Higher stakes in systemic mastocytosis

Karen Titus

June 2021—Mastocytosis is not for quitters.

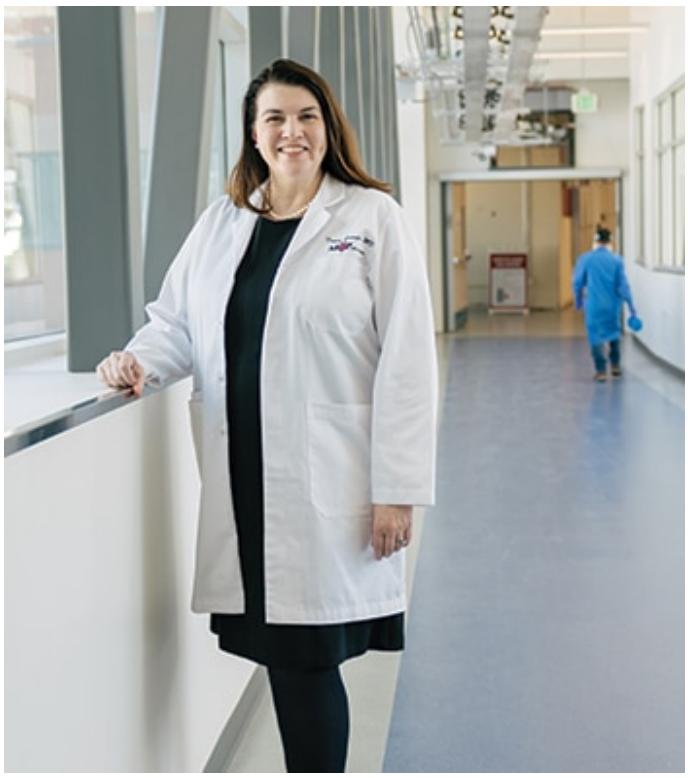
Not at any point, from considering the possible diagnosis, to doing a complement of stains, to looking for mutations beyond *KIT* D816V, to being curious about the presence of mast cells even after making a diagnosis of another myeloid disease.

Patients have already learned this grueling lesson. They can easily spend years seeking answers before their disease is properly identified. Pathologists can speed up that process—and the time to do so is now, says Tracy George, MD, chief medical officer and incoming president of ARUP Laboratories, and medical director of hematopathology.

Notes Dr. George: “There’s some exciting stuff going on with systemic mastocytosis.” New targeted KIT inhibitors appear to be quite effective, including at least one agent for advanced systemic mastocytosis that has been submitted to the Food and Drug Administration. “We anticipate there’s going to be approval by the FDA this summer,” says Dr. George, who’s been involved in the clinical trials for avapritinib (Blueprint Medicines).

This could build on the success of midostaurin, a breakthrough multikinase inhibitor that has been highly successful in treating patients with advanced SM. The newer therapies appear to be successful in patients with indolent disease as well as those with advanced disease, with fewer side effects than earlier medications, says Dr. George, who is also professor, University of Utah School of Medicine.

“Before, the refrain was, *This is a rare disease, and we can’t help you,”* Dr. George says. “But now we have an oral drug [avapritinib].” Just as imatinib helped change the way physicians approach chronic myeloid leukemia, says Dr. George, targeted KIT inhibitors are helping to move the needle on mastocytosis. “Instead of being a deadly disease, or one with incredible, terrible symptoms, this is a disease that people can be treated for and live with.”



Dr. Tracy George at ARUP Laboratories. In addition to

hematopathologists, she says, surgical pathologists and dermatopathologists need to understand not only how to diagnose systemic mastocytosis but also what the disease looks like in those being treated with a targeted therapy.

Eric Duncavage, MD, of Washington University in St. Louis, compares current progress in mast cell disease to what occurred with lung cancer, when targeted therapies spurred awareness and testing. “We have far more requests for *ALK* fusion detection now than in the past. Before there were targeted therapies for *ALK* fusions, there wasn’t a huge clinical demand,” says Dr. Duncavage, professor, Department of Pathology and Immunology, and director of the section of clinical cancer genomics, Division of Anatomic and Molecular Pathology. “Targeted therapies definitely drive interest in doing these molecular assays.”

All this assumes physicians are considering the disease to begin with. But with mastocytosis, that’s never been a given.

It’s easy to *not* think about mastocytosis, which is why many physicians typically don’t. The abundance of nonspecific symptoms—fatigue, allergies, skin rashes, autoimmune indicators—doesn’t necessarily arouse clinical suspicion. “It could be anything,” says Dr. George.

For some patients symptoms are more dramatic. Adult patients may present with anaphylaxis, says Jason Gotlib, MD, MS, professor of medicine (hematology), Stanford Cancer Institute, Stanford University School of Medicine, “which would be one of the more telltale signs of an underlying mast cell disorder,” often triggered by Hymenoptera stings. And unlike for children (who rarely have systemic disease and whose skin lesions almost always spontaneously remit during puberty), for adults who present with skin lesions, 80 to 90 percent will be shown on bone marrow examination to have systemic mastocytosis.

Apart from anaphylaxis and skin lesions, the symptoms can be so vague that Dr. Gotlib calls these mast cell diseases “the great mimickers.” Flushing, weight loss, diarrhea, brain fog, bone pain, and other mast cell mediator symptoms are fairly nonspecific, and therefore it is necessary to connect the dots to arrive at a diagnosis of mast cell disease.

With new treatments likely nearing, those thoughts might start showing up quicker. Publicity around new drugs has its place, say those who’ve often been frustrated by the desultory diagnostic pace. “Having FDA-approved drugs is so important,” says Celalettin Ustun, MD, professor of medicine and the Coleman Foundation chair of hematology/BMT and director of the section of BMT/cell therapy, Division of Hematology, Oncology and Cell Therapy, Rush University Medical Center, Chicago. He recalls seeing oncologist colleagues home in on SM much more often when midostaurin became available.

Such nudges are nothing to sneeze at. Dr. George says it can take patients seven years to receive the right diagnosis, in part because “symptoms are all over the place. Obviously most of those patients have the indolent form of the disease.” Those with more advanced forms will present sicker and receive health care sooner. “But it just shows these patients go through this odyssey of seeing all sorts of different doctors, depending on their symptoms.”

“It needs to be diagnosed earlier,” Dr. Ustun agrees, noting that the range of physicians who might see a patient with mast cell disease is wide: primarily oncologists and hematologists, but with other stops along the way, including GI, cardiologists, dermatologists, and endocrinologists, not to mention family and internal medicine physicians. “Patients keep seeing other doctors for years before someone thinks, *Oh, you might have mastocytosis.*” And that whole time, he says, patients are suffering.

Weighing the possibility should be merely the first in a long line of thoughts. Mastocytosis workups could easily benefit from a simple disclaimer at the outset: *Much assembly required.*

"If you don't think about it, you won't do the right testing," Dr. Gotlib says. He gives the following example: In patients with systemic mastocytosis, the most frequently detected associated hematologic neoplasm is chronic myelomonocytic leukemia, or CMML. Knowing that, it makes sense to order tryptase or CD25 stains. "But sometimes that logical extension isn't undertaken." The hardest part isn't doing these common tests, he says—it's thinking to do them.

Dr. Duncavage agrees. It's not unusual, he says, to receive cases where the oncologist or hematologist suspects mast cell disease. "So we're already clued in that we're heading down this path. And we'll do all the requisite stains and testing.

Dr. Duncavage

"But it's always hard to make a diagnosis when you're not thinking of the diagnosis," he continues. "That happens a lot with these hematologic disorders that occur with mast cell disease."

Systemic mastocytosis is simultaneously uncommon and common enough, says Dr. Duncavage. "I think most pathologists are going to bump into it in their practice," he says.

But what happens beyond that bump quickly grows complicated. Easier, perhaps, to pick the true heir to the throne in 15th-century Britain. Good luck sorting through all those Richards, Henrys, Margarets, and Elizabeths (not to mention a passel of Woodvilles). Do you follow York? Lancaster? Or turn to the Tudors?

What has raised the stakes at Washington University, Dr. Duncavage says, is the widespread use of sequencing-based panels. Next-generation sequencing has both created awareness that mastocytosis is a clonal process and brought it to clinical attention.

Five years ago, when clinical sequencing was relatively new and more expensive, "We didn't do a lot of bone marrow sequencing for our patients," he says. Today, "basically every new patient bone marrow biopsy we do now, we sequence," which will from time to time turn up a *KIT* mutation. "We've picked up a couple of cases like that, where we weren't totally expecting it." In addition to such unexpected cases, NGS can point Dr. Duncavage and his colleagues to cases where mastocytosis co-occurs with another disease and where more follow-up is needed.

The uncommon-common motif ripples through gene sequencing as well. Physicians tend to associate *KIT* D816V with mastocytosis—not surprisingly, since it is the most common mutation, present in more than 90 to 95 percent of cases—but other, less common mutations can also occur. Ten years ago, says Dr. Duncavage, the search focused solely on *KIT* D816V, mostly because that's what the technology allowed for. NGS can target a more diverse set of mutations, "and that allows us to diagnose more cases."

The other big advance on the molecular side, he says, is that NGS can turn up mutations in other myeloid-associated disorders, such as *TET2, ASXL1,* and *EZH2*. "Most centers are now doing these sequencing panels, so we can start putting together the clues from some of these other gene mutations."

Dr. George notes advanced systemic mastocytosis is similar to acute myeloid leukemia in that both are multimutated diseases. Patients with advanced SM have not only the *KIT* D816V mutation but often also other

myeloid gene mutations. Certain ones—she cites the combination of *SRSF2, ASXL1,* and *RUNX1*, the so-called S/A/R panel—carry a worse prognosis and, not surprisingly, appear to respond less well to midostaurin. Responses to avapritinib have been shown in clinical trials regardless of S/A/R genotype.

For these patients, ddPCR for *KIT* would be insufficient. "You also need to do NGS on bone marrow," Dr. George says.

NGS sensitivity is around five percent, she notes; droplet digital is 0.01 percent ("depending on who's running it," Dr. George says). "That's why we recommend both," she says. For patients with indolent disease and very little bone marrow involvement, NGS will miss the *KIT* mutation.

The latest NCCN guidelines, released in April, incorporate these updates. "The importance of pathology in this disease has been recognized, so they've added more pathologist authors to the NCCN guidelines for myeloproliferative neoplasms and mastocytosis," says Dr. George, who along with Dr. Gotlib is one of the document's coauthors.

NGS has become more accessible, but payers haven't always kept pace. "It's been kind of a roller coaster in terms of reimbursement and coverage," Dr. Duncavage says. "It was good in the 2012–2014 era, and then it went way down. But I think payers have finally realized the value," although he says large comprehensive panels seem to be less well covered. "So in-house, we've switched to a smaller, less expensive panel." The coverage rate is high, he reports, matching that of IHC or any other pathology assay. "The coverage indications for smaller panels are pretty broad, so basically most symptomatic patients that you would consider a diagnosis of mast cell disease in would meet a covered indication."

The key at his lab, he says, was to retool the lab's molecular offerings around the more focused panels billed under the lower-value (CPT 81450) code. The larger comprehensive panels (billed under CPT 81455) are reimbursed at a higher rate and can identify more gene mutations, but payer coverage is challenging. "The thinking several years ago was that bigger is better, and you'd potentially miss something if you weren't sequencing hundreds of genes. But for most myeloid malignancies, you don't need a large comprehensive panel of 500 or 700 genes," Dr. Duncavage says. "We just need a handful." Larger panels might pick up a few edge cases, he acknowledges, but that occurs in only a tiny fraction of cases (in a disease that is already relatively rare). And if the mutation occurs in a gene bereft of clinical data, "then it's hard to make informed clinical decisions." While it's good to think about mastocytosis, best not to overthink the molecular testing and jump to a larger panel out of the gate, he suggests. "For most patients, these smaller panels are the better way to go."

Sensitivity of NGS has improved, but it still varies across platforms and labs. "We can definitely sequence with a much higher sensitivity now than we could a few years ago," Dr. Duncavage says, adding that it's possible to sequence for measurable residual disease, thanks to new error-corrected sequencing methods. While these are not quite to the level of ddPCR in terms of sensitivity, they offer the advantage of larger breadth. "But it is possible that you send out for a 40-gene panel to one lab, then realize it wasn't sensitive enough," he says. "And then you'd have to send out for a ddPCR or a higher-coverage panel."

The need for assiduity persists past NGS.

Dr. Duncavage points to one specific diagnostic problem related to flow cytometry. Mast cells tend to aggregate in the marrow, in part because they are often surrounded by fibrosis. "So when you do an aspirate, they don't like to come out. It's challenging—they like to stick in the marrow, so we can't always detect them by flow cytometry."

Sequencing presents less of a challenge, but it can still be problematic, he says. "But from the blood," Dr. Duncavage says, "doing digital droplet is a great way to detect very low-level involvement by mast cell disease," though it remains, for the foreseeable future, more of a reference lab assay. His own lab sends out ddPCR as well as other, more esoteric testing that might be needed to make a diagnosis.

"If you see mast cells, and the patient meets some of the clinical criteria, know to send out for the flow and for the

molecular. Those two things are probably the most critical," Dr. Duncavage says. Keep digging, in other words. "The name of the game is to establish clonality." That can either be flow cytometry, looking at CD2 or CD25 expression, or it could be molecular, looking for *KIT* or one of the associated mutations, for example, in genes that are part of the S/A/R panel.

It can be hard to follow up on early steps, Dr. Duncavage concedes. "You can imagine a situation where the report comes back, '*KIT* mutation is present'"—how do you follow up? Maybe mast cell disease wasn't noticeable in the marrow, but there's this low-level D816V mutation. How do you work it up? What other testing do you need to consider? "Those would be the perfect cases to send out and get experts' advice," he says.

That's what Dr. George is trying to offer, not only at ARUP but beyond.

Dr. George has been a pioneering figure in systemic mastocytosis, developing a central pathology review as a new business model of sorts at ARUP, she says, "capitalizing on the notion that for really difficult types of diseases where pathology diagnoses are critical, it's far better to have a single place or group of experts diagnosing them."

Though the business tackles various types of disorders, hematological disorders are the focus, including mast cell disease. "It's been really fun," Dr. George says. "We're finding that we can gain greater insight into the disease when it's centralized and you have this rigorous review going on all at the same time."

ARUP also recently launched a ddPCR test for the *KIT* D816V mutation. That doesn't eliminate the need for bone marrows, but, as Dr. George puts it: "We're trying to get the word out: *Yes, patients may need a bone marrow for diagnosis.* But like most rare diseases, most patients *don't* have it," she says. "So if the goal is to exclude the disease, far better to have a simple blood test than to have to get a bone marrow biopsy."

In addition to training colleagues at ARUP, Dr. George has set her sights wider. She and others have formed the American Initiative in Mast Cell Diseases (http://www.aimcd.net), which held its second biennial meeting in late May. As part of this effort, the group has been soliciting applications from different sites to become Centers of Excellence or reference centers for mast cell disease. "There's a real need for these patients," says Dr. George. "They don't know where to go. How do they get on these clinical trials? How do they get properly diagnosed?"

Even the non-ARUPs can up their game, however.

Dr. George sees more than her fair share of referrals, and she's often startled by what she sees. The initial workup will note increased mast cells. "That's a start. But that's where it stops," she says. "They don't describe the shape of the mast cells."

Moreover, Dr. George adds, initial reports will often neglect to note whether the mast cells are aggregating. Sometimes the initial workup will fail to cover proper stains to identify mast cells, or some but not all stains will be done to look for aberrant expression. "So the comment will then be, 'This might be mast cell disease.' And I'm thinking, *Argh, this is so unhelpful!"*

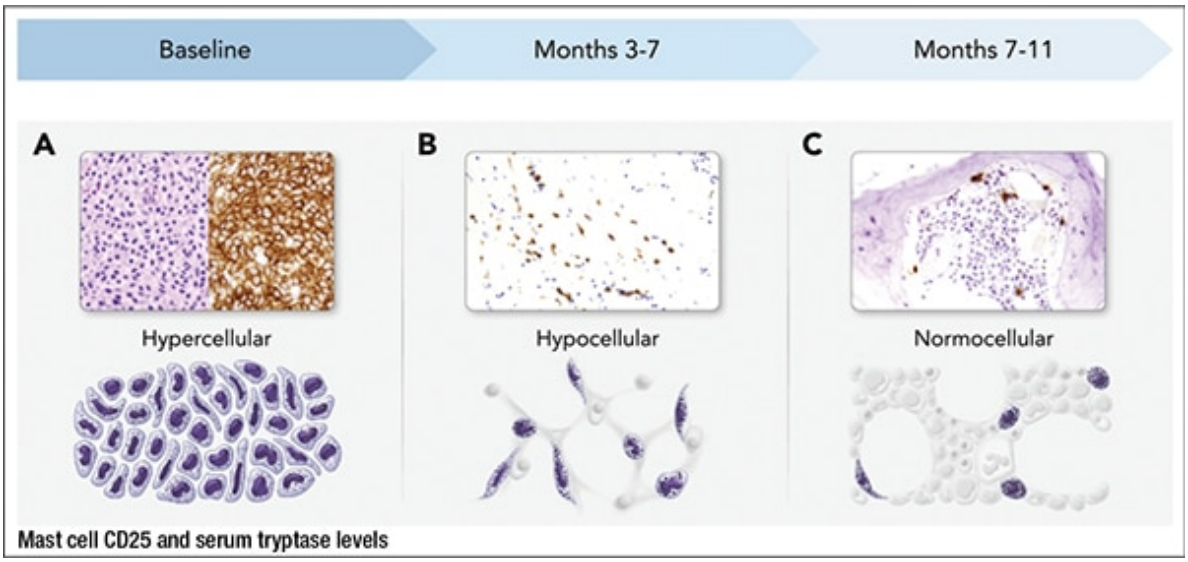
To subclassify the disease requires a bone marrow. But that's often the least of Dr. George's concerns. "Often what I see is an incomplete diagnosis," she says. "It's not just hematopathologists who need to be aware of this, but surgical pathologists and dermatopathologists as well." Not only do they need to understand how to diagnose the disease, but also to know what the disease looks like in those being treated with a targeted therapy, she says.

Patients enrolled in clinical trials at academic centers, Dr. George says, generally have two bone marrow biopsies—one remains in place locally and the other arrives at her lab for central pathology review. "So those pathologists are already seeing the results of those drugs," she says. "It's interesting, because what I've noticed is that as these mast cells go away, they also change their phenotype." (See images.)

As they move from an abnormal shape to essentially a normal shape, their response to staining changes as well. While aberrant mast cells express CD25, normal ones don't. As patients are treated, they'll lose this expression in their cells, Dr. George says. "You have to be aware of those changes as a pathologist who's reading bone marrows,

so you're properly diagnosing these patients and understanding what's happening."

Once physicians understand they're working on a puzzling diagnosis, it's easier to start putting the pieces together. "What often happens," says Dr. Gotlib, "is patients get sent to me with random colon biopsies, and they haven't done the mast cell stains. So for the non-bone marrows, the GI biopsies, we often have to ask for the extra stains to look for mast cell disease."



Bone marrow response to KIT inhibition in patients with systemic mastocytosis. At diagnosis **(A)**, atypical mast cells in dense aggregates fill a hypercellular bone marrow with aberrant expression of CD25 shown. After 3–7 months **(B)** of targeted KIT therapy, the bone marrow is now normocellular to hypocellular with mostly loose clusters of mast cells present as shown by a CD117 stain. The mast cells now express only dim CD25 on a subset of mast cells or lack it entirely (not shown). By 7–11 months **(C)** of targeted therapy, only a few scattered mast cells with a normal immunophenotype are found (tryptase immunostain shown) in a normocellular marrow. Republished with permission of Elsevier Science & Technology Journals, from Reiter A, George T, Gotlib J. New developments in diagnosis, prognostication, and treatment of advanced systemic mastocytosis. *Blood.* 2020;135(16):1372. Permission conveyed through Copyright Clearance Center, Inc.

He'd like to see pathologists take the lead on doing or suggesting additional stains. Depending on the clinical information, "I would hope the pathologist would go back to the gastroenterologist and say, 'What do you think about adding on CD25, CD117, and tryptase to look for mast cells?' There is absolutely a role for closer communication and collaboration between the subspecialist and the pathologist." Dr. Duncavage says he and his colleagues on the heme-path service frequently consult with GI pathologists to sort out the molecular testing on suspected cases of mast cell disease.

Another place to dial up the chatter is when clinical symptoms and pathology findings don't fit snugly into place. Advanced disease is often overcalled, Dr. Gotlib says, with diagnosis based on the presence of mast cells in the bone marrow as well as sclerotic bone lesions. But the diagnosis isn't based solely on mast cell burden; it also requires the right clinical signs and symptoms, he says. "That's where the pathologist and the clinician need to work together to know what type this is." Is it indolent SM? Smoldering SM? Aggressive SM? "Advanced disease is often not only the pathology diagnosis but also frankly as much or more of a clinical diagnosis."

Dr. Gotlib

(The only SM subtype that is a purely histopathologic diagnosis is mast cell leukemia, Dr. Gotlib says, which is based on the presence of 20 percent or more mast cells in the bone marrow aspirate—*not* a biopsy.)

Those who've been involved in the clinical trials for KIT inhibitors, says Dr. Gotlib, have observed that local pathologists ("and frankly, a lot of these are academic centers," he says) don't routinely identify the associated hematologic neoplasm in patients with mast cell disease involving the bone marrow. "They either find the mast cells and don't comment," he says, or they don't discern between a myelodysplastic syndrome and a myeloproliferative neoplasm, or do not appreciate a possible overlap. "A significant proportion of those local reads did not comment on an AHN," though it turned up when it was read centrally, by, for example, Dr. George.

"So I would say that undercalling AHNs in the bone marrow is highly prevalent," Dr. Gotlib says. "That needs to be discussed and reviewed among the pathology community."

The converse can also occur in cases such as a CMML, where physicians don't realize there's also a mast cell component. "That's where the use of tryptase staining could be of value," he says.

Though Dr. Ustun reports progress in SM diagnoses, he too expresses concern about ongoing gaps. He typically sees patients with either a cutaneous mastocytosis diagnosis or allergic reactions, with an elevated tryptase. "People order tryptase much more than in the past. And overall awareness is increasing, but it's not great yet. Oncologists and hematologists think more common diseases when they see blood abnormalities in patients, such as MDS or AML."

If they're suspicious for AML, and a bone marrow biopsy confirms it, too often that's where the matter ends. The diagnosis is correct but not complete. "They can miss that there is also occult SM. It's minor, but it's there." But if neither the pathologist nor the clinician thinks to do additional stains, mast cells will be easily overlooked. "So we think some patients go without a diagnosis," Dr. Ustun says.

The more common problem, though, is that patients with more common hematologic neoplasms—AML, MDS—may have an SM component. Finding a *KIT* mutation when working up a hematologic malignancy is a reason to look for SM. "It's remarkable that quite a few patients have SM in this group," Dr. Ustun says.

Another area to pay attention to is bone. "Not bone marrow—bone," Dr. Ustun says. Oncologists may encounter patients with serious bone pain—an x-ray reveals osteolytic bone lesions, which are small and quite dense, says Dr. Ustun. The apparently obvious diagnosis is a cancer that metastasized to bone. But follow-up steps—interventional radiology, bone biopsy, CT scans to identify a primary cancer—may not turn up an explanation for the very real lesions. In such cases, it may turn out that the abnormal cells are mast cells, linked to SM. "This happens more frequently than people think," he says.

The final area of concern is the liver. "Personally, I do more and more liver biopsies in patients with systemic mastocytosis already diagnosed to understand what is going on in their liver," Dr. Ustun says. Blood tests aren't adequate, in his opinion. "I have had almost completely normal liver function tests, and when I did liver biopsy I saw tremendous fibrosis in the liver, due to mast cells."

Despite the seeming similarities, the differences are real and worth sorting out—like making the distinction between Prince Hal and Hal Prince.

So why do physicians short-sheet their diagnostic efforts? Dr. Gotlib has a few hunches. "It's just one of those

things if you make a diagnosis of a mast cell neoplasm, one may not consider the presence of a co-occurring neoplasm. Or," he says, reciting the by-now familiar refrain, "it's just a matter of, you need to think about it in order to work it up."

The lapse may be understandable, but it comes at a cost, and not just in terms of quality of life. Dr. George estimates five to 10 percent of patients with indolent disease will progress to aggressive SM, though "we're still trying to understand what is different about those patients," she says.

"If the mutation burden of *KIT* D816V is relatively high," Dr. Gotlib says, "or if additional mutations beyond *KIT* D816V are found, this could indicate disease beyond the indolent stage." A high *KIT* D816V allele burden may reflect multilineage involvement of the *KIT* mutation, which means not only in the mast cells but in the granulocytic lineages—something that's more likely to be seen in patients with smoldering or advanced disease. "Which means they're already transitioning," he says.

Dr. Ustun

Dr. Ustun asks: "If we diagnose them earlier, can we prevent them from developing additional mutations?" No one knows how many progress, or why, he concedes. "From my experience, though, I do see patients start as indolent, and maybe a decade later they were really in trouble."

Dr. Duncavage would like to head off such trouble sooner. "I suspect a lot of pathologists think of associated mast cell disorders as an esoteric diagnosis," he says, thinking that may be furthered along because mast disease is considered indolent in most cases (quality of life issues notwithstanding). "Is it really something they should aggressively work up? Especially as a secondary disorder. But now that it's treatable, it's definitely something that should be considered and worked up appropriately."

He and his colleagues will see a CMML once or twice a week. "We're comfortable with that," he says. "But it's easy to overlook these other diseases that can co-occur with CMML. Because you're very focused on, basically, the main diagnosis."

The risk is that even when the CMML is treated successfully, the mast cell disease may continue to expand, says Dr. Duncavage. "The oncologist needs to be aware that there are two kinds of clonal processes going on."

That's probably the hardest challenge he and his colleagues see on the heme-path service, he says. "We've made one diagnosis. We think we're done. And then all of a sudden we're clued in to the fact, *Gee, there's a lot of mast cells here. We should work this up more.*"

Clinicians may think about ordering a serum tryptase level; if it's elevated, "certainly mast cell disease is on the differential," Dr. Gotlib says.

The question then becomes: What meets the WHO criteria for a diagnosis of systemic mastocytosis?

The major criterion is multifocal aggregates of mast cells on an extracutaneous organ (which is almost always the bone marrow biopsy).

There are four minor criteria:

- Atypical mast cells (immature or spindle-shaped);

- CD25 expression on mast cells, with or without CD2;
- *KIT* D816V mutation; and
- Serum tryptase level above 20 ng/mL.

The diagnosis requires one major and one minor criterion or at least three minor criteria.

From a pathology standpoint, says Dr. Gotlib, "there are nuances to making sure that one correctly identifies these major/minor criteria."

The GI pathology is incredibly challenging, says Dr. George, pointing to the considerable confusion about what mastocytosis looks like in the gut, compared with other diseases like irritable bowel syndrome, which can present with increased normal mast cells.

Naturally, mast cells can be increased in other disorders as well. With myeloid and lymphoid neoplasms with eosinophilia, says Dr. George, the presence of increased mast cells is well documented. They can even look spindle-shaped and thus mark aberrantly. And these, too, are rare diseases.

"This is where you have to do NGS," Dr. George says. "You'll often have to do FISH or PCR for *PDGFRA, PDGFRB*, or *FGFR1* mutations. These are some really substantial workups."

"Ultimately, if you're going to make the WHO diagnostic criteria for systemic mastocytosis," says Dr. Gotlib, "you need to do a bone marrow biopsy" to identify multifocal aggregates. Moreover, he notes, two of the minor criteria require a bone marrow biopsy. "You need to find the atypical mast cells and that they express CD25, and you can't do that off of peripheral blood." But to address sensitivity issues, he recommends that the *KIT* mutation assays be done with ddPCR or *KIT* allele-specific PCR.

"Having said that," Dr. Gotlib continues, "it's possible to do a 'dirty' screening test off the peripheral blood." But unless the patient has mast cell leukemia, mast cells will not be circulating in the blood. Some subtypes of advanced mast cell disease, however, such as SM-AHN, will often carry the *KIT* mutation, which can be picked up in the blood. "But at the end of the day, if you're going to be doing a bone marrow, then do it off the bone marrow." With a nod to the infamous quote from bank robber Willie Sutton, he jokes, "That's where the money is."

"It's the same thing with bone marrow," he explains, where multifocal aggregates of mast cells can be found. In contrast, mast cells circulate in the blood only in rare cases of mast cell leukemia.

NGS does have advantages, Dr. Gotlib says. Patients with other types of advanced mast cell disease, particularly SM-AHN, have other myeloid mutations apart from *KIT* D816V, which are well known and easily picked up by NGS, such as those on the S/A/R panel.

But many other mutations are myeloid in nature, such as *CBL, JAK2,* and *EZH2*. Other mutations, including *TET2* and *DNMT3A*, are more neutral, but clearly have been found in advanced mast cell disease.

NGS panels should be part of the standard workup, Dr. Gotlib says, "because they are now part of new diagnostic scoring systems to provide more nuanced evaluation of prognosis," as well as identifying whether there's an AHN.

The clinical treatments are very different. Patients with a myeloid neoplasm with eosinophilia but a *PDGFRA* mutation will respond "very, very well to very low doses of imatinib," Dr. George says. "But you could have a patient with systemic mastocytosis—that looks very similar in the bone marrow because you also see eosinophils that accompany mast cells." These patients will have a *KIT* D816V instead of a *PDGFRA* mutation. "There's a number of ways pathologists can be misled if they don't do or understand the entire workup."

Clearly, much of this needs to land in a reference lab—most labs simply don't offer this type of specialized testing. Dr. George is sympathetic.

“I’m at a reference lab, so I can get it all done,” she says. “But even so, it takes time to do all these tests.”

“There is a challenge, I think, on the pathology side,” she adds, “especially if you’re in a community practice. You’re so busy. I was in community practice when I first came out of training, and I remember: You’re *busy*. You’re seeing all sorts of different malignancies.”

Despite the seemingly endless frustrations, it’s worth persevering. “It’s uncommon in the sense that you’re not going to see it every day,” says Dr. Duncavage. But like snow in April, “It’s common enough that you’re going to see it eventually.” He calls these “dangerous diagnoses,” given the ease with which they can elude a physician’s awareness. “You’re not thinking about it in every case. But it’s not a total zebra that you’ll never see.”

Karen Titus is CAP TODAY contributing editor and co-managing editor.