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Released: 02/28/2025
Valid until: 02/28/2026
Time needed to complete: 38m

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Diagnosis and Treatment of Systemic Mastocytosis With an Associated Hematologic Neoplasm

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Dr. Rein:
This is CME on ReachMD. My name is Lindsay Rein, and again, Dr. Tracy George joining me today to talk about a case.

So this time I have a particularly interesting 83-year-old female who came to my clinic for evaluation. This particular patient had some pretty mild anemia, thrombocytosis, with the platelet count around 600,000, and an enlarged spleen. Interestingly, with this particular patient, she had had a macular rash that had been intermittently present for years, although really never had that worked up. And we went ahead and did a bone marrow biopsy.

And so interestingly, this particular marrow was hypercellular, so 80% cellularity, with some multilineage dysplasia. There was some areas of patchy mild to moderate fibrosis, so MF1, maybe a few areas of MF2, and really no increase in blasts. And then, interestingly, on this particular marrow, there was an atypical mast cell infiltrate, and this was involving approximately 20% of the marrow space. And in these marrows, these mast cells, we saw the aberrant expression of both CD2 and CD25.

Dr. George:
Right. So I mean, these findings you've described are classic for systemic mastocytosis associated with a myeloid neoplasm, and so the myeloid neoplasm I'm thinking about is some sort of myeloproliferative neoplasm just because of that thrombocytosis and knowing that any of the MPNs can present with thrombocytosis. And you've got some myelofibrosis, right? So don't pass go, time to do NGS panel for myeloid mutations looking for a driver mutation. Is it JAK2 positive, or is there something else going on?

The other things that you need to do, I find, on any myeloid neoplasm is you need to get an iron stain – always very important – looking for ringed sideroblasts. The fact that you've got multilineage dysplasia, that makes me think we've got to expand the differential diagnosis to an MDS/MPN. So, again, we're going to want to characterize the dysplasia, especially for the megakaryocytes.

And then from the mast cell perspective, I mean, knowing you, Lindsay, you would have already gotten a serum tryptase level and we would definitely have done a high-sensitivity KIT assay in blood and bone marrow. So it's quantitative PCR, either via ddPCR or ASO PCR. And then, of course, I mean, any heme patients would have definitely had a CBC and a metabolic panel. You've got to add on the liver function tests because mast cells can involve the liver. And you need to do an alkaline phosphatase as well.

And then you get a bone marrow. You've got to look for an abnormal karyotype, and that's the data that came out of Andreas Reiter's lab that showed those patients with an SM-AHN, a subset of those have an abnormal karyotype. And in fact, if you have an abnormal karyotype in that setting, you've got SM-AHN. So that's kind of basic myeloid neoplasm workup.

Dr. Rein:
As you said, we got the sensitive assay, the ddPCR, and that was, in fact, positive for the c-KIT mutation. Interestingly, when you look at

the VAF, it was about 11.9%, 12%, so a reasonably high frequency there. We sent a myeloid NGS panel and a lot of abnormalities, interestingly, on the panel.

So a karyotype was normal. A FISH MDS was also normal. And then when we sent a tryptase for this patient, it was over 200. So a significantly elevated tryptase within the context of this particular patient.

And interestingly, you mentioned the importance of CMP, looking at liver function tests and alkaline phosphatase. And so they were all abnormal across the board. So this patient had a transaminitis and also had an elevated alkaline phosphatase. And so in this particular patient, the final diagnosis, what we think is that this is potentially consistent with an MDS/MPN, and based on the classification would be MDS/MPN with SF3B1 and thrombocytosis. And then also in the setting of a concurrent systemic mastocytosis, and so SM-AHN.

We used to call SM-AHN "SM-AHN," associated hematologic neoplasm, and now we, based on what criteria you look at, we actually call it SM-AMN. And so from a path perspective, has that really changed anything that you do or anything that you look at, or is it just a difference in the classification?

Dr. George:
So I see it as a difference in the classification. I mean, we've always known that among the SM-AHNs, the AHNs, like 80% of the time or more, are a myeloid neoplasm. And they're MPS and MPNs, usually chronic myelomonocytic leukemia, but they can be AML, they can be MDS, they can a straight old MPN. And they are usually clonally related to the SM.

So there's been really nice studies that have come out of Austria and Germany and other places as well where if you look for mutations, you're going to find them in both components of the disease. And so you can find the KIT mutation in both components. Or let's say you've got an AML with 8;21, you could look with FISH with 8;21, and you'll find it in both components of the disease. Whereas what we see with plasma cell neoplasms and lymphomas or CLLs or something like that, is usually they are not clonally related; it's just 2 separate neoplasms. Although, there have been rare cases that have been described where they are clonally related. So, for me, it doesn't make a difference.

Now, when we had a big pathology academic meeting for the Society of Hematopathology back in 2019 in Arizona and we talked about mastocytosis. And so what we try and do is to grade each component. So we diagnose the myeloid neoplasm, in this case, just like you did, using WHO or ICC criteria. And then we look at the SM component and we'll classify it, or at least we try. And that's harder to do because you've got this associated myeloid neoplasm also present in the bone marrow. But the fact that your mast cell infiltrate is 20%, that's much more likely to be an ISM. Whereas I find if it's 40% or more or you've got increased atypical mast cells in the aspirate smear and it's starting to increase over 5%, that's more likely to be an ASM, for example. So based on this, it seems to me that your mast cell component, your SM, is more likely an ISM and is probably not driving diseases much in this patient as the myeloid neoplasm.

Dr. Rein:
This is really the key point, I think, to this. As clinicians, how do we make that decision of what needs to be treated? So do we treat the myeloid neoplasm component and do we approach it from that perspective, or do we really treat this from the mastocytosis perspective?

Dr. George:
What's really interesting, too, is we're just looking at the bone marrow, but obviously these patients have other areas of involvement. It can be very tricky to tease out.

And with the papers that have come out from the clinical trials in advanced systemic mastocytosis, we know that you can get the mast cell component with either midostaurin or avapritinib down really low. And just leaving you, then, the myeloid neoplasm to treat, which is interesting because sometimes the myeloid neoplasms are difficult to treat, and you know you can maybe knock the blast count down, but you're not going to eliminate the underlying clones unless you go to transplant.

Dr. Rein:
Well, thank you, everybody, for your attention today. We appreciate your time and hope that you can utilize some of this information in the context of your clinical practice.

Announcer:
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