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Is it Nonresponsive/Progressive ISM?

Announcer:
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Dr. Rein:
Hi, everyone. This is CME on ReachMD. My name is Lindsay Rein, and I'm joined today with Dr. Tracy George, and we're going to start our discussion today with a case.

And so I have a 52-year-old female patient who has a diagnosis of indolent systemic mastocytosis. So upon initial presentation, this patient came in after having had an anaphylactic reaction to an insect bite. Also, at that time, had some associated gastrointestinal symptoms, so some food intolerance, reflux disease, and then associated diarrhea. And this was all in her mid-40s. So at that point in time, a KIT mutation assay was sent and, interestingly, this was negative, although, of note, this was not done by a sensitive assay.

Dr. George:
Yeah, it sounds like a really interesting case, Lindsay. I mean, obviously, as a pathologist, I need a bone marrow so I can meet the major and/or minor criteria.

So the first thing to do is to get a sensitive assay, like droplet digital PCR or ASO quantitative PCR, so that you can look in the patient's peripheral blood and/or bone marrow. And I bring up the bone marrow because this patient doesn't sound as much like indolent systemic mastocytosis as they sound like bone marrow mastocytosis, which is a new either entity or clinical variant, depending on if you do the WHO or ICC classification, which has a really great prognosis. And these are patients who have bone marrow involvement only without skin lesions.

But what's really interesting is that Alberto Orfao's group in Spain published a nice series of patients where they looked for KIT D816V mutation using sensitive methods, and they compared blood versus bone marrow.

And what they found is that, although in advanced SM blood and bone marrow were very concordant, when you start looking at the nonadvanced SM, specifically indolent systemic mastocytosis and bone marrow mastocytosis, you start seeing discordance.

Dr. Rein:
And this discussion made me think of some data that was recently presented at the ASH meeting in 2024 looking at, specifically, within the PIONEER study. So this was a phase 2 study for indolent systemic mastocytosis. Within that population, looking at the assays that were utilized to detect KIT mutations, because there was, in that subset, some patients who were negative, who on more sensitive assays were noted to actually be positive for KIT mutations.

So just to continue with this case, after confirmation of diagnosis, was treated with various mast cell stabilizing agents. So H1/H2 blockers, leukotriene inhibitors, some cromolyn. Initially, found that to be quite helpful and then, unfortunately, over time, really developed a progression of symptoms despite stable dosing of these, what we call, best standard care medications.

So at this particular point in time from a path perspective, what additional testing, if any, would you recommend in patients who seem to

progress despite therapies?

Dr. George:
And so some of it comes back to basics, right? Is the serum tryptase level rising? If the patient is KIT D816V positive, is their KIT VAF increasing? Have they developed new laboratory findings, like just the CBC and metabolic panel, and then also liver function tests since mast cells like to go to bone marrow, spleen, liver, skin, among other findings. And then alkaline phosphatase is really helpful.

And then, obviously, as a pathologist, I'm going to tell you get another bone marrow and see what the mast cell burden is doing. But this is also a patient where I would start thinking about doing a myeloid mutation panel by NGS, right? Because I want to know –

Dr. Rein:
Absolutely.

Dr. George:
Is it just KIT mutated only, or is this a multimutated neoplasm and has additional mutations, which as you know can affect prognosis.

Dr. Rein:
Yeah, absolutely. I think that's a huge key point, is where does this myeloid NGS really come into play? So really in my mind, not from a diagnostic perspective, because as we talked about, those sensitive assays really are better at detecting the KIT mutations, but it's really helpful from a clinician's perspective to see what additional clonal evolution is happening, if any, what we may be able to glean from additional mutations. Again, really interesting data that's been presented. I think the AAAAI meeting in 2024, again, looking within the context of the PIONEER study at VAF mutational burden for c-KIT.

And patients who were above 6% in terms of frequency perhaps had higher-risk features in the context of indolent systemic mastocytosis as opposed to patients with a lower VAF.

Dr. George:
And what was very interesting is that in these patients who started off at 25 mg/day with avapritinib, over time, in a subset of patients who had this higher KIT VAF in the blood, you saw increasing mast cells on their aspirate smears and also increasing mast cell burden in the biopsy. And so the question is, what does this mean? And my understanding is that those patients then, some of them, went on to higher doses of avapritinib, 50 mg/day, I believe.

Dr. Rein:
For this particular patient we did opt to initiate avapritinib again, which, based on the PIONEER data, showed improvement in mast cell burden by various measures in patients with indolent SM, as well as markers of symptom burden and quality of life.

Dr. George:
You're familiar with the data, but for our audience, what we see is marked decreases in the mast cell burden in the bone marrow biopsy. We also see loss of aberrant antigen markers, like CD25 and CD30. And then, interestingly, the mast cell morphology also reverts back to a normal morphology.

Dr. Rein:
Thank you, Tracy, for this wonderful discussion. This is a fascinating case, and from a clinician perspective, again, really helpful to hear how we can better get to a diagnosis in these patients and perhaps utilize some of these assays in development to really better treat our patients.

Announcer:
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