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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

What Is Macrophage Activation Syndrome?

Announcement:
A rare, deadly disease that leaves patients in critical condition and doctors searching for answers, knowing the signs can save a life. This is Investigating HLH, a podcast about hemophagocytic lymphohistiocytosis, brought to you by Sobi, Inc.

Moderator:
Hello, everyone. Adam Narloch here, and I'd like to welcome you back for another episode of Investigating HLH, a podcast about hemophagocytic lymphohistiocytosis sponsored by Sobi, Inc.

For this episode, we'll be talking about macrophage activation syndrome, or MAS, a rare, potentially fatal, hyperinflammatory syndrome. Joining us are two highly respected experts who've played a critical role in advancing our understanding and knowledge about MAS.

First, Dr. Daniella Schwartz is a rheumatologist in Pittsburgh, Pennsylvania, and affiliated with the University of Pittsburgh Medical Center, Presbyterian Shadyside, and UPMC McGee Women's Hospital. In addition, she's an Assistant Professor of Medicine at the University of Pittsburgh.

Also Dr. Randy Cron. He is a pediatric rheumatologist at Children's Hospital of Alabama, and a Professor of Pediatrics and Medicine at the University of Alabama. He's also the Director of the Division of Pediatric Rheumatology and the Pediatric Rheumatology Fellowship Program at Children's Hospital of Alabama and the Alabama Chapter Endowed Chair in Pediatric Rheumatology of the Arthritis Foundation.

Both Dr. Schwartz and Dr. Cron are experts in rheumatology, and I'm excited to hear them share about MAS. Welcome to the podcast, doctors. Thank you for joining us, and if you'd like, please tell us a little bit more about yourselves and your experience with MAS.

Dr. Cron:
Okay, well, thanks for having us. And as mentioned, I'm a pediatric rheumatologist, but during my medical school training, I took some time off and ended up getting a PhD in immunology, which really kind of sparked my interest in rheumatology, because much of what we do is based on manipulating the immune system.

My interest in cytokine storm syndromes like macrophage activation syndrome really got sparked when I was formerly in Philadelphia at the children's hospital there. I had a patient that we were consulted on in the intensive care unit who had a macrophage activation syndrome, was severely ill—actually for me probably one of the sickest children I've ever taken care of, who came out of the ICU essentially unscathed at that time. And we had tried to help her as best we could, but things weren't really going well in terms of kind of the standard therapies at the time. This is back in, I think, 2004, somewhere around there, about 20 years ago.

So we spoke with the family, we spoke with the care team, and we decided to try a novel approach, which was blocking one of these proinflammatory cytokines, specifically interleukin-1, and she remarkably got better. She was on multiple support systems, whether it was maximal ventilatory settings. She was on multiple pressors to support her cardiac output. She had every organ system failing—kidney, liver; her brain was not happy.

Anyway, I have a basic science or translational immunology lab where I primarily was studying CD4 T-cell transcription. And it took me a while, but eventually I switched over to essentially studying macrophage activation syndrome, mostly using humans as a model system.

Moderator:
Thank you for that, Dr. Cron. Dr. Schwartz?

Dr. Schwartz:
Thank you also for inviting me to participate in this. It's going to be a lot of fun.

So I came by my interest in immunology and cytokine storms kind of on the back end of rheumatology. I did all my clinical training up front, and then did a pretty prolonged postdoctoral fellowship in basic immunology lab—actually two of them—after my fellowship. And in the course of this, started to see patients with genetic disorders of the innate immune system called autoinflammatory syndromes that are typified by really high production of these proinflammatory cytokines, not quite at the level of macrophage activation syndrome.

And then at the end of my training, came over to Pittsburgh, thinking that I would be treating this very small group of adult patients with these hyperinflammatory syndromes, and that everyone said, 'Well, this will be vanishingly rare, so you probably won't have enough clinical work to keep you busy. You're going to have to boost yourself by doing some general rheumatology.'

And that was absolutely not the case. I started to see multiple really profound cases of cytokine storm when we were on the consult service, patients coming to see me in clinic after they'd had a lot of cytokine storm, and realized that this is probably, in the adult rheumatology world, which is where I live, an increasingly, let's say, appreciated, maybe not as well recognized, cause of morbidity in adults.

Whereas, as Randy—as Dr. Cron mentioned, we can make like a really big difference in reducing mortality and morbidity using the targeted treatments that we have.

And I also have a translational lab where we focus more on the genetic drivers and mechanisms of some of these diseases, using more, I think, the inborn errors side. But that's kind of how I got into cytokine storms.

Moderator:
Amazing. It's so great to have you both here to have this conversation. So thank you.

I think a great place to start would be just a general overview for our audience of what MAS is. We can get into a little bit more detail about how MAS relates to HLH—this is the Investigating HLH podcast—in just a little bit. But how would you both typically explain MAS to someone that may not be familiar with the disease? Dr. Schwartz, why don't we keep with you?

Dr. Schwartz:
Yeah, so I would characterize MAS—it's kind of in the name—something either you have generally in association with this autoinflammatory, innate immune activation background. Something's poised to make your macrophages a little bit more prone to activating on a hair trigger. And then you tip into this storm condition where your macrophages are pouring out these hyperinflammatory cytokines, typically interleukin-1 and interleukin-18, which are going to spark a very brisk, very extreme inflammatory response that is characterized by a set of clinical features.

These patients are extremely sick. They can have end-organ involvement, liver failure, neurologic disease. And the sort of, I guess, what we call the terminal effector, which is the final culprit that's pouring out a lot of the inflammatory mediators, is that activated macrophage either because it directly is prone to becoming more activated, or because something indirectly triggers it.

In general, we tend to use macrophage activation syndrome to describe this in the setting of an underlying rheumatologic disease. And so it's not your patient who came in and they've had cancer and are getting tumor immunotherapy and got activated, but they had typically this rheumatologic condition called Still disease, or adult-onset Still disease, that would tip them into it. Although there are other, of course, rheumatologic conditions that can predispose you to developing this flavor of cytokine storm.

Dr. Cron:
Macrophage activation syndrome, as Daniella said, is really what the rheumatologists call cytokine storm syndromes in the setting of rheumatic illnesses. A lot of them are kind of innate-driven, like Still disease, which is probably the most common cause in pediatric rheumatology.

On the adult side, actually, it's probably more likely lupus, because it's a more common disease, and lupus tends to be kind of the prototypic autoimmune disease. But again, you can't really say that one disease is driven by just one or two cell types, right? So it's very complicated. So lupus is another cell type where we see this quite frequently.

And actually, as kind of Daniella was alluding to, the adult world is slightly less familiar with this because there is a genetic form of this disease called HLH, or hemophagocytic lymphohistiocytosis, which primarily affects newborns or infants because they have a homozygous defect, typically in the perforin killing pathway that both natural killer cells and cytotoxic CD8 T lymphocytes employ. And so it shows up very, very early in life. It's rare. It's about 1 in 50,000 live births. But from that perspective, pediatricians may be a little

more aware of it.

It's also complicated with lupus, because if they get a cytokine storm macrophage activation syndrome with lupus, it's often at presentation, and a lot of the laboratory and clinical features overlap with bad lupus itself. The rheumatologists call it macrophage activation syndrome. The hemato-oncologists call it HLH. And there's things like cytokine release syndrome, you get a little more advanced. And like, things that are iatrogenic actually from treating advanced cancers; they're not all the same, but they share a lot of common features.

Dr. Schwartz:
Thinking of something as a cytokine storm syndrome makes you think, yes, they had a cytokine storm. But why did they have a cytokine storm? Why did this patient—and Randy is absolutely right, lupus is pretty common in adults, also vasculitis. I've seen it in patients with sarcoidosis. Really many underlying immune defects can make you prone to it. And then on top of that, you often have an acute insult—it's maybe a viral infection or certain bacterial infections that might have tipped you over into this cytokine storm state.

So saying your patient has cytokine storm tells you that they're very, very sick and that they need a certain type of targeted therapy and that they need a certain type of workup, but it doesn't tell you why they came into cytokine storm. Whereas, saying that they have macrophage activation syndrome can almost make you stop your workup and you say, well, I've diagnosed them, they have macrophage activation syndrome. And that's not true.

And even in the genetic realm, we see patients who have what we call somatic mutations, which are not necessarily acquired at birth but later on in life in some of these same genes, and they can develop these activation syndromes and these cytokine storm syndromes as well. So even in the adult world, it's important not to forget genetics.

Moderator:
What would you both say the typical outcomes are for patients with MAS?

Dr. Schwartz:
If you recognize many of these cytokine storm syndromes early, and if it's MAS, which we're thinking about the rheumatic diseases, the outcomes are usually very good. I think there are great studies showing that with good treatment, you can have recovery in well over 90% of your patients. But if they're unrecognized and they end up going untreated, then the prognosis is pretty grim.

Dr. Cron:
Yeah. I mean, that's generally true, fortunately for rheumatologists. Although we often have cytokine storms that are not rheumatic, because we have expertise in this and we know the therapies that are often used. But particularly if it's a Still disease patient, number one, we probably already know they have Still disease, or maybe it's a diagnosis we don't, but we can make that diagnosis. And like Daniella said, the earlier we recognize it, the earlier we start treating it, the better the outcomes are. And maybe that's, in part, that, or maybe it's just because the drugs—the therapies we use, like IL-1 blockers, work really well for this in that setting.

Moderator:
So one thing that we were already kind of touching on, you had mentioned this umbrella of cytokine storm disorders—and by the way, thank you both so much for those explanations—in some of our previous episodes on this podcast, Investigating HLH, we spoke about the symptoms and diagnostic processes of HLH. And while there's a lot of similarities as we already started to touch on with MAS, there's also some key differences that you started to allude to. So before we dig into those, could we just kind of touch on, again, the rheumatology field's current understanding of where MAS fits under that wider umbrella that you were talking about, and some of the differences between MAS and everyone else's understanding of HLH? Sort of talking to that overlap. Dr. Cron?

Dr. Cron:
Even in patients with Still disease or lupus, where we more commonly see macrophage activation syndrome than other rheumatic diseases, a lot of those patients—30 to 40%—maybe share single-copy or heterozygous mutations in some of these same genes that cause a familial disease. And we think some of these mutations—you have to do the extra work, take them back to the lab and study them—may actually contribute to the threshold of why they develop that disease as opposed to someone else who doesn't get MAS in that setting.

So a part of it is a terminology problem. So cytokine storm is an umbrella term. Again, they're not all identical. And like the familial form of HLH is highly fatal, right? It's 100% fatal if you don't recognize it and treat it. Although, for whatever reason, patients with Still disease can get MAS over and over again. And it's not all of them; it's a subset—maybe 1/3 to 1/2 of the patients. Typically, the secondary forms, if you can get them through their first cytokine storm, you often don't see it again.

Dr. Schwartz:

Yeah, so I would say kind of the same in that HLH is an umbrella term. And you can talk about primary HLH, which is the genetic form which Randy had alluded to, which is this very early-onset pediatric form, which is its own beast.

And then in the adult world especially, we talk a lot about secondary HLH, which is essentially that same cytokine storm syndrome downstream of any cause that isn't a pure genetic disease. So even these patients with heterozygous mutations in genes that—in homozygosity if you have two copies would have caused the pediatric form and now they're getting it in adulthood—we still often call those patients a secondary HLH because they don't have the true pure genetic architect or primary form. But there's a lot of overlap, and clinically they look very similar.

Also multiple specialties coming to the same syndrome in parallel. So what happened was that around the same time you have rheumatologists recognizing this cytokine storm syndrome and hematologists recognized it, and maybe we were seeing kind of shades of the same thing, but we each developed our own classification systems, and our own criteria, and our own treatment algorithms.

Moderator:
So as far as the observed manifestations when we're talking about MAS, we're talking more about rheumatologic-based illness, and some of the classical understandings of HLH being a little bit more from the heme-onc world. As the patient manifests, can these manifestations—hyperferritinemia, persistent fever, cytopenias, et cetera, and even the outcomes of these patients—be similar and different? And could you guys talk about that just a little bit?

Dr. Schwartz:
I mean, I think the main difference in outcome is really that the patients who have Still disease, who have rheumatic diseases, tend to do a lot better, and even lupus. If you compare a lupus patient with MAS with a lymphoma patient with MAS, obviously the lupus patient is going to do much better, and that's even more true when you look at the Still disease patient.

So I do think that prognostically, there are differences. And how much of that is due to the actual cytokine storm syndrome versus the fact that lymphoma is a much more aggressively fatal disease than Still disease is probably a little bit up for debate. But certainly, if you look side by side at the mortality of patients who have this syndrome, who have Still disease versus who have lymphoma, you're going to see that over 85% of the patients with Still disease are going to do really well.

So in terms of the presentation, cytokine storm syndromes, at clinical presentation have a lot of overlap. I mean, it's essentially a patient who's hyperinflamed—they're sicker than they should be—is probably the easiest way to describe it. And so there's going to be a lot of overlap clinically in that patient who's coming in. And then within that HLH, MAS, the hyperferritinemia. Again, you're going to see hyperferritinemia—or maybe not obviously—in a lot of these patients. And so clinically, they're going to look extremely similar, one to the other.

Dr. Cron:
That's basically the case. Essentially, all these patients, at least over 95%, are going to have fever. And it's typically a sustained fever, which is a little bit different than the Still disease flare fever, which tends to be more kind of spiking or quotidian. This tends to be a more persistent high fever.

And so clinically, like Daniella said there, it's very hard to distinguish the etiology of HLH versus MAS based on clinical and lab features. They overlap a lot, and there are criteria out there that share a lot of the same kind of diagnostic and laboratory features.

But hyperferritinemia, I think, is a simple, easy early screen. I end a lot of my lectures with: if you're sick enough to be in a hospital, child or adult, anywhere on the planet, and you have a fever—even if you know why you're in the hospital, like you've got Dengue or whatever, you know why you're there—if you have a fever and you're sick enough, like then you are worthy of a serum ferritin on day one. And there are things that will raise your serum ferritin, like chronic liver disease or multiple blood transfusions and things like that, but you often can pull that out of the history. But if you're having a fever and you're sick enough to be in a hospital, a ferritin is a really simple early screen.

And if it's high, then you can start working them up for other features, laboratory findings, or pathology that would push you in that direction. And if you want, you could potentially start treating them early with things that are relatively benign but potentially very, very helpful. Because again, the earlier you recognize it and treat it, the better the outcomes are going to be.

Dr. Schwartz:
Let's say you get the ferritin, and it's 2000 to 3000, and you're not really sure if you're catching something early that's progressing into a cytokine storm, or whether this is one of those many other causes. Trend it. The trend in the ferritin, it's very benign to just wait a day or two, check it again. Check it again. And if you're going from 3000 to 2000 to 3000, that's maybe a little bit more reassuring. But if you check it and it's 3000, and then the next day it's 4000, and then the next day it's 6000, then you have a problem on your hands, and you

should really start thinking about cytokine storm syndromes and HLH specifically.

Moderator:
This is so helpful because both of you mentioned that the key to better outcomes is an earlier diagnosis, a prompt diagnosis and treatment, and that can make a huge difference. So as we know with any type of HLH, that prompt diagnosis is so important.

In talking about this MAS more in the rheumatology space, another thing that can potentially, for those listening, make MAS so difficult to identify is the lack of standard diagnostic criteria across MAS patient populations and backgrounds.

So would you both tell us just a little bit about how you approach the diagnostic process? We already started on it with this ferritin, Dr. Cron; I think that's so helpful. But when you start to suspect a patient might be tipping into this MAS state, how do you make that prompt diagnosis? And how can we learn from both of your expertise in this very important part of diagnosing MAS?

Dr. Cron:
I'd say the two biggest problems we have right now in the field is, number one, recognition. So if you miss the diagnosis, it's not going to go well. So we just need to get the word out there. We do need to have criteria that are easily used and can help you get to the diagnosis. But just even educating people on that this exists, I think, is really important.

The other issue is just the lack of some of these targeted therapies around the world. In the United States, for example, we have access to most all these good therapies that we're currently using, and the list keeps getting bigger and broader, which is great, but that's not the case worldwide.

So to me, those are the two biggest issues.

But diagnostically, there are multiple criteria. The original criteria were developed by hemato-oncologists to describe this familial or genetic form—the HLH-04 criteria—and they've been modified slightly. So you can have a genetic diagnosis, but most newborns don't hand you a card that says, 'I've got two perforin mutations, that's why I'm really, really sick,' unless, of course, they've had family members. I'm being a little facetious.

So they have eight criteria, most of which are lab-based, some are clinical-based. And if you meet five of those, then theoretically you have HLH—a pretty good chance. The problem is, some of those criteria are not easily, quickly available at most institutions around the world, whether that be a soluble CD25 level or a natural killer cell function, so you're starting to lose available criteria. So that's one.

Personally, what I do—because I've been doing this for a while—is more Gestalt. Like, if this was a clinical trial, sure, you'd have to have established criteria. But for the patient that we see in the hospital, again, like Daniella mentioned, is this child or adult sicker than you'd expect them to be for why they're here? And I think a real easy, simple screen is ferritin. But there are some real simple things that you can do, both helpful diagnostically as well as to track over time, like tracking the ferritin over time, like Daniella was mentioning—both diagnostically and in terms of how the patient's doing. But there are some simple labs, for example, platelet count or any of the cytopenias. But I really like the platelet count—it tends to move quickly with how the patient's doing. C-reactive protein, or CRP, is another one. Liver enzymes like AST. Those are all pretty cheap, readily available tests worldwide, but they all kind of push you in the direction of a cytokine storm.

And then once you've made that diagnosis and start treating them, they're pretty easy things to follow. As well as just looking at the patient, right? Like, is their fever going away? Are they off less pressors? Are their vent settings going down? All those things are valuable tools.

Dr. Schwartz:
So I have to say, I don't love the diagnostic criteria or the classification criteria. I think they have utility, I think they identify our really sickest patients, and I think they perform well in those populations. My bias is that those scores and those criteria tend to identify patients once they're really, really sick. And the best time to identify patients is before they're really, really sick. And I've many times been asked to see a patient and told, 'Well, their H score isn't very high, so I don't think that they could have HLH or macrophage activation syndrome.' And it turns out that they do, but they're just on the earlier end of that trend.

So I think many of us who see a lot of these patients—I also use Gestalt, for lack of a better word. But the things that I think about in my Gestalt are, I look at those counts, and I look at the cytopenias and the AST and the ALT, but I also really, really value that trend in ferritin. And so I see a lot of patients whose ferritins aren't hopefully yet in that 25,000–30,000 range, because by that time, they usually are quite sick. But they just might be a little bit earlier on the spectrum. And then we check some of our more sort of cytokine storm biomarkers, and they do seem to be relatively elevated.

And so I completely agree that all of these criteria were developed—they tend to perform well at identifying the patients who have MAS

or HLH within their specific diseases. I think that they miss some patients. Now, maybe some of those patients could do well with steroids without receiving targeted therapies in the first place, but I do think that they miss patients who are on the spectrum. And we're not going to completely understand what is the natural history of cytokine storm and what does cytokine storm look like in its totality if we don't maybe lower our threshold a little bit for identifying these patients.

Dr. Cron:
I'll also add that there's often a coagulopathy that ensues in patients with cytokine storms, and even simple things like a D-dimer, which are very sensitive but not all that specific, but should get you thinking along those lines. And in the same time, the fibrinogen, which goes up early often as a marker of inflammation, tends to get consumed when the coagulopathy worsens. So it's kind of a balance of the coagulopathy versus this acute-phase reactant fibrinogen going up. So when the fibrinogen starts trending down, even if it's in the normal range, that's often concerning, because it means the coagulopathy/MAS is often getting worse.

And at the same time, the erythrocyte sedimentation rate—another relatively simple test that can be done almost anywhere—often goes way up in inflammation, Right? It's a very non-specific marker of inflammation. But fibrinogen happens to be one of the proteins that's really responsible for sitting on the red cell and sinking it to drive the sed rate up. And so as the fibrinogen gets consumed in the coagulopathy, the sed rate tends to drop.

So in a patient who's getting sicker who, for example, the ferritin or CRP is going up but the sed rate is coming down, that usually is ominously bad. And so actually you can do a ratio of a ferritin to the erythrocyte sedimentation rate, and we did it primarily for Still disease patients, but you can use it beyond that too.

And that's a relatively simple test, and, for example, 11, right? So if you do it nanograms per ml of your ferritin and millimeters per hour of your erythrocyte sedimentation rate, if that ratio is over 11, there's a pretty good chance you might have a cytokine storm. So a real simple test of two tests that come back that are cheap and are relatively fast to just give you a feel for what's going on.

Dr. Schwartz:
Yeah, I think that's true. I mean, the main thing, again, is just like overreliance on any one criterion, on any one lab, on any one ratio, you're going to potentially miss some of these maybe less typical cases, or somebody who doesn't have Still disease or has it in a different context. And so what I would say is just sort of trend the labs you can trend, and if things are going in an ominous direction, or things are going in the wrong direction, to have a low threshold.

And I think there are now enough people out there who write about this and talk about this, and our emails are really pretty much all on our lab website. So physicians who really have a patient who they think might have cytokine storm and they need a second opinion from an expert, even over email with the identified data, I don't think any of us would say, Oh no, I'm not going to counsel you over email because you don't work at my hospital.

Moderator:
Yeah, you guys are such a wonderfully collaborative community. This has been so informative, all these explanations. Catching this diagnosis early, paying attention to the trends, not being over-reliant on one thing to tell you what's going on, I think is so helpful for the community to hear.

In closing, a little bit, what additional advice or context would you both feel like it's important for HCPs to know about these potential patients with MAS?

Dr. Schwartz:
So I think we haven't really talked that much, other than mentioning that targeted treatments are available and that they work. But just that when you catch these cytokine storms, if you get patients on appropriate therapies—if you get patients on therapies that block interleukin-1 and you do that early, you already have the potential to make a massive difference in your patient's mortality.

And if that doesn't work, you haven't sort of hit the end of the line. There are also therapies that directly or indirectly block interferon-gamma. There are emerging therapies, there are established therapies. There's sort of a lot of a tendency to sort of, especially in the community, you put patients on steroids and then maybe straight go straight to some of these less selective therapies. But that we do have an understanding of the pathobiology of this disease that allows us to target it and to treat it ways that can make massive differences in the mortality of these patients, and that the earlier we start those treatments, the better.

Moderator:
Thank you so much, Dr. Schwartz. Dr. Cron?

Dr. Cron:
Yeah. I mean, ditto that. I'm like a broken record on this: if you're sick enough to be in the hospital and you have a fever, even if you

know why you're in there, you are worthy of a serum ferritin.

I mean, it made a big difference to our hospital, for example. It took me a long time to do it and it took a change in leadership in some of the places in the hospital, but getting a serum ferritin added to, like, our sepsis protocol in the emergency department and/or the ICU has made a huge difference in the number of referrals we get to come see these kids. So get the serum ferritin, start thinking about it. So recognition I think is huge.

But in the end, high doses of glucocorticoids work really well. And a lot of times the intensive care docs or the infectious disease docs, or even us as rheumatologists, we're a little chicken to use them because if this is an infection that's driving the process—which it often is—is it going to make things worse from that perspective?

But if they're broadly covered by antibiotics, or if they've got like CMV and you're treating them with ganciclovir, for example, or something, you sometimes just have to resort to using glucocorticoids. And those tend to be typically available worldwide. If you're really stuck up against the wall, they're our best friends and our worst enemies, but they're really good at treating these cytokine storms.

Moderator:
Really appreciate it, both of you. We've covered a lot of information in this short amount of time so far, and I appreciate so much, both of you, taking the time to teach us more about MAS. I'm positive that your insights will be a helpful guide to our listeners as they suspect they might be dealing with this condition in their own practice.

Thanks to both of you for taking the time to be here with us today. Dr. Cron, Dr. Schwartz, I can't tell you how much we appreciate your valuable insights on this topic.

This has been another episode of *Investigating HLH today,* speaking about macrophage activation syndrome. I'm Adam Narloch, and thanks again for stopping by.

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