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A Deep Dive into the Diagnostic Process for ISM

Announcer:
You're listening *Project Oncology* on ReachMD, and this episode is sponsored by Blueprint Medicines. Here's your host, Dr. Charles Turck.

Dr. Turck:
This is *Project Oncology* on ReachMD, and I'm Dr. Charles Turck. Here with me today to dive into the diagnostic process for indolent systemic mastocytosis, or ISM for short, is Dr. Cela Ustun. In addition to being a Professor in the Department of Internal Medicine, he's also the Coleman Foundation Chair of Blood and Bone Marrow Transplant and Section Chief of Bone Marrow and Stem Cell Transplant at Rush University Medical Center in Chicago. Dr. Ustun, welcome to the program.

Dr. Ustun:
Thank you for having me.

Dr. Turck:
Now before we get into the diagnostic aspects of ISM, Dr. Ustun, would you describe its underlying pathology at a molecular level?

Dr. Ustun:
Indolent SM is a disease of uncontrolled neoplastic mast cells growing and causing a lot of symptom burdens. The molecular pathology of ISM has been really well defined. There is a mutation in the gene tyrosine kinase receptor called KIT, specifically at the region exon 17, KIT 816V mutation. This mutation makes the mast cells grow and gives them survival advantage. And as a result of it, the mast cells keep growing in organs. And if it is in the skin, the patients can see it. There are dark spots, we call it urticaria pigmentosa, and this grows and increases over time. As the mast cells grow, obviously the symptom burden likely increases.

Dr. Turck:
Now in relation to that underlying pathology, what are hallmark signs and symptoms that would raise suspicion of a diagnosis of ISM?

Dr. Ustun:
Yeah, it's a very good question, and unfortunately, many patients go through years before they have appropriate diagnosis. It is a difficult diagnosis because it's an orphan disease, it's not very common, and it can affect many organs and organ systems, and therefore can cause symptoms of multiple body parts, if you will. And patients can be seeing GI tract doctor for mastocytosis or a cardiologist because of palpitation, and they can be seeing an allergist or immunologist because of hypersensitivity reactions and anaphylaxis or can see hematologists because of some blood type abnormalities or generally, hematologists come in for making diagnosis. So by having these multiple symptoms affecting multiple organs, it is hard to know it's caused by one disease, and everybody looks different. It's specific diseases instead of one common disease, so therefore, it can be missed for years unfortunately. Like I said, GI tract, skin reactions, and cardiac symptoms are the most important symptoms. Tiredness is very common, brain fog, and anxiety can affect their daily life too, and they may be seeing neurologists or psychiatrists for that reason.

Dr. Turck:
Now given the signs and symptoms of this disease are nonspecific, would you tell us more about the common challenges clinicians face when diagnosing ISM and the other conditions it's often confused with on the differential diagnosis? What kind of patient presentation would lead you to dig deeper into whether ISM is a potential diagnosis?

Dr. Ustun:

Very good question. So I am in a center that I am generally referred by doctors, but patients can also refer themselves to me. If they have had the symptoms I mentioned—GI tract symptoms, skin reactions, and cardiac symptoms—and have not found any specific disease, the patients start thinking about, do I have indolent systemic mastocytosis? And I also suggest my colleagues to think at that time to look for systemic mastocytosis.

Skin lesions are a very specific. Thankfully, if it is in the skin and if someone has seen indolent systemic mastocytosis skin lesions, once you see it, you diagnose it. It's very easy. The GI doctors may do endoscopies and biopsies. And the biopsy by chance, if someone looked at the stained mast cells, they can see increased mast cells. However, the mast cells, as I mentioned, need to be stained specifically, even in the bone marrow biopsies. And a pathologist needs to know what they are looking for, which is mast cells. And mast cell staining is different than regular staining. And in some of the advanced cases—not in indolent SM, but in advanced cases—other hematological malignancies may obscure mast cells and therefore cause other diagnostic challenges. So I think the key is clinical suspicion and ordering serum tryptase. Serum tryptase is a good marker. If it is greater than 12 and if it is particularly greater than 20, I will certainly look into indolent systemic mastocytosis.

Dr. Turck:
For those just tuning in, this is *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Cela Ustun about the diagnostic process for indolent systemic mastocytosis, or ISM.

So, Dr. Ustun, you started getting into this a little bit, but given the challenges that we've been discussing, what more do we need to confirm a diagnosis of ISM?

Dr. Ustun:
So when I have a patient referred by my colleagues or a patient comes directly, what I do is go through the history, obviously, and then diagnosis. WHO criterias are very specific, and to me, easy and very nicely defined and described. So we have to show that this is neoplastic and they're abnormal mast cells in tissues. When we say tissues—and we said mast cells are in tissues, and perhaps in every single tissue—if we do get biopsy samples from tissues, we can diagnose ISM. However, as you know well, the safety issues will prevent us doing biopsies for many, many organs. But as a hematologist, we do bone marrow biopsies. And bone marrow biopsies are relatively safe, and with the current pain medications and anesthetics, it can be done without any pain. So the bone marrow biopsies are routine to show the major criterion of WHO diagnosis of ISM, which is aggregates of mast cells, generally more than 15 mast cells in the tissue. And once a pathologist stains for these neoplastic mast cells, they will recognize these aggregates of mast cells, and they are generally abnormal looking. The normal mast cells are round mast cells, and in systemic mastocytosis, they become spindle shaped. They also carry aberrant expression of CD2, CD25, and CD30 presentations on their surface, which is again aberrant. It shouldn't have that. KIT D816V mutation, I want to talk about a little bit more, and then serum tryptase. If anyone has one major, one minor, or if no major, three minor criteria will make diagnosis of ISM.

Dr. Turck:
Now with those considerations in mind, is there anything else that we should know about applying the WHO criteria to diagnose ISM?

Dr. Ustun:
As I mentioned, it's really easy and very clear. Tissue biopsy is important, which is almost always bone marrow biopsy. That's why my colleagues refer to me. They generally say the patient has cutaneous mastocytosis, the mast cells in the skin. The question becomes, do they have systemic mastocytosis as well? To confirm or rule that out, we have to have tissue biopsy, which is bone marrow. So I explain to patients why we are doing bone marrow biopsy. And what are we ordering from the bone biopsy? When we order bone marrow biopsy, we make sure that pathologists know this is for mastocytosis, so the staining is different. The flow cytometry generally can be negative, so I caution my colleagues not to rely on flow cytometry much. And at the same time, KIT mutation is sent from the bone marrow biopsy. The recent molecular techniques have really evolved dramatically that there are very sensitive KIT D816V mutation-specific PCR tests. One is digital droplet; the other one is double allelic PCR. Both of them are incredibly sensitive. And if someone is hesitant to do bone marrow biopsy, the patient doesn't want to whatsoever, I will send this test from peripheral blood. They are sensitive enough to come back positive and very reliably.

Dr. Turck:
And as our program comes to a close, Dr. Ustun, do you have any final recommendations on how we can improve the diagnostic accuracy of ISM?

Dr. Ustun:
I think, again, knowing the mutation analysis is very important. If my colleague is ordering an NGS, next-generation sequencing, for KIT mutation, and if it comes back negative, it's possibly false negative if someone is likely to have SM. So it should not deter them to or

make them conclude that the patient doesn't have SM. So it's very important what type of molecular testing is being ordered, communicating with the pathologist, and communicating with the referring doctors. If I have a patient that I diagnose with systemic mastocytosis and they have some abnormal skin lesions that I don't know or doesn't look like mast cells, I refer to my mast cell expert dermatologist. I always refer my patients to allergists to manage their allergic reactions and educate them about allergies and hypersensitive reactions. So these patients really need a couple of or a few doctors to manage them and collaborate in managing them. It's a very interesting disease; patients are getting much more educated, and I see that doctors are now much more knowledgeable about this rare disease.

Dr. Turck:
Well, as those reflections bring us to the end of today's program, I want to thank my guest, Dr. Cela Ustun, for helping us navigate the challenges associated with diagnosing indolent systemic mastocytosis. Dr. Ustun, it was a pleasure speaking with you today.

Dr. Ustun:
Thanks so much.

Announcer:
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