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A case-based *OncLive Peer Exchange*® summary

Advanced Systemic Mastocytosis: Expert Insight Into Epidemiology, Diagnosis, and Treatment

SYSTEMIC MASTOCYTOSIS (SM) is a rare disease that often first presents on the skin. It is characterized by the overaccumulation of mast cells (MCs), which can then penetrate such internal organs as bone marrow (BM).¹ Challenges in identification and diagnosis suggest that SM is underdiagnosed despite its low prevalence. Prognosis for cutaneous and indolent cases of SM is excellent, but it can be variable for patients with advanced cases.¹ Symptoms often vary depending on the location of the MC proliferation, rendering diagnosis and treatment difficult.

In a recent *OncLive Peer Exchange*® video series, an expert multidisciplinary panel reviewed 6 clinical cases to illustrate both the complexity of SM and the best diagnosis and treatment practices for affected patients. This article presents highlights from the panelists' discussion, with an emphasis on the epidemiology, diagnosis, and treatment of advanced SM.

EPIDEMIOLOGY AND CLASSIFICATION

At the outset of the conversation, panel host Daniel J. DeAngelo, MD, PhD, from the Dana-Farber Cancer Institute in Boston, Massachusetts, highlighted the complexity of SM stating, "[SM] is a challenging condition with multiple classifications and presentations." Part of this convolution stems from the variety of MCs themselves, which exist in most tissues and play a role in immunity and immune-related inflammation.^{2,3} Mast cell progenitors (MCPs) come from the BM, migrate through the blood, and usually mature in vascularized tissue.^{2,4} There, influenced by blood vessels, nerve endings, and the local environment, MCPs take on phenotypes from their specific tissues.² In these tissues, stem cell factor (KIT ligand) provokes MCPs to develop into mature MCs.²

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DeAngelo, whose clinical practice is focused on the treatment of patients with acute and chronic leukemias as well as myeloproliferative disorders, added that this variety presents a fundamental challenge for all MC disorders, including SM. “[MCs] can be hard to elucidate [microscopically],” he said. Panelist Sa Wang, MD, a professor in the Department of Hematopathology, Division of Pathology/Lab Medicine, and section chief of the Department of Hospital Flow Cytometry Laboratory at The University of Texas MD Anderson Cancer Center in Houston, concurred, saying, “[MCs] can be very subtle.” She added: “especially in the [gastrointestinal (GI)] tract,...[MCs] can mimic a lot of things...like plasma cells. When plasma cells [lose] the cytoplasm, they can look like MCs, too.”

The panelists underscored that the diversity of MCs leads to a wide range of MC activation triggers, a variety of MC functions, and heterogeneous MC disorders, and a host of MC disorder symptoms. Allergens, drugs, venoms, and physical stimuli can activate MCs, which then can secrete a variety of mediators that can directly or ultimately affect blood vessel diameter, inflammation, T-cell activation, autocrine and paracrine activity, and other processes.² MCs appear to play a role in a large number of physiologic and pathologic mechanisms.²

The panelists acknowledged that MC disorders may result from pathologic increase in clonal MCs or pathologic activation of MCs.^{2,4} Nevertheless, a patient can receive a diagnosis of both mastocytosis—in which MCs expand and accumulate in the skin, bone marrow, and visceral organs—and MC activation syndrome (MCAS), a condition in which MCs are activated in a severe, recurrent, acute, and systemic manner.^{1,3,5} DeAngelo noted the complexity of this overlap, stating: “I find this to be the most challenging. Patients will have...MC activation syndrome, some with a clonal MC process, some without.”

Panelist Patricia L. Lugar, MD, MS, an associate professor in the departments of medicine and pediatrics at the Duke University School of Medicine in Durham, North Carolina, agreed, adding that mastocytosis and MCAS have similar clinical presentations. “We don’t have...fantastic clinical markers or biomarkers to...guide us

for MC activation as opposed to a true clonal MC disorder,” she said. The diagnosis is further complicated because these 2 diseases and their symptoms “mimic so many others that are cardiovascular or have origins in other organ systems,” she noted. “Pulmonary [problems], postural orthostatic tachycardia syndrome, multiple food sensitivities, and food [allergies]” all cause symptoms that overlap with mastocytosis and MCAS, and they must be ruled out in a diagnosis, Lugar emphasized. “By symptomatology alone, it’s very confusing to really figure out what the patient is experiencing.”

Classification of SM can also be a challenge. To account for the heterogeneity of the disorders that fall under the mastocytosis classification¹ and in keeping with findings of other clinicians and investigators,^{6,7} the panelists cited the World Health Organization’s (WHO’s) 2016 criteria for the classification of myeloid neoplasms^{1,8} as foundational to understanding and classifying SM. These criteria set SM apart from localized MC tumors and varieties of cutaneous mastocytosis, which are not systemic.¹

The distinguishing feature of SM is the penetration of MCs into internal organs—including the BM—at multiple locations within the organ or organs.¹ As DeAngelo explained, to diagnose SM according to the WHO, “you have to have 1 major and 1 minor or 3 minor criteria.” The major criterion is multifocal clusters of at least 15 MCs per cluster in 1 or more visceral organs. Clinicians usually see this clustering in the BM. Of the 4 minor criteria, the first is that at least one quarter of MCs in the BM are atypical or spindle-shaped if they are in the visceral organs. The second is a *KIT* point mutation at codon 816 in infiltrated organs. The third is exhibition of CD2 and/or CD25 in an infected (but extracutaneous) organ or in the blood. The fourth—which is not a valid criterion if an unrelated myeloid neoplasm exists—is a baseline serum tryptase level above 20 ng/mL.¹ DeAngelo presented his first case as a clear example of SM, stating, “This person had these huge, dense infiltrates ..., a *KIT* mutation..., a CD25...aberrantly expressed..., [and] tryptase [level]...in the 100s [ng/mL]... so he clearly met 1 major and 3 minor

[criteria]. Any way you slice or dice it, this patient met the diagnosis of [SM].”

Panelist Prithviraj Bose, MD, associate professor in the Department of Leukemia, Division of Cancer Medicine, at The University of Texas MD Anderson Cancer Center, concurred with DeAngelo’s diagnosis. “Absolutely,” he said. “This is a very clear-cut case of SM, meeting multiple criteria.”

Bose also called attention to WHO’s subclassifications of SM into indolent SM (ISM), smoldering SM (SSM), SM with an associated hematologic (non-MC lineage) neoplasm (SM-AHN), aggressive SM (ASM), and MC leukemia (MCL).¹ Adding that DeAngelo’s first case had “a lot of C findings [that indicate organ damage from MC infiltration], as well,” Bose highlighted that the WHO defines most of these SM classifications according to the presence or absence of B findings (that indicate high MC burden across multiple organs or the blood but without organ damage) and C findings. ISM and SSM have no C findings; SSM has 2 or more B findings. ASM and MCL have C findings; MCL has MCs of 20% or more on BM smears.¹ ASM and MCL are classified as advanced SM (AdvSM); SM-AHN is sometimes considered an AdvSM and otherwise considered as additional to 1 of the other 4 classifications.^{1,6}

Bose underscored that, once the presence or absence of C findings has been determined, WHO guides clinicians to determine whether an associated hematologic (non-MC) lineage neoplasm (AHN) is present and SM-AHN can be diagnosed. “Traditionally,” Bose added, “we are taught to...clinically assess whether the C finding is attributable to the mast cell component or to the AHN.” This is in an effort to treat the diseases separately and requires both the application of other disease-related markers and the classification of the AHN according to separate WHO criteria.⁹ However, Bose highlighted that WHO’s SM-AHN model has been challenged. A mutation-adjusted risk score (MARS) for AdvSM that was proposed in 2019 may improve up-front treatment stratification for these disease states by guiding clinicians to diagnose according to 5 risk factors associated with overall survival (OS): age older than 60 years, anemia (hemoglobin < 10 g/dL), thrombocytopenia (platelets < 100 × 10⁹/L), presence of 1 high-molecular-risk gene mutation (ie, in *SRSF2*, *ASXL1*, and/or *RUNX1*), and presence of 2 or more high-molecular-risk gene mutations.⁶ As AdvSM has a poor prognosis, as SM-AHN accounts for 70% to 80% of all patients with AdvSM (if considered an AdvSM), and as SM-AHN is the most heterogeneous SM subtype, diagnosing according to MARS may improve AdvSM outcomes.⁶ Bose added that therapeutic advances have also made distinguishing between SM and a concurrent AHN less important. *KIT* D816V is the most important somatic mutation in SM-AHN and, in a large majority of patients, exists in both the SM and the AHN.⁶ “If the *KIT* [variant allele frequency (VAF)] is very high,” and “if you can hit that [*KIT* D816V] target,” the distinction between

SM and AHN “is a bit moot.” He added, “Even other [AHN] lineages such as eosinophils and monocytes can go down with avapritinib,” which is a selective *KIT* D816V inhibitor.

SYMPTOMS, REFERRAL, AND DIAGNOSTIC PATTERNS

The specialists noted that most of their patients with SM come by way of referral. Lugar, an expert in allergy and immunology, underscored that anaphylaxis frequently is a presenting symptom. “We [often] see patients with recurrent anaphylaxis. As part of the workup, if the story fits with other symptoms, we will usually screen for muscle disorders,” she noted. The next most common symptom is reaction to venom stings (eg, from flying insects). “Individuals [who] have had either profound allergic symptoms during the sting [eg, anaphylaxis or cardiovascular symptoms, syncope, difficulty in resuscitating, need for multiple doses of epinephrine, evidence of a possible previous anaphylactic episode] will be screened,” Lugar explained.

DeAngelo observed that he gets referrals from allergy and immunology experts for patients with recurrent anaphylaxis or reactions to flying insect stings who have met the criteria that Lugar outlined. However, working in a general hospital, he also gets referrals from dermatologists, gastroenterologists, and fellow hematologists. “Dermatology will [see] a rash, [suspect] urticaria pigmentosa or the telangiectasia [macularis] eruptiva perstans, make a biopsy, and refer a patient. Additionally,” he noted, “patients with irritable bowel syndrome come to an urgent evaluation, and a gastroenterologist [will] refer [them to me].”

Referrals are also common from hematologists, added Bose. “Usually, they’ve been picked up by a dermatologist who’s biopsied the rash and sent them to a community hematologist, who then refers the patient to us.”

According to Lugar, the screening includes a physical examination. In this, the clinician is looking for telltale clinical symptoms (eg, urticaria pigmentosa, telangiectasia macularis eruptiva perstans). “We do a skin exam, take clinical history, and then screen for serum tryptase [levels]. We don’t usually do urine histamine or prostaglandin [levels] at that point in time,” said Lugar. “Screening... may also be warranted,” she continued, “... even if the tryptase [level] is not excessively over the reference range, if a patient has symptoms that have been persistent, such as flushing, or if we do see signs of possible lesions consistent with cutaneous mastocytosis.” At that point, she noted, clinicians may consider *c-KIT*, looking for mutations D816V and *c-KIT* by peripheral blood testing. “If we see signs and symptoms that it’s very likely the person has a [MC] disorder, and based on the level of tryptase, [I] would we go ahead and actually recommend a [BM] biopsy,” Lugar said.

Given the noted difficulties of understanding and identifying the mechanisms of SM, diagnosis is often made differentially, Lugar added, which itself is associated with several challenges. “[W]e don’t have ... fantastic clinical markers or biomarkers to also guide us for [MC] activation [compared with those for] a true clonal [MC] disorder,” Lugar said. “We’ve had a number of people

with monoclonal [MC] disorders where the aggregates on biopsy might be quite small but [the patients] have a mutation at *c-KIT*.”

Lugar observed that she examines what brings on the symptoms and what has worked before measuring the serum tryptase level for a baseline. “[If patients] feel that they’ve had anaphylaxis or symptoms that are characteristic, potentially of an allergic reaction, I’ll try to get them to get a tryptase [level] at that time so we can prove that it’s [MCs] [that are] bringing about this complex set of symptoms,” said Lugar. She further explained that genetic analyses may be important even if the clinician does not suspect a diagnosable MC disorder, because understanding the mutation can help.

Genetic testing, such as next-generation sequencing, which DeAngelo referred to as a “rapid heme panel,” can identify specific mutations (eg, in *KIT*, *SRSF2*, *TET2*, and *COX1*) that may respond better to certain therapy. If a targetable mutation is not identified, Lugar observed, clinicians likely need to experiment with a treatment plan that ameliorates some of the symptoms. “It is [often] a long-term [process], where you start with your assessment, and you continue to assess and use whatever tools available to try to work toward a diagnosis,” she noted.

Given these challenges, the panelists underscored that the information from referring physicians is critical for an accurate diagnosis. However, they noted that this path can be complicated. Sometimes, noted DeAngelo, “the referring physician [does] not...specif[y] to the pathologist [her suspicion of mastocytosis],” and the hematologist can miss it. Moreover, according to Wang, hematologists often “cannot afford to do an [MC] workup for every GI biopsy. They have to have some suspicions,” and these must come from the pathologist or referring physician. Additionally, Bose reiterated that if “SM is not on the radar, then absolutely, it could be missed.”

CURRENT AND EMERGING TREATMENT OPTIONS FOR ADVANCED SM

Treatment options for advanced SM are limited, which likely reflects the diagnostic challenges and lack of clinical

biomarkers. Historically, clinicians have relied on chemotherapy and stem cell transplants to treat aggressive SM, but targeted options are available, and others are in development.

Midostaurin

Midostaurin is an oral multikinase inhibitor that inhibits D816V-mutated *KIT*. It is FDA approved for the treatment of patients with advanced SM. In a 10-year follow-up study from a phase 2 trial evaluating patients with organ damage who received 100 mg of midostaurin given twice daily, the overall response rate (ORR) was 69%, and median OS was 40 months. Additionally, 2 of 26 patients achieved complete remission (CR) with ongoing therapy. The BM MC burden was reduced by greater than 50% in 68% of patients, and serum tryptase levels were reduced by more than 50% in 46% of patients.¹⁰

When treating patients with midostaurin, DeAngelo noted, patients may experience nausea. For one of his cases, DeAngelo said, “I tried maximizing his antiemetics, [and] I had to reduce the dose to 50 mg twice daily.” Over the course of several months, the patient was able to tolerate the reduced dose and antiemetic regimen, which allowed DeAngelo to increase the dose back to 100 mg given twice daily. “My experience has suggested that patients have a dose-response curve, so I try to get as much drug as I can,” he explained. After over 1 year of therapy, the patient still had an elevated serum tryptase level, but it was under 20 ng/mL, which is part of the criteria for remission.

Imatinib

For patients with aggressive SM who do not have the D816V *c-KIT* mutation or whose mutational status is unknown, imatinib is an FDA-approved treatment option. Wang described one of her cases, noting that imatinib may be effective for patients with well-differentiated SM with mastocytoma, a rare, often misdiagnosed type of an already rare condition. “[The patient] actually responded beautifully to [imatinib], and all the symptoms resolved—skin lesions, systemic symptoms. However, actually, she was [nonadherent], and [it] came back and recurred again. It was SM,” said Wang.

VIDEO INSIGHTS

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Wang also emphasized the importance of not classifying these patients as having MC hyperplasia because their disease may be associated with numerous other conditions (eg, lymphoplasmacytic lymphoma [which is also associated with a proliferation of MCs], chronic MC leukemia).

Avapritinib

In June 2020, the FDA approved avapritinib for the treatment of adult patients with advanced SM, including those with aggressive SM, SM with an associated hematologic neoplasm, and MC leukemia. Avapritinib is a potent and selective KIT D816V inhibitor. In the phase 1 EXPLORER trial (NCT02561988), patients receiving avapritinib achieved a 75% ORR per modified International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis (IWG-MRT-ECNM) criteria.¹¹ Responses were rapid with complete remissions over time. Investigators also observed improvements in MC burden, organ damage, patient symptoms, and quality of life.¹¹

Results from the phase 2 registrational PATHFINDER trial (NCT03580655) that were recently presented at the American Association for Cancer Research Annual Meeting 2021 showed the potential benefit of avapritinib in patients with advanced SM.¹² In all, 52 patients with a diagnosis of advanced SM with at least 1 evaluable C finding received a starting dose of 200 mg of avapritinib given once daily. Patients with platelet counts less than $50 \times 10^9/L$ were excluded from the study.

The primary end point in the evaluable cohort was adjudicated ORR by modified IWG-MRT-ECNM criteria on mastocytosis. A prespecified interim analysis was planned after 32 patients had sufficient follow-up. Notably, 53% of patients in the interim analysis efficacy population received midostaurin previously, and 13% of patients in this population were treated with cladribine.¹²

Interim analysis demonstrated an ORR of 75%, with 19% of patients achieving CR with partial hematologic recovery. In all, 31% of patients achieved partial remission, and 25% of patients experienced clinical improvement.¹² “Clinical improvement means that their C finding improved or resolved, which, for most patients, is why they’re referring to [hematologists],” DeAngelo explained. Looking beyond the broader study population, DeAngelo noted that the findings held up across histological subtype and prior treatments. “The interesting thing about this study is that responses were seen regardless of the histologic subtype,” he said. “Responses were relatively equivalent regardless of whether patients were previously exposed to midostaurin, like the case I showed you, or whether they were midostaurin naive, [or] whether this was an initial treatment.”

With a median follow-up of 10.4 months, all responses are still ongoing. Median time to response was 2 months, and responses were maintained after dose reduction. Median time to CRs with partial hematologic recovery was 5.6 months. Patients’ responses also improved with time.¹²

Avapritinib therapy led to a notable reduction in BM MCs, with 88% of patients achieving a greater than 50% reduction and 60% of patients achieving elimination of marrow MC aggregates. Additionally, 93% of patients achieved a greater than 50% reduction in serum tryptase level, 60% of patients achieved a 50% or greater reduction in variant allele frequency, and 66% of patients achieved a greater than 35% reduction in spleen volume.¹²

Regarding adverse events (AEs), 5% of patients discontinued the regimen because of treatment, and 68% had a dose reduction because of an AE, most commonly, cytopenias.¹²

Finally, patients receiving avapritinib experienced a significant reduction in total symptom score, with a mean change from baseline of 9.8 ($P < .001$) and a reduction in individual symptom scores.¹² According to DeAngelo, these findings may have particular meaning for patients. “One of the important features of our job is to make patients feel better. And so here, you can see this significant rapid reduction in their total symptom score. All of these symptoms improved in patients who had them, so I think that that is just an important observation.”

Lugar agreed and expressed hope that these results would bear out in continued evaluation of avapritinib. “I hope that the same symptom score for indolent [cases] as well carries over in further trials, because that’s the most difficult thing—managing the chronic symptoms,” she said. “Even if we know these patients are stable, they don’t have a disease that’s going to be progressive, the majority of them, but managing the day-to-day symptoms is such a [benefit toward managing] the burden of disease.”

Bose noted that the PATHFINDER findings coupled with the EXPLORER data are particularly exciting because of not only the ORR, but also the rate of CRs. “This is a drug [that] is hitting the target to a greater depth,” said Bose. “This is a more potent and more selective inhibitor of mutant *KIT*, so I hope we are sparing wild-type *KIT* a little bit more. Not entirely, because we see myelosuppression, but hopefully more than we do with midostaurin,” he said.

CONCLUSIONS

As testing methods and treatment options expand, the rarity and complexity of SM will continue to present significant challenges regarding identification and management. “This is not an easy landscape to toil,” noted DeAngelo. Given the importance of making a definitive diagnosis, both from a molecular and a histopathologic perspective, DeAngelo believes that clinicians and pathologists must work together to ensure diagnostic accuracy. “You really [have] to help the pathologist out,” he said. “That’s where the interaction is so important, to really talk to the pathologist or your referring physicians.” Improved communication among specialists, coupled with emerging treatments that could potentially be used in broader populations, may better enable clinicians to optimize outcomes for patients as the field continues to evolve. ■

For the full list of references, visit [OncLive.com](https://www.onclive.com).

CASE 1

Presentation

- 75-year-old man
- 3-month history of fatigue, abdominal distention, and lower-extremity edema

Main diagnosis: SM

- BM exam:
 - Big, dense infiltrates of MCs into BM
 - Rapid heme panel (RHP): *KIT* D816V mutation
 - Flow cytometry: MCs expressing aberrant CD25
- Tryptase blood test (tryptase): 187 ng/mL

Subtype diagnosis: SM-AHN (with leukocytosis)

- Age > 60 years
- Blood counts:
 - White (WBC): $27 \times 10^9/L$
 - Hemoglobin (Hgb): 8.2 g/dL (anemia)
 - Platelet: $64 \times 10^9/L$ (thrombocytopenia)
- BM exam:
 - RHP: *SRSF2*, *TET2*, and *CUX1* mutations
 - Flow cytometry: MCs expressing CD117 and aberrant CD2
 - Cytogenetics: 46,XY
 - Hypercellular marrow with 40% mast cells
- Blood differential test: 1 nucleated red blood cell (NRBC) (per 100 WBC)
- CT scan: pathologic lymphadenopathy, small pleural effusion, ascites, and splenomegaly

Treatment

- Started midostaurin 100 mg twice daily
 - Difficulty with nausea; maximized antiemetics
 - Reduced dose to 50 mg twice daily
 - Able to slowly reescalate over 3 months back to 100 mg twice daily
- Completed 16 months of therapy
 - Ascites resolved. Hepato-splenomegaly resolved.
 - BM shows partial remission from SM and tryptase level 19 (ng/mL, < 11.5)
 - Remains on midostaurin

EXPERT INSIGHT FROM BOSE

▶ “[An important] point [from this case is that] the [next-generation sequencing (NGS)] miss[ed] the mutation....[W]e, too, had a number of cases [of missing these important mutations] before we started doing the digital droplet PCR [polymerase chain reaction], where we were finding them to be *KIT* wild-type....We’ve [now started to] reflexively order the digital droplet PCR or the molecular diagnostics...if [we] find the NGS is negative.”

CASE 2

Presentation

- 46-year-old woman
- On hospice care
- Chronic diarrhea,* weight loss,* and abdominal distension

Main diagnosis: SM

- BM exam:
 - Big, dense infiltrates of MCs into BM
 - Flow cytometry: MCs expressing aberrant CD25
- Tryptase: 774

Subtype diagnosis: SM-AHN (with leukocytosis)

- BM exam:
 - Flow cytometry: MCs expressing CD117
 - MCs > 30% of the cellularity
- CT scan: ascites, hepatosplenomegaly, no palpable lymphadenopathy
- Histamine level test: 4777 (elevated)
- Esophagogastroduodenoscopy: esophageal varices, gastric erythema, and a duodenal nodule
- Colonoscopy: pan-colonic edema (cecum, ascending, transverse, and descending)
- Transjugular liver biopsy: elevated hepatic pressure gradient

Treatment

- Started midostaurin at 100 mg twice daily
- Completed 12+ years on midostaurin
- Was on total parenteral nutrition at start of therapy
 - Weaned off after 3 months
- GI symptoms resolved
- Remains on midostaurin, but slowly developing asymptomatic progression based on tryptase and BM results
- Enrolled in PATHFINDER study, patient responded

*GI symptom of mast cell disease

EXPERT INSIGHT FROM BOSE

▶ “It’s been great to be a part of the avapritinib story. I find it very impressive that the ORR is 75%, not just in PATHFINDER but also in EXPLORER, which makes it 85 evaluable patients....And...a lot of them are [complete responses]....This is a drug [that] is hitting the target to a greater depth. This is...a more potent and more selective inhibitor of mutant *KIT*, so I hope we are sparing wild-type *KIT* a little bit more....[O]verall, a very exciting drug.”

CASE 3

Presentation

- Urticaria pigmentosa, more prominent after showers, syncope

Main diagnosis: SM

- Skin biopsy: urticaria pigmentosa (confirmed)
- BM exam:
 - Dense MC aggregates (10%-15%)
 - RHP: *KIT* D816V mutation
- Tryptase 79 ng/mL

Subtype diagnosis: ISM

- No C findings
- Normal blood counts

Treatment

- Metastatic *EGFR* exon 19 deletion-mutant lung cancer
 - Treated initially with erlotinib
- Switch to osimertinib, developed anaphylaxis, returns to erlotinib
- Brain progression, desensitization No. 1, recurrent anaphylaxis, back to erlotinib
- Desensitization No. 2, recurrent anaphylaxis
- Started midostaurin 100 mg twice a day
- Started osimertinib 40 mg; well tolerated; no issues
 - Increased dose to 80 mg
 - Good response in brain

EXPERT INSIGHT FROM LUGAR

▶ “Desensitization in [someone with] mastocytosis is certainly not as successful as [in] somebody without mastocytosis....[W]e sometimes use omalizumab [in cases like this],...but [it was a] brilliant [choice to]...just treat the SM directly with an agent like midostaurin. I think that’s exactly what you have to do. And it makes complete sense that [the patient] would’ve responded then with the reduction in mast cell burden. So your only options are to do anything you can to reset that reactivity of the mast cells. You are not going to get around it any other way.”

CASE 4

Presentation

- 68-year-old woman
- Medical history of polymyalgia rheumatica; presented with respiratory distress

Main diagnosis: none

- BM exam:
 - Anaplastic-looking BM cells
 - Flow cytometry: MCs expressing aberrant CD25
- Tryptase: 775 ng/mL
- No *KIT* D816V mutation

Subtype diagnosis: MCL

- Blood counts:
 - WBC: $14.6 \times 10^9/L$
 - Hgb: 9.5 g/dL (anemia)
 - Platelet: $245 \times 10^9/L$
 - Mean corpuscular volume: 102
 - 76% neutrophils, 10% lymphocytes, 4% monocytes, and 9% eosinophils
- No organomegaly
- Cytogenetics: normal karyotype
- Positive for *TET2* mutation
- BM exam:
 - MCs > 20% of the cellularity

EXPERT INSIGHT FROM WANG

▶ “The only diagnostic [criterion] required for mast cell leukemia is more than 20% mast cells on the bone marrow aspirate smears. We question whether this definition is valid. [A] lot of patients [have] 60% [or] 70% infiltration[, but] they don’t come out on the aspirate smears because [of] fibrosis. [And w]e don’t call those mast cell leukemia....A lot of them are leukemic. So *KIT* D816V mutation is less frequent, but they may have a...*KIT* mutation. They may be sensitive to [a] tyrosine kinase inhibitor....*CD2* and *CD25* [are] frequently negative. Cells are often round, immature, or anaplastic rather than spindly, and they may have...other mutations. I don’t know...about mast cell leukemia diagnosis’... only requirement [being] more than 20% mast cells on aspirate smear. [I]s [this] a good [criterion] or just one form of aggressive systemic mastocytosis?”

CASE 5

Presentation

- 24-year-old woman
- Persistent pruritic maculopapular rash on chest and back since childhood (beginning age 4)
- Nausea, vomiting, abdominal pain, joint pains, and weight loss (beginning age 17)
- Skin examination: diffuse faint maculopapular rash, mainly on the upper chest and back (confirmed)

Main diagnosis: none

- BM exam:
 - Round BM aggregates in loose clusters
 - Flow cytometry: *CD30* (no *CD2* or *CD25*)
- Tryptase: 47.1 ng/mL
- NGS: no *KIT* D816V mutation

Subtype diagnosis: well-differentiated SM

- BM exam:
 - MCs > 20% of the cellularity
- No *FIP1L1-PEGFRA* mutation
- Cytogenetics: normal karyotype
- NGS: *KIT* exon 1-21 (codon 1-977)

Treatment

- Patient responded very well to tyrosine kinase inhibitor.
 - All symptoms—skin lesions and systemic systems—resolved.

EXPERT INSIGHT FROM WANG

▶ “[S]ome may call this chronic mast cell leukemia because there [are] more than 20% mast cells on [the] bone marrow aspirate smear[,] but we know that this is well-differentiated SM. What is unique about this type of SM? The patient usually has skin involvement,...they are largely *CD25* [and] *CD2*...negative[,] and they do have [an] elevated serum tryptase [level]. They usually lack [the] typical *KIT* D816V mutation. [H]owever, they do [have] aberrant expression of *CD30*. If we see here the cases [I’m discussing], 8 of 9 cases actually [had] expression [of] *CD30*, none of them [had the typical SM] expression [of] *CD25*....*CD30* can help to identify aberrancy in the cells because when we have this type of SM the question is: Is this reactive mass of hyperplasia or actually a systemic mastocytosis, because they [look so much] like normal mast cells? *CD30* can help you to identify [that] this is [an] aberrant mast cell.”

CASE 6

Presentation

- 47-year-old man
- Leukocytosis, anemia, and splenomegaly

Main diagnosis: SM

- BM exam:
 - Small mast cell aggregates
- NGS: *KIT* D816V mutation
- Flow cytometry: MCs expressing aberrant *CD25*

Subtype diagnosis: SM associated with chronic myelomonocytic leukemia (CMML)

- BM exam:
 - MC hypercellularity
- Blood counts:
 - WBC: $57 \times 10^9/L$
 - Hgb: 7.5 g/dL (anemia)
 - Platelet: $654 \times 10^9/L$
 - 21% monocytes
- Cytogenetics: normal karyotype
- NGS: *ASXL1* and *U2AF1*
- Flow cytometry: aberrant *CD34*, *CD5*, and *CD117*

EXPERT INSIGHT FROM DEANGELO

▶ “[I]n this case[,]...the variant allele frequency for the *KIT* mutation was 41%. [This suggests] that...the disease is probably being driven by *KIT*. The rest of the questions [might be] moot because SM-AHN is the disease and...*KIT* [mutation is the] drive[r]. Are the C findings driven from the mast portion [or the] CMML portion? Does it matter whether they are all driven by *KIT*[?]....I have had patients [like this] who...respond well to *KIT* inhibitor...avapritinib.”

