal set of, genes in the mast cells that regulate the functioning of the mast cell, then all of those extraordinarily potent mediators, the weapons the mast cell has developed over time to be able to deploy in different situations as needed.

All of those weapons stay largely bottled up inside the mast cell. They don't cause any trouble. The problem that the central problem that the mast cell activation syndrome patient has is that the the weapons, the mediators are now being deployed.

They're being released inappropriately. And why is that happening? Well, in occasional cases, it seems like it may be an autoimmune disorder. There are a couple of specific autoantibodies we've learned about that really do have the potential to attack.

And in the process of attacking the mast cell, activate the mast cell. But this is a relatively uncommon, relatively rare phenomenon. What the research today just shown, though, is that in the vast majority of M-class patients, these patients, unfortunately, are acquiring, mutations in various mast cell regulatory genes, which lead to inappropriate, release of the mast cell mediators, not only at a baseline level, what we call constitutive mediator release, but also inappropriate releases of mediators in a reactive fashion so that when the marcelle is presented with a specific threat, you know, there ordinarily should be a specific set of mediators released in a particular pattern to deal most effectively with that threat.

But these mutations lead, the mast cell to both, constitutively, behave abnormally and to reactively behave abnormally. And it's when you get the release of these mediators in, fashions that are not normal fashions that don't, contribute to resisting and recovering from insults to the body.

Well, that's when you run into problems because the, the receptors and all these other cells in the body that these released mediators are targeting, these receptors are present on a vast array of other types of cells all throughout the body.

And these other cells, of course, they they don't know that they are being presented with mediators in an inappropriate fashion. All all the cells, they're they're just biologically programed to react in a certain fashion when a particular mediator let me.

So just, just, when you mediators are just our way of saying, chemical signals in use, you know, and so in this case, the thousand or so chemicals. Right.

So when these signals come to dock with these other cells, the other cells start reacting and if it's in a situation where these other cells should not be reacting, then that doesn't contribute to health.

That doesn't help you recover from anything. It just actually makes you sick in one fashion or another. When various cells are starting to do things that they're not supposed to be doing, at that time. So the next part of your question, you know, where are the mast cells in the body, in truth or everywhere?

They are present in every vascularized tissue in the body, which is to say, just about every tissue in the body. But it's very clear that there are a couple of particular areas where they're dominantly sighted.

See, in most tissues in the body, they're very sparsely distributed. You would be hard put if you were to do a random biopsy in most tissues, you'd be hard to find even a single mast cell.

But where the mast cells are dominantly cell number one at the environmental interfaces. So the skin, the the respiratory tract, the, the GI tract and the genital urinary, the GU tract, which is kind of where you want your primary sentinel against threats to the body.

That's where you'd want your primary sentinel to be positioned, to be able to most quickly detect assaults upon the body.

Symptoms Across the Body

So number one, there at the environmental interfaces and good numbers. And the other place where we dominantly find them is in the walls of all vessels in the body, the blood vessels, the lymphatic vessels.

So this is where they dominantly are. And therefore it's no surprise that, you know, the dominant symptomless. And this gets to the third part of your question, what are the specific symptoms that are typically seen here?

It follows from the biology, you know, where are the mast cells. Well they're at the environmental interfaces. And in, in the walls of the vessels. And, and what what are the dominant themes of the effects of these mediators?

Well, I said information is the dominant theme. So we see, for example, in the skin, we see plenty of rashes. And we see something called dramatic graph is, where if you scratch your, the skin lightly, you'll see a very quick, red flaring in the skin in the track of the scratch.

And it lasts, an unusually long period of time, in somebody who has a mass cell activation syndrome. Well, why is the skin turning red there? Well, it's because there is an infusion of extra red blood cells into the area.

Well, how can there be an additional amount of red blood cells infusing into that area? Well, let's. Because the blood vessels in that area have dilated to be able to accommodate more blood flowing into that area.

So again it goes back to the biology of as well, the mast cells there at the environmental interfaces like the skin and in the walls of all vessels. And you better believe there are some mast cell mediators that can potentially dilate blood vessels as well as other mass.

So mediators actually can potently constrict blood vessels. So that's the skin in the respiratory tract. We have all the symptoms of inflammation in the respiratory tract, the excess mucus production, the coughing, the sneezing, the the runny nose, the post nasal drip, the the coughing, in the GI tract, copious inflammatory issues with discomfort and pain and abnormalities in bowel motility like alternating diarrhea and constipation.

There are inflammatory phenomena in the bowel that can lead to, absorption, nutrient absorption problems that can have an awful lot of diverse downstream manifestations.

And in the genital urinary tract also. Yes. Many women with this disease have quite an array of inflammatory issues in the genital tract, and, and in the urinary tract.

Not to say that men don't, but, it's more common in the women because, I mean, think about it. Their genital, and urinary tracts are a little bit more exposed to the environment than the male, genital and urinary tracts.

So there are plenty of women who suffer frightful amounts. Yes. Vo Vitus, vad Unitas, dyspareunia. Yeah. And excessive uterine bleeding. So, yeah, that that's, I guess, a short summary of men.

You know, I would what always is why I love your summaries of these things is because I like to think that I think of everything. But I don't, you know, I mean, like I said, I, you know, the the the gue tract. Yes.

You know, some, some forms of interstitial cystitis even. But but I didn't really connect the excessive uterine bleeding, which makes sense. It's inflammation.

And so it's a little bit more than it is inflammation. But there's another aspect to the biology too that's relevant because I mean where does the bleeding coming from.

From the endometrium. Right. Which is a heavily vascularized source. Right. Okay. So there are a lot of mast cells

in the enemy atrium, including the walls of those vessels.

But another key piece of the biology here, of the relevant biology here goes back to the media, the specific mediators. You know, again, you and I were taught the only mast cell mediators are taste and histamine.

But it turns out the very first mast cell mediator ever discovered back in the 1930s, and actually one of the dominant mediator products of the mast cell is heparin.

And have, you know, most people think of heparin just as a drug, the very potent anticoagulant drug. But it turns out heparin is not just a drug. It's also a natural product of the human body.

And for all intents and purposes, there's only one type of cell in the human body that makes heparin, and that's, cells. So if you have normal mast cells up in the enemy atrium, not a problem.

You have normal functioning there. But if you got a bunch of dysfunctional mast cells there in a heavily vascularized tissue, and these mass cells are frequently getting inappropriately activated and thereby dumping their loads of heparin into that heavily vascularized tissue, you're going to get exactly the same result as if you were to inject, a load of heparin and say, a subcutaneous tissue somewhere.

And everybody knows you get plenty of bleeding and bruising when you do that. It's the same thing going on. Well, well, that this, you know, should you.

I'm sure you have given courses for free doctors just to. I mean, just going through the tissues because you said we, you know, we think about the things we think about, but what, what we, you know, cells is as well is the unknown unknowns that, that really get us into trouble.

You know, I mean, that that was exactly what I was looking for was like, okay, what's the regular and what's to those of us? You know, we call the zebras.

You know, but again, when you have a full understanding, they're not the they're not zebras because you would think about them. But when you don't know enough, it's the unusual event.

That's fascinating. Let me just just run back to to I'm going to go to a few other symptoms. But one of the things I was, I'm interested in, I know you talk a lot about mast cells.

Having, mutations, but are there, do you also have issues with, just changes in the, the epigenetics in the mast cell of expressing different genes? You know, you're you're you're right.

And I was oversimplifying before, but, well, I just, I just that, that clarify for me, I think there may be an infinite number of dimensions of complexity of this disease, but, yeah, the, the, the, the recent research suggests, because you have to ask the question, you know, why or the mutations in these Marcell regulatory genes being acquired.

We we know from the research today that they're fairly uncommonly inherited mutations. And rather most of these mutations are acquired or somatic mutations rather than germline mutations.

So you have to ask how are these mutations developing. How are they being acquired. And the research on that front is even more preliminary at this point.

But the what the idea that that's presently, the dominant idea that's presently emerging is that there are epigenetic mutations and these most likely are inherited.

And the effects of these are the principal effects of these epigenetic mutations are to, confer upon the genome the actual genes, not the epi genes, but the genes, in the genome, state of fragility.

So ordinarily our genome is very robust. Yes. Mutations are developing all the time in our genome. You know, there

are trillions of cells replicating every day.

And, so, so you can't help but develop mutations, fairly frequently. But we've evolved, very good mechanisms for detecting, when a new mutation has arisen and then either fixing it or targeting that cell for, essentially suicide, apoptosis, so that those mutations can, persist.

Well, if the mechanisms for identifying and fixing the mutations are no longer working as robustly as they ought to, that creates a state in which it becomes easier for an acquired mutation to persist.

And furthermore, other research is is suggesting that, when you have that sort of a state of genomic fragility, that when that genome, that frail genome is assaulted by one sort of cytokine storm or another that emerges rapidly from various organ systems in the body, anytime we're under one sort of stressor or another, that there are very complex interactions that then go on between that cytokine storm and the frail genome, that ultimately lead to the induction, the the creation of a new mutation.

And when it happens to be a mutation that just happens to be in a stem cell, and it just happens to be a mutation in a gene that is of regulatory importance to the mast cell, then congratulations.

All of the mast cell progeny of that stem cell, all the mast cell progeny of that newly mutated, stem cell are going to bear that same mutation, and they will start misbehaving in whatever fashion is dictated by that particular mutation.

And at that point, welcome to mast cell activation syndrome.

Genetics, Epigenetics, and Disease Progression

And over time, as that frail genome gets exposed just through the random acts of life, get exposed to more and more and more stressors, then more mutations develop and you develop, further sub clones, so to speak, of ever more dysfunctional, ever more mutated, and therefore ever more dysfunctional mast cells.

So the disease, I mean, this is the observed natural history of the disease that over time, it's always acting to some degree. But the baseline about which it functions tends to be pretty stable over time.

But then from time to time, there can be significant escalations in the baseline level of misbehavior of these dysfunctional mast cells. And it's been observed that these escalations, which tend to be permanent, tend to emerge fairly shortly, anywhere from a few days to at most a few months, following a major stressor, either a major physical stressor or a miss or psychological or emotional stressor.

And because it's mutations that are developing and being acquired, this is why these major escalations as differentiated from just a flare of the disease, these major escalations tend to be permanent, because they're the consequence of yet another mutation or 2 or 3 having been acquired.

So we're not saying we're not saying in a mast cell patient that that all of their mast cells are mutated and dysfunctional, because that's not the case.

As I said, these mutations almost never are germline. They're not inherited. Rather they're acquired. And therefore it's only a portion of the patient's mast cells that are misbehaving.

But the mediators that are coming out from these dysfunctional mast cells in an inappropriate fashion are so potent. That's how this disease is able to cause so much havoc.

At a clinical level. Yeah. Right. Because you you might only have a few mast cells, but the language they speak is understood universally. You know what what what they put out the information.

And this I don't want to digress too much, but someday you and I will have to have a long conversation about, doctor, doctor Navios concept with the CDR one, two and three.

Because you see, the CDR one is when you have this acute inflammation stage, and that's when you're not methylated and you kind of open Pandora's box in your genome because you expose lots of parts that usually are nicely covered by histones.

Okay. And the CDR two is what you, you know, you call that that that, actually what you and Doctor Shoemaker refer to as more like proliferative when you start getting the hypertrophy of tissue, you get those cofactors being released by the mast cells.

But this is a long story and we won't, I won't digress. I just want to throw that out there just for your brain, because I'm going to come back at you someday with, I with a, I yeah, I'd like you to talk to a few other people because what I, I'm a great believer in, triangulation or just the fact that over the years, I just keep learning so much from different really smart people.

And what I find is that really smart people like you, you bring us this incredible amount of light, you know, but, you know, the very nature of your work, you know, you, you, you know, you're working in one area and it's nice to bring people from different perspectives together, you know, because I have a superficial knowledge of a lot of things.

You guys have deep knowledge, and that's what is really wonderful to get in the same room rarely happens, unfortunately, because you all operating in different fields, you know, but I think there's I think there's, just, a possible, of illumination because, you know, the more light you have, the better your brain is going to work, because you got a very you do a very good job.

But so just just before we wrap up, just when I realize, are there a few more? I said, in medicine we call zebras. You know this the saying in medicine in in heels, if you hear a horse beats, you know, think horses, not zebras, you know, at least at least in the United States in general, that would be a, a good thought.

But the zebra is the thing you don't expect to see. But it still could be there. I actually knew someone who had a ranch in Texas that had zebras. So, can happen.

So on that note, I mean, what is what are some of the unusual, presentations? I mean, I'm going to throw out one that probably not unusual to me, to you, but, I mean, just the bone pain, is something that, you know, I do believe and correct me, I, I now think in terms of history and myself.

Well, that's an interesting symptom. Because it's actually the mast cell patients who have, that deep seated bone pain, it's a pain that is essentially the same type of deep seated bone pain that sickle cell patients have.

And this goes back to your notion of triangulation, connecting the dots. Yes. And it's been very interesting. If you follow the research in the sickle cell arena over the last decade, it has begun emerging from the, the bench researchers in that area that, you know, it always used to be thought that what was driving the pain and sickle cell disease, the bone pain in those paid for patients was, the basal occlusion.

Well, it, you know, from the sickle, the red blood cells. Right. Well, it turns out no, it's actually mast cell activation. Okay. And in fact, the drug that is most commonly used to help settle, bone pain on a chronic basis in sickle cell patients.

Hydroxyurea, actually turns out to be a helpful drug in settling bone pain in, number of mast cell activation syndrome, patients. And furthermore, if you wonder, I don't know how much experience you've had with sickle cell patients in your career.

So hematologist, I had quite a bit. Yeah.

Unusual Presentations and Sickle Cell Links

But, yeah, nobody was ever able to explain to me why about 80, 85% of sickle cell patients have a relatively benign phenotype of that disease. They're they're fully functional people.

They have a normal life. They work a they enjoy life. They they do have an occasional vaso occlusive pain crisis, but they're almost always able to fairly easily manage that at home with relatively modest, drugs.

And, and the crisis comes and goes in just a few days and it happens, you know, maybe once, twice, three times a year that, that that's it. But then there are the other 15 to 20% of sickle cell anemia patients who suffer every.

No. Yeah. Yeah. They live in or merge that disease and they they're pricey. They are almost always, seemingly, almost always in crisis when they have a crisis, it doesn't last three days.

It last three weeks. They're in the hospital for, you know, two, three, four weeks. They're always in the emergency room with one problem or another. These are the sickle cell patients who have, the gallbladder failures, the heart failures, the kidney failures.

And and because all sickle cell anemia patients have exactly the same aim point mutation in their beta globin, gene, how could there be such a division?

And these, sub phenotypes of, mast cell, of sickle cell disease. And as I was starting to get into the mast cell activation arena, I began realizing pretty quickly that the same here was that all of the constantly sick sickle cell patients had sickness in a fashion that was potentially consistent with, cell activation.

And so I began testing them, and I actually published a paper on this some years ago. And it turns out that an awful lot of the constantly sick Marcell, constantly sick sickle cell anemia patients actually have a definable, Marcus.

And when you start treating the M-class in these patients, the previously uncontrollable sickle cell troubles all of a sudden get better. And it actually is possible to transform one of these very high resource consuming sickle cell patients into a comparatively low resource, patient just by recognizing, diagnosing, and effectively treating the mass cell activation that's in them.

And the percentage even makes sense because the epidemiologic research in mast cell disease has suggested that about 15 to 20% of the general population actually has MERS in one form or another, one fashion another to one degree or another.

And that's pretty much the percentage of the sickle cell population that has bad sickle cell disease. I've seen plenty of other zebras. I mean, heck, just look at the first three chapters of the book.

The first patient, Polly. So for me, a very, which actually was not Polly. So the image of era, right, was just an idiopathic, Polly. So theming an excess of red blood cells, that made no sense until you learned what mast cell disease can do.

The very this. The second patient had exactly the opposite problem of far too few red blood cells. She had a rare hematologic condition called pure red cell, a pleasure which usually is driven by one sort of viral infection or another.

But she didn't have any of these other identifiable causes of BRCA.

Closing Thoughts on Diagnosis and Treatment

And ultimately we found it was mast cell activation. We treated it and this terrible, transfusion dependent anemia, she it had just went away in a month.

I think, you know, it's unfortunate we we're almost at a time. And, you know, we it's funny, we didn't even get to the micro tassel, but it doesn't matter, because I think the point that I wanted to get, you know, and you've done beautifully is that when the inflammation and when your symptoms just are all over, you know, talk to your doctor, think about, read about that.

Mast cells may be playing a role. You know, if you're the person who everything you take flares you every time you've been tried, you've been, you know, every time you take a binder, you flare.

Okay. Think about mast cell. You know, it's it's that, you know. It's just, you know, you have a hoax every time they try to put you on an antibiotic or nerve.

Think about mast cells. I mean, these are the underlying cause of so much unnecessary misery, especially in our world. And something. And there's another topic I'd love to discuss with you.

And another time is we're seeing so much more of this now. Is it just because we're seeing it or because, you know, just seems like allergies have and which I think is the tiny tip of the iceberg.

You know, that is a topic for another time for sure. Yeah. Okay. Yes I'm sure. But anyway, I just want to thank you as again, Doctor Afrin is a pleasure.

I love listening to you and learning from you. It's, really an honor. So thank you so much for your time. And thank you for the opportunity, doctor Gordon.

Okay.