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https://reachmd.com/programs/cme/managing-indolent-systemic-mastocytosis-a-multidisciplinary-case-review/18089/

Released: 04/24/2024
Valid until: 04/24/2025
Time needed to complete: 30 minutes

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Managing Indolent Systemic Mastocytosis: A Multidisciplinary Case Review

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[CHAPTER 1]

Dr. Akin:
Systemic mastocytosis is a heterogeneous group of disorders characterized by increases in numbers of aberrant mast cells and their activity. Patients with the indolent form, or ISM, frequently report a symptom burden disproportionate to a measurable disease burden. Diagnosis and treatment of ISM requires the expertise of a multidisciplinary team, including allergists, hematologists, and gastroenterologists. Today, we will be presenting 2 unique ISM cases, stressing first the importance of the multidisciplinary team in managing ISM, and second, how the expansion of a novel TKI [tyrosine kinase inhibitor] from its original approval in advanced systemic mastocytosis into the indolent space may help clinicians optimize outcomes for their patients.

This is CME on ReachMD, and I'm Dr. Cem Akin. I'd like to welcome my colleague, Dr. Dan DeAngelo, to our case discussion today, where we'll address this exciting clinical development.

Dr. DeAngelo:
Thank you very much. I'm glad to be here.

Dr. Akin:
Thank you, Dr. DeAngelo. I'll take the first case. Let's look at a 55-year-old female who's presenting with a 5-year history of maculopapular hyperpigmented skin lesions covering most of her chest, abdomen, and upper parts of her legs. These lesions get red and itchy with friction and after hot showers. In addition, she has episodes of facial and upper body flushing several times a week, lasting for about 15 to 30 minutes, and these episodes are associated with tachycardia and lightheadedness, sometimes requiring her to sit down or lay down. She also reports episodes of abdominal cramping and diarrhea alternating with constipation. She has word-finding difficulties, which she reports as brain fog. Three years prior to her presentation, she was stung by a wasp and passed out. Workup to date included a skin biopsy, which showed increased mast cells in upper dermis, consistent with urticaria pigmentosa or mastocytosis lesions in the skin. A serum tryptase at her baseline was elevated at 45 ng/mL. And, for reference, a normal tryptase is considered less than 11.5 ng/mL. And her complete blood count with differential was normal.

Upon diagnosis of mastocytosis in the skin, she was placed on cetirizine at 10 mg daily, famotidine 20 mg once daily, and oral cromolyn sodium 200 mg 4 times daily, and was prescribed a self-injectable epinephrine for her possible wasp venom reaction.

While these medications helped improve the severity of her itching, she is still experiencing recurrent flushing and abdominal pain several times a week, which is affecting her quality of life due to unpredictable nature of these episodes.

So at this point I will outline my approach to this patient. First of all, this is an adult patient presenting with skin lesions, and we know that the great majority of adult patients with skin lesions have what we call systemic mastocytosis, which is presence of systemic disease in the bone marrow. So the first thing that I would discuss with this patient is referral to a hematologist for a bone marrow biopsy to establish the diagnosis and to look for the World Health Organization criteria for systemic mastocytosis.

From the allergist standpoint, this patient has many symptoms of mast cell activation and mediator release, and her treatment would need to be optimized. And in order to optimize her treatment, we follow a similar approach to treatment of chronic urticaria. For example, sometimes going up on the doses of H1 antihistamines as needed and make sure that she is also on an H2 antihistamine and a mast cell stabilizer, such as cromolyn, if needed. From the gastrointestinal standpoint, we would consider endoscopy after a gastroenterology referral if her abdominal symptoms and diarrhea are not responsive to initial treatment. And finally, from the endocrine standpoint we know that about 1 out of 3 patients with mastocytosis may present with osteoporosis, and we always include a bone densitometry DEXA scan in our initial workup. And if this shows osteoporosis, an opinion from an endocrinologist would be a good idea.

In terms of the initial laboratory workup, I routinely check a complete blood count with differential to rule out presence of another hematologic disorder. Bone densitometry, as I mentioned, and a peripheral blood *KIT* D816V mutation by using a highly sensitive method such as allele-specific PCR or digital droplet PCR. And this is not only important for diagnosis, but also for prognostic purposes because a variant allele fraction should be done if it is possible in the laboratory, not only just presence or absence of the mutation, but what percentage of the *KIT* alleles contain this *KIT* D816V mutation, which is a target of avapritinib. And if it is greater than 10%, for example, those patients may be classified as having smoldering systemic mastocytosis and may have a higher likelihood of advancing to a more advanced variant such as a variant associated with hematologic disorders or aggressive systemic mastocytosis.

In terms of other workup, I mentioned endoscopy, EGD [esophagogastroduodenoscopy], or colonoscopy. So these are usually evaluated on random biopsies with staining for CD117 and CD25 on gastrointestinal biopsies. And also, because of the question on wasp venom allergy, an allergy workup should be initiated with blood and skin allergy testing for bee or wasp venoms, and the patient should be on venom immunotherapy for desensitization if she's found to have these allergies.

Dr. DeAngelo what is your take on this case, and how do we make sure that this patient has indolent disease and not a more advanced variant?

Dr. DeAngelo:
Thank you, Cem. That was a wonderful review and really thorough diagnostic evaluation. I guess, as a hematologist, I would add that it's really important to review the peripheral blood smear to make sure that there's no additional cells or immature cells. And the one thing that I would add is to make sure that the hematopathologist looks at the non-mast cell component. As you know, there are frequent cases of SM-AHN [systemic mastocytosis with an associated hematological neoplasm] where there's an additional hematologic neoplasm and sometimes that can be missed. The referral goes in, I'm ruling out a patient for systemic mastocytosis, and that's what the pathologist focuses on. And in addition, an NGS [next-generation sequencing] profile, which is much more common nowadays than it was when we first started working together, in order to look at additional mutations that may be present to help figure out whether the patient has a more advanced form of systemic mastocytosis.

Dr. Akin
Thank you, Dr. DeAngelo. So this patient appears to have failed anti-mediator therapy because the patient is still symptomatic despite being on multiple anti-mediator therapies. So at this point I think it would be appropriate to bring up the next step in managing this patient, which would be the use of a cytoreductive agent, avapritinib, as it remains the only cytoreductive tyrosine kinase inhibitor that is approved by FDA for treatment of indolent systemic mastocytosis. It is a selective D816V *KIT* inhibitor, and in the clinical trial called PIONEER, it has shown significant benefits in improving skin and other symptoms, as well as reducing the mast cell burden-related surrogate disease markers.

I think, as you know, avapritinib has been approved also for advanced disease at higher doses, but the dosage that is approved for treatment of indolent disease is much lower, 25 mg as opposed to 200 mg. And I think it's important to recognize the side effects that were noted in the advanced disease trials, which I'm sure you will touch on. But with the 25 mg dosing we have not seen any serious adverse events that were noted in the advanced trials. And the most common adverse events were actually related to peripheral edema or eyelid edema.

The most impressive reduction in symptom scores occurred in the skin domain, but there were also reductions in neurocognitive domains like brain fog, headaches, as well as the gastrointestinal domains.

In terms of the surrogate marker reductions, both serum tryptase and peripheral blood variant allele fraction of the *KIT* mutation were reduced significantly. For example, 50% reduction in serum tryptase was seen in 54% of the patients in PIONEER trial versus none of

the patients in placebo. And the variant allele fraction greater than 50% occurred in 68% of patients on avapritinib versus only 6% in placebo. And the quality of life was also significantly improved, 34% versus 18%, using a tool called mast cell [MC]-QoL.

Another additional benefit was the reduction of polypharmacy. These patients, such as this patient, are on multiple different classes of anti-mediator drugs, and 35% of the patients in the PIONEER trial were able to reduce the dosing or discontinue completely these anti-mediator therapies. And they were only on avapritinib. And this also comes with an improvement in quality of life.

In this case we discussed a patient, a typical patient with multiple symptoms not responding appropriately to anti-mediator treatments who might be a good candidate for avapritinib treatment.

[CHAPTER 2]

Dr. Akin:
For those just tuning in, you are listening to CME on ReachMD. I'm Dr. Cem Akin, and here with me today is Dr. Dan DeAngelo. Our focus today is discussing the multidisciplinary management of indolent systemic mastocytosis and how best to optimize outcomes for these patients.

Dr. DeAngelo, would you take us through the second case, please?

Dr. DeAngelo:
Yes. Thanks, Cem. So the second case is a very similar case to Cem's in some aspects. A 70-year-old woman initially diagnosed with cutaneous mastocytosis through a dermatologic evaluation as she had developed a skin rash after taking ibuprofen. The lesions were biopsied and found to be consistent with urticaria pigmentosa. She was followed for many years but then eventually developed symptoms of palpitation, some shortness of breath, rhinorrhea, dizziness, some chest pressure, and periorbital edema. Her symptoms progressed to fatigue and some decrease in stamina, some occasional flushing, episodes of mental fog and difficulty with concentration, intermittent headaches, and some bone pain. She was found to have food intolerances that would manifest themselves as experiences of episodes of intense abdominal pain, typically associated with nausea, vomiting, and sometimes diarrhea. She was unclear about the triggers, but that she thought that it was due to heavy foods or fatty foods, chocolate, red wine. And her reactions even occurred in the absence of some of these triggers that she was trying to elucidate. She didn't have any known environmental triggers.

Her primary physician, due to routine health, had been having skeletal imaging from the bone pain, and no lytic lesions or other abnormalities were identified. And a routine bone DEXA scan was abnormal and showing low mineral density to the point of osteopenia.

She had not had any episodes of anaphylaxis. She did require the use of an EpiPen on occasion because of the symptoms that she would experience. She did have 2 instances of urticaria pigmentosa flares that she thought was related to sun exposure, although she wasn't clear. Some lightheaded and dizziness also occurred, which resolved after lying down. So this eventually led to the finding of a serum tryptase level, a she saw an allergist, which was sky high at 161. Again, the normal level is less than 11; abnormal is clearly more than 20. And she was referred to myself as a hematologist for further evaluation.

We performed a bone marrow examination given the presence of cutaneous mast cell disorder and an elevated tryptase, thinking that she really had systemic disease. In order to prove this we asked our pathologists to look at the mast cell component. And the diagnosis of systemic mastocytosis requires 1 major criterion, and the major criteria are dense aggregates, typically classified as 15 cells or more within the bone marrow core biopsy, and at least 1 of the minor criteria. Or patients can have 3 minor. And the 4 minor criteria are atypical morphology, spindle-shaped in 25% or more cells; CD25 expression but also CD30 and CD2 expression; an elevated serum tryptase level of more than 20, clear in this case; and a *KIT* mutation – a *KIT* D816V. The new WHO [World Health Organization] 2022 adds other activating mutations in addition to the D816V.

And so this patient met the major criteria and all 4 minor criteria as having dense aggregates, spindle-shaped morphology, CD25 expression, elevated serum tryptase, and a mutation. Her allele burden was actually approaching 20, so it was actually very high in the peripheral blood. Her allergist had already started her on levocetirizine and famotidine, both an H1/H2 blocker. There was some improvement in her symptoms, but not great. The levocetirizine was then up-titrated to 10 mg twice a day. Because of her GI [gastrointestinal] complaints that had not been alleviated by this approach, she was started on cromolyn 200 mg 4 times per day, but again only minimally improved. We assessed her ISM symptom score, and this was markedly elevated at 65.

And so given the patient's symptoms that were really inadequately controlled with supportive care, both H1, H2, and cromolyn, and given the fact that this patient clearly met the criteria of having systemic mastocytosis, we assessed her for her disease. And one of the things that I think it's important, as a hematologist or allergist, whosever taking care of these, is to differentiate patients with systemic mastocytosis between those with B symptoms, that is the presence or absence of disease of burden, and that would classify patients of having smoldering systemic mastocytosis.

And so these are patients who have mast cell burden in their bone marrow more than 30%, tryptase of more than 200, organomegaly – either hepatomegaly or splenomegaly. A new criteria, which this patient does meet but would not have met prior, was a *KIT* allele burden of more than 10%. That's a new criteria. And then advanced disease – advanced systemic mastocytosis, which is treated very differently. Our patients with C findings, C for cytoreductive. So it's pretty easy to remember. Smoldering have B symptoms for burden, and advanced have C symptoms, meaning they need cytoreductive therapy.

And these C symptoms include, really, I like to think of them as organ damage. So marrow involvement to the point of cytopenias – neutropenia, anemia, and thrombocytopenia – the presence of splenomegaly, the presence of ascites or pleural effusion, weight loss, abnormal liver function tests with no alternative other than mastocytosis hypoalbuminemia. So these are examples of C findings. And this particular patient, at least at the time when I saw her, had no B or C findings. I did mention that the allele burden is a new consideration for smoldering. But she was classified as having indolent systemic mastocytosis and therefore was a candidate for avapritinib at a dose of 25 mg per day. And that was the approach that we took in consultation with the allergist who was treating her.

I think that these patients really do require a multidisciplinary team. They're often referred in from either dermatology to a hematopathologist, or from allergy for a hematopathologist to do the assessment, and obviously, usually, at least in most institutions, the hematologist is the one that's doing the bone marrow exam. And then a gastroenterologist to try and differentiate whether or not the GI symptoms, if they are present, are due to the systemic mastocytosis, really requiring either an upper or lower endoscopy with random biopsies. And it's very important that, again, the pathologist is aware of the differential diagnosis so that he or she can look for the presence of tryptase-positive cells, or mast cells, in the biopsies. And then an endocrinologist to try and manage the osteoporosis, or osteopenia, which is so often present in these patients.

In terms of following the patient, avapritinib was initiated, and I typically will follow the serum tryptase level. If there's an elevated, as there was in this case, a *KIT* allele burden, I will repeat that. That can be done from the blood. Many patients have a very low burden and so that's not something that can be done from the blood; it has to be done from the marrow. And then, at least in my, you know, I'm a hematologist so I do what we do, which is repeat a bone marrow examination. And I like to repeat one after 3 to 6 months of therapy just to make sure that we're actually moving in the right direction and that there is a reduction in the mast cell burden. That's very helpful especially in patients where the tryptase improves but plateaus. And in those cases some patients will have hereditary alpha-1 tryptasemia [HaT] where you get a reduction in the tryptase, but it just kind of flattens out in the mid-20s, and you're not sure whether or not this is due to resistance disease or whether there is a hereditary component.

Cem, did you want to comment for us on the evolution and diagnosis of HaT, which is really a common finding in some of our patients with systemic mastocytosis.

Dr. Akin:
Sure. I think HaT is a relatively recent discovery. And it turns out, 7% of the US population have elevated tryptase levels with or without mastocytosis. And that is because multiple copies of a gene called TPSAB1, which encodes for alpha tryptase. And if you have, you know, one more copy, you'll have a higher tryptase; if you have 2 more copy you have even higher tryptase. So HaT itself is not a pathology. It may act as a disease-amplifying factor. For example, if somebody is allergic to bee venoms and they have HaT, then they would have more amplified symptoms. And interestingly, in mastocytosis patients, the prevalence of HaT, in our study, we found it to be 18% as opposed to 7% in general population. So it appears to be seen in higher frequency in mastocytosis. So having HaT does not necessarily rule out mastocytosis per se, and you would still need to do a bone marrow biopsy to rule it out or confirm the diagnosis of mastocytosis if the patient's presenting with red flags like mast cell activation symptoms.

Dr. DeAngelo:
Thank you very much. That was great. I actually wasn't aware that it was that high in the patients with SM. But this patient that I'm describing was started on avapritinib at the FDA-approved dose of 25 mg, had a remarkable improvement in her symptoms, was able to reduce some of her supportive therapy, but not all. And eventually, the decision was made to actually escalate her dose from 25 to 50, which is not a current label, but is being done on the PIONEER study, as you're aware. Patients who have the elevated *KIT* allele burden are the ones that seem to benefit the best from dose escalation, but we are looking at that now. And this patient was dose escalated with marked improvement, or I should say, further improvement in her mediator symptoms allowing her to further reduce some of her antihistamine therapy. But she still remains on some supportive care.

Overall, her cutaneous lesions have lightened and almost all disappeared and her quality of life has dramatically improved, specifically the neurologic symptoms with cognitive improvement and her ability to concentrate, which is really interfering with her work. She's still working in spite of her age of 70 years.

And I think that avapritinib, in this particular case, was really dramatic in terms of improving this patient's symptoms and overall quality of

life.

Dr. Akin:
Thank you, Dan. I think this looks like a success story with avapritinib. Do you monitor for any laboratory values after prescribing avapritinib in these patients?

Dr. DeAngelo:
So what I usually do, other than repeating a bone density every 6 months or once a year, depending on whether they have osteopenia or osteoporosis, is I will monitor the serum tryptase level usually every 3 to 4 months just to assess. I'll repeat the marrow, as in this case when the patient's tryptase level doesn't return to a normal level, or at least less than 20 just to make sure I'm not missing anything. I'll often follow up with gastroenterology again if the patient is having more symptoms. But from my perspective, in addition to routine hematologic parameters and a metabolic panel, liver tests to make sure there's no abnormalities, a tryptase every 3 to 4 months.

Dr. Akin:
Thank you, Dan. And I think, before closing, we should also review some of the contraindications for avapritinib therapies. As you mentioned, it was also approved for advanced disease and currently it is contraindicated in people with platelet counts less than 50,000, which we don't fortunately see in indolent systemic mastocytosis, because those patients are more prone to intracranial hemorrhages. And another contraindication would be somebody who is planning to be pregnant because these tyrosine kinase inhibitors have the potential to be teratogenic.

Do you have anything else to add to that list, Dr. DeAngelo?

Dr. DeAngelo:
No. I think that really summarizes it nicely. You know, obviously, if you have patients with chronic thrombocytopenia, you're worried about other marrow disorders, you'll figure that out on the bone marrow examination. There are patients with chronic ITP [immune thrombocytopenic] that can run in this low range, but we didn't see that in our ISM study. The pregnancy issue, though, is very important. I did have a patient recently who was working at having a fertility workup and was interested in starting avapritinib, and we decided to, you know delay the initiation of avapritinib until she finishes with her pregnancy, and then we'll reinstate it at that point. But it's a very important point.

Dr. Akin:
Thank you, Dr. DeAngelo.

Today we discussed 2 indolent systemic mastocytosis patients, reflecting both allergists' and hematologists' approaches to diagnosis and management. We hope these case presentations were valuable and will be useful to your practice. Unfortunately, that's all the time we have today, so I want to thank our audience for listening in, and many thanks to Dr. Daniel DeAngelo for joining me and for sharing his valuable insights. It was great speaking with you today.

Dr. DeAngelo:
Thank you, Cem, for inviting me. I had a wonderful time. I hope it was very informative.

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