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Accurate Diagnosis and Management of Hereditary Alpha Tryptasemia

Announcer:
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Dr. Boggs:
This is CME on ReachMD. I'm Dr. Nathan Boggs. Joining me today is Dr. Tracy George. Let's start our discussion with a case.

A 34-year-old male dive instructor presented to an allergist following an episode of syncope and flushing that occurred 20 days prior while preparing for a dive in a community swimming pool. The episode began while he was organizing equipment prior to the class. He described the sensation of warmth and lightheadedness, followed by tunnel vision. He noted to the allergist that emergency medical services arrived while he was unconscious. He was told that EMS identified low blood pressure, and they subsequently started intravenous fluids while en route to the emergency department. He awoke in the ambulance and was told that his blood pressure had improved by the time he had arrived to the ED. The ED physician noted that he had a normal EKG, negative troponins, and normal echocardiogram.

The patient showed the allergist the lab results from the ED on his smartphone. The allergist noted that the ED physician ordered tryptase, which was 75 ng/mL, and this result returned several days after the ED visit. The patient had consumed no food within 2 hours of the event. The patient revealed a concern about this event happening again while underwater.

Review of symptoms revealed monthly episodes of flushing and lightheadedness lasting 4 hours for the past 5 years that required the patient to lie down. Medical history was notable for an L2 compression deformity, requiring a lumbar spinal fusion 2 years ago.

Physical exam revealed no skin lesions and no palpable spleen or liver. The allergist obtained a baseline serum tryptase that was 17 ng/mL, and a next-generation sequencing panel of blood, which included the KIT gene, found no pathogenic variants.

So, Dr. George, what are your thoughts about this case? Where would you start with the diagnostic evaluation?

Dr. George:
I think you do need to start with some of the basics, which is like a CBC with metabolic panel, liver function tests, and alkaline phosphatase. The basal serum tryptase level, if I recall correctly, is a little bit below 20, and then after the event it was markedly elevated. And so my differential diagnosis at this point is I'm thinking about systemic mastocytosis, which you can talk more about, Nate. But I'm also really worried about hereditary alpha tryptasemia.

So first off, you need to repeat the peripheral blood for KIT D816V. I know NGS is sensitive, but it's not as sensitive as the assays that are performed by digital droplet PCR or ASO quantitative PCR. Those are a magnitude more sensitive. So just getting that negative NGS by peripheral blood, you still could miss a positive KIT D816V.

The other thing, in terms of HAT, you want to do tryptase genotyping by digital droplet PCR. And then just going back to the lumbar fusion and kind of the bone history, I just would go back and see if he had DXA just to rule out, like, osteoporosis.

Would you do anything else?

Dr. Boggs:
I think the tryptase genotyping is probably the most important test from my perspective, but most likely this person would end up getting a bone marrow and becoming one of your patients in your microscope either way.

If the tryptase genotyping came back normal, it would really raise the level of confidence that we have that there's a high likelihood of SM being present.

Dr. George:
I do think a bone marrow examination is important if you're going to totally exclude systemic mastocytosis. On the aspirate smear, it's going to be important that flow cytometry is performed, looking specifically for mast cells. So the lab has to make sure that they have expertise in looking at mast cells. You're also going to want to do a karyotype off the bone marrow aspirate, and as well as I would extract-and-hold for any NGS testing, if you decide to do that off the aspirate. And then on the bone marrow biopsy, you're going to do the evaluation for mast cells using immunohistochemistry. You want to use a panel. I like KIT or CD117. It's the brightest in mast cells, very easy to see, so you can look for aggregates or increased interstitial mast cells. You'll also want to get a mast cell tryptase stain, which is the most specific marker. And then you need to look for aberrancy in mast cells, and so that's CD25 and CD30. I prefer to look for CD2 via flow cytometry, not per immunohistochemistry. So I think that's going to be important as well as doing special stains.

Nate, how would you establish a diagnosis of systemic mastocytosis based on all this testing?

Dr. Boggs:
I guess probably in the community, I think the most beneficial thing is if the hematopathologist and the allergist work together to kind of ensure that all the appropriate testing is kind of teed up and ready to go. In terms of the subtype, this person probably would – I think we're both probably thinking of the same subtype, but probably bone marrow mastocytosis given the absence of the skin lesions.

Dr. George:
You raise a really great point. This doesn't seem like indolent systemic mastocytosis per se; it really sounds more like bone marrow mastocytosis. And I almost forgot that you will want to repeat the KIT D816V testing on the bone marrow. And that's specifically because in bone marrow mastocytosis, there can be a discordance in KIT testing in blood versus bone marrow wherein up to 50% of those patients, they can be negative for KIT D816V in the blood but positive for KIT D816V in the bone marrow when you use a sensitive technique like ddPCR or ASO quantitative PCR.

So, Nate, how would you treat this patient depending on if they have ISM and HAT, with or without HAT, or just HAT alone?

Dr. Boggs:
So, Tracy, in terms of the treatment of systemic mastocytosis, TKIs are really becoming the mainstay of treatments for non-advanced SM and for advanced SM. And in particular, as an allergist, as someone who predominantly sees patients with indolent SM, I think, for instance, the PIONEER study with low-dosed avapritinib showed patients who have chronic daily symptoms that are moderate or severe can take avapritinib, and after time, their symptoms improve substantially and their quality of life improves substantially.

And as we talked about, the tryptase values will decrease on tyrosine kinase inhibitors, including avapritinib, and the KIT D816B variant allele frequency will also decrease on avapritinib.

Dr. George:
Yeah, the data also shows that the mast cell burden decreases in those patients who are on avapritinib. And interestingly, they lose expression of CD25 and CD30 and they start to normalize their morphology, going from spindle-shaped to more round, well-differentiated mast cells.

Dr. Boggs:
That's very cool, yeah.

So I think that probably wraps up this case. I appreciate this conversation and thank you to the people who are listening.

Announcer:
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