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Improving Diagnostic Accuracy in Systemic Mastocytosis

Announcer:
You're listening to *Clinician's Roundtable* on ReachMD, and this episode is sponsored by Blueprint Medicines, a Sanofi Company. Here's your host, Dr. Alexandria May.

Dr. May:
This is *Clinician's Roundtable* on ReachMD, and I'm Dr. Alexandria May. Joining me to talk about how we can address common misconceptions and improve diagnostic accuracy in systemic mastocytosis is Dr. Tracy George. She's the President and Chief Scientific Officer at ARUP Laboratories as well as a Professor of Pathology at the Spencer Fox Eccles School of Medicine at the University of Utah. Dr. George, welcome to the program.

Dr. George:
Thank you, Dr. May. I'm delighted to join you.

Dr. May:
Well, let's dive right in, Dr. George. How do you approach the common misconception that a normal or mildly elevated serum tryptase level can rule out systemic mastocytosis?

Dr. George:
So it can't. Let's be very clear. There have been multiple publications, including from myself at my institution, which have found that many patients with non-advanced systemic mastocytosis—primarily bone marrow mastocytosis and indolent systemic mastocytosis—have serum tryptase levels that are less than 20.

So if that's your screening criteria, you're going to miss a whole bunch of patients. So it's a big misconception. And you need to realize that you're going to have patients who have normal serum tryptase levels but will still have systemic mastocytosis.

Dr. May:
Even when initial testing appears reassuring, what clinical clues prompt you to continue evaluating for systemic mastocytosis?

Dr. George:
So there are a number of clinical clues. First of all, there are very characteristic skin lesions of mastocytosis. For those patients who are adults who have skin lesions that look like mastocytosis—and we recommend that a skin biopsy be performed in those situations—you need to stop; don't pass go. These patients actually do have systemic mastocytosis, and they need to proceed to have a bone marrow examination to figure out which subtype of systemic mastocytosis that they have, and they need to also have genetic testing for the KIT mutation and etc. to establish that diagnosis.

But that's just one thing. So then there are patients who may not have skin lesions of mastocytosis, but, for example, they have unexplained allergies, especially to hymenoptera. And so those patients also need to be explored further for systemic mastocytosis.

Then there's, for example, the middle-aged man who has osteoporosis or fragility fractures that are unexplained. That's a classic sign that you're probably dealing with systemic mastocytosis. And then there's a whole host of other symptoms that you can see across multiple organ systems, which are maybe less specific, but when you combine them together—you know, you've got the patient with fatigue, with unexplained diarrhea and cramping, and then maybe they also have osteoporosis, and they've got multiple food allergies—that's when you start thinking, Hey, I am concerned that this patient may have systemic mastocytosis, and we need to evaluate them for that.

Dr. May:
And you mentioned this briefly, but skin involvement can be another important clue. So when you encounter findings like biopsy-confirmed cutaneous mastocytosis, how does that influence your decision to pursue further evaluation?

Dr. George:
So there have been a number of studies that have shown that if you are an adult who has biopsy-proven skin findings of systemic mastocytosis, then overwhelmingly you will have systemic mastocytosis in the bone marrow and other organs. And so in that situation, I recommend proceeding straight to bone marrow biopsy and examination—definitely doing the serum tryptase level and KIT mutation analysis by a highly sensitive method and doing all of the pathology things that you need to do in the bone marrow examination. Your pathologist will take care of those things,

But it's so common, in fact, that when I have an adult patient with skin findings of mastocytosis, more than 96 percent of the time they have systemic mastocytosis. And if they don't and if the bone marrow is clean, then it could be a sampling error, honestly. And so then I'll recommend that we wait 6 to 12 months and then repeat the bone marrow biopsy.

Dr. May:
For those just joining us, this is *Clinician's Roundtable* on ReachMD. I'm Dr. Alexandria May, and I'm speaking with Dr. Tracy George about addressing challenges and misconceptions in systemic mastocytosis testing.

So, Dr. George, let's continue our conversation by zeroing in on diagnostic criteria. The World Health Organization and International Consensus Classification frameworks define systemic mastocytosis using a combination of major and minor criteria, including histopathologic findings, molecular markers, and biochemical signals. Since these criteria are intended to be applied together, can you tell us how you use them as a combined framework rather than relying on any single result?

Dr. George:
Yeah, absolutely. So the WHO and the ICC definitions for systemic mastocytosis are very similar. We have the major criterion: the presence of multifocal dense aggregates in the mast cells, which are defined by 15 or more mast cells and close approximation. Then there are the minor criteria. The minor criteria include a serum tryptase level of more than 20, a KIT D816V mutation or other activating mutation, of course, analyzed using a highly sensitive technique, aberrant mast cell morphology—that's spindle shape mast cells or immature mast cells, including 25 percent or more out of total mast cells showing that aberrant morphology—and then aberrant antigen expression on the mast cells—that is the presence of CD2 and/or CD25 and/or CD30 on mast cells.

So the major and minor criteria are exactly the same for WHO and ICC. What differs is how you apply them. So the WHO requires a presence of one major and at least one minor criteria to make the diagnosis of SM. The ICC allows you to make the definition of SM with only the presence of the major criteria, but there are some footnotes there. You still need to make sure that if your KIT mutation is negative, you've excluded morphologic mimics and other mutations that could be causing morphology that looks a lot like systemic mastocytosis, like alterations in PDGFR alpha or beta, FGFR1, and there's some other mutations and combinations that you can see for myeloid and lymphoid neoplasms with eosinophilia and these recurrent genetic abnormalities.

But I think what most of us use is the one major and the one minor or at least the three minor criteria. And indeed, most of these patients will meet those criteria right off the bat. It's only the patients with maybe very early indolent systemic mastocytosis and bone marrow mastocytosis who really don't have the major criterion where you're looking at just the minor criteria.

Dr. May:
As a follow up to that, when do you decide it's appropriate to move forward with additional testing, such as KIT mutation analysis or bone marrow biopsy?

Dr. George:
Yeah, that's a great question. So in my mind, if you are suspicious for systemic mastocytosis based on your patient's symptoms, then you need to do all of the analysis, right? Especially if you're going to go ahead and do bone marrow examination, then sending peripheral blood for highly sensitive KIT testing is a given as well as the serum tryptase level, and your pathologist will do the other analyses. So your pathologist will send flow and do an immunohistochemistry looking for an aberrant antigen expression on the mast cells. Your pathologist is going to be looking under the microscope and describing what those mast cells look like and quantitating the percent of mast cells on those bone marrow biopsies.

So, in my opinion, every patient deserves a diagnosis, and if you're going to do the diagnosis, then you need to investigate each of those criteria that I outlined for the WHO and ICC classification systems for systemic mastocytosis.

Dr. May:

Lastly, Dr. George, what strategies can help clinicians avoid premature diagnostic closure and ensure patients receive a timely and accurate diagnosis?

Dr. George:
So as I recommended, I think if you are looking for a diagnosis of systemic mastocytosis, you need to explore all the criteria. There are problems if you do, for example, an algorithmic approach where you say, 'you know what, I'm just going to look at the serum tryptase level and I'm only going to use 20.' We discussed that originally. Well, there's plenty of patients who have non-advanced systemic mastocytosis with serum tryptase levels of 20 or less. So you don't want to do that. Or let's say you go, 'you know what, I'm going to look for a KIT mutation.' But did you use a highly sensitive method? You really need to use a method that has a limit of detection down to 0.01 to 0.03 percent variant allele frequency, and I see plenty of patients where a less sensitive method was used.

Then, let's say you're suspicious, but you did the highly sensitive method. And it came back as negative. 'Oh no, my patient doesn't have systemic mastocytosis.' Well, there have been some really interesting studies out there, primarily from Dr. Alberto Orfao and his colleagues in Spain, where they found that there's discordance between KIT results in blood versus bone marrow. And what they found is that up to about 50 percent of the time for bone marrow mastocytosis—so that's the very minimal involvement in the bone marrow but still clonal—the blood is going to be negative, but the bone marrow is going to be positive for a KIT D816V mutation. So if you just are stopping at peripheral blood analysis for KIT, you're going to miss those patients. And 15 percent of the time, patients with indolent systemic mastocytosis, which is the most common subtype, are going to be negative in the blood and positive in the bone marrow. So for those patients for whom I'm still suspicious, I recommend repeating the highly sensitive KIT testing in the bone marrow if the peripheral blood is negative.

And then although more than 95 percent of your patients with systemic mastocytosis are going to have the KIT D816V mutation, there are still a few percent, less than five, who will have an alternative KIT mutation. Remember: our highly sensitive methods like digital droplet PCR will not detect those. So you need to do other techniques in order to look for those additional KIT mutations if you're sensitive.

And this is important, right? Because the type of mutation that you have drives the type of therapy that you should get. And we know that the vast majority of patients with these KIT mutations are insensitive to treatment with imatinib. And so that's why alternative TKIs have been developed for those patients.

Dr. May:
With those practical strategies in mind, I want to thank my guest, Dr. Tracy George, for joining me to discuss how we can more accurately identify systemic mastocytosis. Dr. George, it was great having you on the program.

Dr. George:
Thank you, Dr. May.

Announcer:
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