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Indolent Systemic Mastocytosis (ISM): Tools to Diagnose ISM

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Dr. Gotlib:
Welcome, listeners. My name is Jason Gotlib, and I'm from the Stanford Cancer Institute in Stanford, California. Welcome and real excited today to be able to talk with Dr. Cem Akin from the University of Michigan. And we're going to have a conversation about indolent systemic mastocytosis. So really hope that this provides substantial educational value regarding the diagnosis and treatment of this disease. Welcome, Cem.

Dr. Akin:
Thank you, Jason.

Dr. Gotlib:
This is CME on ReachMD.

So, Cem, what are the diagnostic criteria for systemic mastocytosis, and can you discuss some of the basic differences between the variants that comprise non-advanced systemic mastocytosis versus advanced systemic mastocytosis?

Dr. Akin:
Sure. So systemic mastocytosis is a disorder; it's a neoplastic disorder of the mast cell lineage, most of them associated with the KIT D816V activating point mutation. And in this disorder, mast cells accumulate in the bone marrow, as well as other internal organs and skin, and they cause different symptoms of mast cell activations, such as flushing, itching, gastrointestinal symptoms, sometimes cardiovascular symptoms. In this disorder, there could be different variants, as you touched on. There are so-called benign and malignant variants, and, essentially, the benign forms do not impact the life expectancy, but they do cause a lot of symptomatic impairment and reductions in quality of life.

So if you break it down into these 6 WHO variants, the most common variant is indolent systemic mastocytosis, which is seen in more than 70% of patients with systemic mastocytosis. And patients with this disorder, again, will have mast cell collections in the bone marrow but will not usually experience any shortened survival due to this disease but will need to be managed for the different symptoms caused by mast cell activation. And then the advanced variants are systemic mastocytosis within associated hematologic neoplasm. Those patients present with other usually myeloproliferative neoplasms which determines the life expectancy of these patients. Aggressive systemic mastocytosis, in which the mast cell infiltration is also associated with tissue dysfunction such as bone marrow failure, liver dysfunction, or splenomegaly or pathologic bone fractures, those patients can also have malabsorption with weight loss and so on and will have shortened life expectancy.

Dr. Gotlib:
Now, before we go into the workup of systemic mastocytosis, including the indolent form, can you touch on some of the presenting signs or symptoms of the disease? And, you know patients with mast cell disease may ultimately end up seeing multiple subspecialists, and I was wondering if you can talk about who these subspecialists are and why it can take sometimes months to years for the diagnosis to be correctly rendered in these patients.

Dr. Akin:
The average time to diagnosis from the onset of the symptoms, in my experience, is about 7 years, so these patients go from specialist to specialist without any diagnosis, unfortunately, because most physicians don't think about this diagnosis when they see a patient presenting with flushing or hypotensive syncope. So the most obvious physical examination finding to look for in a patient with mastocytosis, or suspected mastocytosis, is skin lesions. Skin lesions are present in more than 80% of the patients. So the problem becomes when the patient does not present with the skin lesions, so what symptoms should alert the physician to look for systemic mastocytosis and order that diagnostic procedure, which is the bone marrow biopsy and aspiration, to establish the diagnosis.

So those symptoms are typically flushing, itching, anaphylactic-type symptoms like hypotension, especially pre-syncopal or syncopal episodes, gastrointestinal symptoms, such as diarrhea, nausea, vomiting, bloating. So those are the main symptoms. As you could imagine, these patients could see a gastroenterologist. They could see a dermatologist. They could see an endocrinologist, especially because some patients may also have problems with osteoporosis and osteopenia before they are finally diagnosed. And allergists and immunologists and hematologists are usually the critical specialists to think about this diagnosis and perform the diagnostic procedures to establish or rule it out.

Dr. Gotlib:
So, you know, expanding upon that theme about diagnosis, Cem, can you touch on kind of the core elements of a diagnostic workup and what they mean?

Dr. Akin:
Yes, absolutely. So we diagnose mastocytosis based on World Health Organization's guidelines. So in order to be diagnosed with systemic mastocytosis**,** the patient needs to have either the major diagnostic criterium plus 1 of the 4 minor criteria or, in the absence of the major diagnostic criterium, 3 of the minor diagnostic criteria. So what are those? The major diagnostic criterium is multifocal dense mast cell infiltrates, consisting of more than 15 mast cells per infiltrate in the bone marrow biopsy, or another extracutaneous organ biopsy, but most often the bone marrow biopsy.

And then the minor criteria are 25% of the mast cells being spindle-shaped. The second minor criterium is the KIT mutation at codon 816. It is the most commonly encountered mutation, but there are other rare mutations that can be found in other regions of KIT, especially in younger patients, so KIT mutation is another minor criterium. And the third one is the immunophenotypic abnormalities of the mast cell. So normal mast cells express KIT, which is CD117, and high-affinity IGE receptor, which is very useful in determining the flow cytometrically, but you can also determine the mast cells by doing a tryptase staining on bone marrow biopsy sections immunohistochemically. So these mast cells, if they express also CD2, CD25, or CD30, one of these 3 molecules would satisfy the third minor diagnostic criterium. And then the last minor criterium is the elevated tryptase level. So tryptase is a fairly specific mast cell protease, and it can be used in diagnosis, as I mentioned before, in immunohistochemical staining. But it can also be measured in serum or plasma, and the level of tryptase directly correlates with the level of mast cell burden. Now, one interesting point to make here is that the mast cell burden does not necessarily correlate with the symptoms of mast cell disease. So we can see patients with very minimal increase in mast cell burden who may be highly symptomatic, and conversely, somebody with a tryptase level of 200, 300 may have very minimal symptoms. So it's also important to keep this in mind.

Dr. Gotlib:
For those just tuning in, you're listening to CME on ReachMD. I'm Jason Gotlib from the Stanford Cancer Institute, and here with me today is Dr. Cem Akin from the University of Michigan, and we're discussing the role of diagnostic tools in the management of indolent systemic mastocytosis.

So let me just kind of pivot a little bit, and that is sometimes it's very obvious with additional testing, or even at presentation, that a diagnosis of mast cell disease is likely, and based on the tryptase level, that it's more likely to be indolent disease. But can you just touch on, briefly, what is a differential diagnosis of a patient with indolent mast cell disease? Can you talk about other entities that are not anchored to increase numbers of mast cells per se – and maybe they are, but they don't maybe meet full criteria for systemic disease by WHO criteria?

Dr. Akin:
Yeah, so I think that's an important point. If somebody is presenting with signs and symptoms of mast cell activation, like flushing,

abdominal pain, diarrhea, presyncopal episodes, and so on, at the end of the day, you may or may not diagnose that patient with systemic mastocytosis. So it's important to be knowledgeable about the differential diagnoses. And the most common scenario that we see in a patient presenting with episodic mast cell activation symptoms is a diagnosis called "mast cell activation syndrome." In terms of the next step before going to the bone marrow biopsy, some physicians may want to check a peripheral blood D816V KIT mutation as the next screening assay. So that has to be done by a highly sensitive PCR [polymerase chain reaction]-based assay, like allele-specific PCR or digital droplet PCR, and I have to say that the next-generation sequencing technologies, or any technique based on sequencing, is unfortunately not sensitive enough, because we are talking about a somatic mutation that is represented only in a minor fraction of the cells, especially in the peripheral blood. So it is very important that the right test is used. You may want to consider checking this mutation in peripheral blood in a patient with an elevated tryptase level or in a patient presenting with hypotensive anaphylaxis or other signs and symptoms of systemic mastocytosis that we discussed earlier.

Dr. Gotlib:
Yeah, that's a great description of the workup and the diagnostic considerations, particularly KIT mutation testing, because that's so important to be able to identify the KIT D816V mutation because that does tailor our treatment according to available KIT inhibitors. Because certain inhibitors, such as imatinib, often are not useful on the disease.

You know, with that, let me segue to the issue of treatment and start with a general question. And that is, what are the goals of therapy in indolent systemic mast cell disease?

Dr. Akin:
The major goal of the treatment is to counteract the mast cell activation symptoms and to counteract the effects of the mediators. So that's the primary purpose. So we only start with anti-mediator treatment with antihistamines. We usually start with H1 and H2 antihistamines to counteract different symptoms, like flushing or itching or abdominal symptoms. And then there are other anti-mediator drugs, including leukotriene antagonists or cromolyn, that can be used in a stepwise fashion. And the problem is that not all patients respond well or completely to these anti-mediator drugs, and the question is, then, do we need to do something beyond the anti-mediator therapy for these patients? And there comes the tyrosine kinase inhibitors into the picture. As you mentioned, because KIT is a tyrosine kinase and D816V mutation causes the tyrosine kinase to be activated, the natural way of thinking is to use a drug that specifically inhibits D816V KIT mutation. Now, a couple of these drugs – midostaurin and avapritinib – have been approved by FDA for treatment of advanced systemic mastocytosis, but there is nothing approved by FDA at this point that can be used for treatment of indolent systemic mastocytosis.

So having said that, there are a few agents that are specific KIT D816V inhibitors that are in clinical trials for indolent disease. The first one, which is the one that is farthest along in the clinical trial stage, is avapritinib. Avapritinib, actually, there's a trial called PIONEER; the results indicate that the drug is effective in reducing the symptoms in indolent mastocytosis patients as compared to placebo. It reduces the skin lesions, and this improvement in skin lesions and symptom reduction is also associated with improvement in markers of mast cell burden, such as the tryptase levels, KIT D816V allele burden, and the bone marrow mast cell burden. So that could be a treatment modality that changes the way that we think about treatment of indolent mastocytosis as not only targeting the mediators, but also targeting the mast cell burden itself in the future.

Dr. Gotlib:
Oh, that's great. And let me ask you, before we wrap up Cem, can you share your one take-home message with the audience?

Dr. Akin:
Sure. I think good skin examination and especially consider mastocytosis in patients presenting with hypotensive anaphylaxis without urticaria or angioedema. And check for KIT D816V mutation in peripheral blood in those patients if you have a high suspicion and if you don't have any other cause for these symptoms.

Dr. Gotlib:
Well, that's an important point to leave on, and with that, I want to thank our audience for listening in, and thank you, Cem, for joining me and for sharing all of your valuable insights. It was really wonderful speaking to you today.

Dr. Akin:
It was a pleasure, Jason. Thank you.

Announcer:
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