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Case Report

J Hematol. 2024;13(3):128-136

Unraveling the Rare Entity of *KIT* D816V-Negative Systemic Mastocytosis

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Abstract

Systemic mastocytosis (SM) is a rare type of myeloproliferative neoplasm characterized by abnormal proliferation and infiltration of different tissue by clonal mast cells. The uncontrolled proliferation and activation of mast cells trigger the release of vasoactive and inflammatory mediators, resulting in a cascade of systemic symptoms. Around 95% of SM arise from a gain-of-function mutation at the *KIT* gene, specifically at codon 816, which highlights its essential role in SM and makes it an attractive target for therapy. Although *KIT*-negative SM is exceptionally rare, the increased number of cases documented in the literature makes it an intriguing dimension of this disorder. The reported clinical manifestations of *KIT*-negative SM are widely variable, but many are similar to *KIT*-positive SM. KIT-targeted therapeutic options have been a game-changer in *KIT*-positive SM, however their role in *KIT*-negative SM remains controversial. This report aimed to further understand *KIT*-negative SM by presenting two cases of *KIT*-negative SM, one of which was responsive to KIT-targeted therapy, and analyzing reported cases in the existing literature.

Keywords: Systemic mastocytosis; *KIT*-negative systemic mastocytosis; Tyrosine kinase inhibitor; Imatinib; Avapritinib; Midostaurin

Introduction

Mast cell disorders represent a category of myeloproliferative neoplasms characterized by aberrant clonal mast cell proliferation [1, 2]. These abnormal mast cells infiltrate various tissues and get activated, leading to clinical manifestations mimicking allergic reactions without an identifiable allergic trigger [3, 4]. The International Consensus Classification (ICC) and World Health Organization (WHO) recently updated their classification of mastocytosis. It classified mast cell disorders into cutaneous mastocytosis, systemic mastocytosis (SM), and mast cell sarcoma (MCS), with further subclassifications depending on the extent of involvement within each category (Table 1) [1, 5-10]. The diagnostic criteria for SM in the WHO fifth edition and in ICC were revised to require a major criterion with one minor or at least three minor criteria (Table 2) [1, 8-11].

SM (SM) is a rare type of mast cell disorder characterized by the infiltration of various tissues, including but not limited to the bone marrow, gastrointestinal organs, and other extracutaneous tissue, by dysregulated mast cells [1, 12]. Although identifying *KIT*-activating gene mutation, specifically at codon 816, is considered a fundamental part of the diagnosis and is one of the four minor criteria according to the ICC diagnostic criteria for SM, its negativity does not exclude the diagnosis [1, 13]. Few patients do not reveal a *KIT* mutation; however, these cases are rare [12]. In this case report, we report two cases of *KIT*-negative SM and a review of the cases reported in the literature. We aimed to enhance our understanding of this exceedingly rare entity's distinctive features, the diagnosis, and management.

Case Reports

Case 1

A 49-year-old previously healthy female was referred to our care with a 4-year history of painless and nonpruritic cutaneous eruptions affecting her upper and lower extremities, as well as the abdomen. These eruptions occurred spontaneously, without identified triggers. In the year preceding her hospital visit, the patient experienced unexplained episodes of dizziness accompanied by nausea and vomiting. The diagnostic investigation revealed thrombocytopenia (C-finding) and a high serum tryptase level (157 µg/L). Computed tomography (CT) imaging showed splenomegaly (B-finding) and multiple lytic lesions (C-finding) (Table 3) [1, 9]. A subsequent bone marrow biopsy disclosed 70% cellularity, with 40% mast cells, consist-

Manuscript submitted April 16, 2024, accepted May 28, 2024
Published online June 28, 2024

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doi: https://doi.org/10.14740/jh1279

Table 1. The WHO Fifth Edition (WHO 5th) and the ICC Classifications of Mastocytosis

Cutaneous mastocytosis	ICC	WHO 5th
	1. Urticaria pigmentosa/maculopapular cutaneous mastocytosis	1. Urticaria
	2. Diffuse cutaneous mastocytosis	Pigmentosa/maculopapular cutaneous mastocytosis
	3. Mastocytoma of skin	Monomorphic
		Polymorphic
		2. Diffuse cutaneous mastocytosis
		3. Cutaneous mastocytoma
		Isolated mastocytoma
		Multilocal mastocytoma
SM	ICC	WHO 5th[a]
	1. Indolent SM (includes bone marrow mastocytosis)[b]	1. Bone marrow mastocytosis[d]
	2. Smoldering SM[b]	2. Indolent SM
	3. Aggressive SM[b]	3. Smoldering SM
	4. SM with an associated myeloid neoplasm	4. Aggressive SM
	5. Mast cell leukemia[c]	5. SM with an associated hematologic neoplasm
		6. Mast cell leukemia
Mast cell sarcoma	ICC	WHO 5th[a]

[a]In the WHO classification, well-differentiated systemic mastocytosis (WDSM) is a morphologic variant that can occur in any SM subtype, including mast cell leukemia. [b]In the ICC, those variants of SM must be correlated with B- and C-findings. [c]In the ICC, mast cell leukemia must meet the diagnostic criteria of SM and have ≥ 20% atypical immature mast cells. [d]Bone marrow mastocytosis (BMM) typically lacks the B-findings and with normal/near normal serum tryptase. The WHO classifies BMM as an SM subcategory, while in ICC, it is considered a variant of indolent SM. SM: systemic mastocytosis; WHO: World Health Organization; ICC: International Consensus Classification.

Table 2. The WHO Fifth Edition (WHO 5th) and the ICC Diagnostic Criteria for SM

WHO 5th[a]	ICC[a]
Major criterion	
Infiltrates of mast cells (≥ 15 mast cells in aggregates) in BM or extracutaneous organs[b]	Infiltrates of tryptase- and/or CD117 positive mast cells (≥ 15 mast cells in aggregates) in the BM or extracutaneous organs[b]
Minor criteria	
≥ 25% of all mast cells are atypical cells (type I or type II) or are spindle-shaped	≥ 25% of all mast cells are atypical cells or are spindle-shaped
KIT-activating *KIT* point mutation(s) at codon 816 or in other critical regions of *KIT*[c]	*KIT*-activating *KIT* point mutation(s) at codon 816 or in other critical regions of *KIT*[c]
Mast cells express at least one of the following markers: CD2 and/or CD25 and/or CD30[d]	Mast cells express at least one of the following markers: CD2 and/or CD25 and/or CD30[d]
Baseline serum tryptase > 20 ng/mL[e]	Baseline serum tryptase > 20 ng/mL[f]

[a]For SM diagnosis at least one major and one minor or three minor criteria must be met. [b]Spindle-shaped mast cells do not count as an SM criterion when they line vascular cells, fat cells, nerve cells, or the endosteal-lining cell layer. Valent et al. describe detailed morphological criteria [11]. [c]For *KIT* mutation, high-sensitivity PCR is recommended to avoid false negatives. In the absence of a *KIT* D816V mutation, exclusion of *KIT* mutation variants is strongly recommended (this includes codons 417, 501 - 509, 522, 557 - 560, 642, 654, 799, 816, 820, 822, the list of variants provided in the appendix of WHO proposal [1]. In cases of negative KIT, particularly those with eosinophilia, tyrosine kinase gene fusions associated with myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions must be excluded. [d]By flow cytometry or immunohistochemistry or by both techniques. [e]In the WHO classification, patients with hereditary alpha-tryptasemia (HαT) need adjustment for tryptase level (although not standardized). The suggested correction is to divide the basal tryptase level by (1 + the extra copy numbers) of the alpha tryptase gene. For example, when the tryptase level is 60 and three extra copies of the alpha tryptase gene are present, the corrected tryptase level is 15 (60/4 = 15) and thus it does not meet this minor SM criterion. [f]Per ICC, elevated tryptase does not count as a minor SM criterion in SM with an associated myeloid neoplasm. SM: systemic mastocytosis; WHO: World Health Organization; ICC: International Consensus Classification; BM: bone marrow.

Table 3. The WHO Fifth Edition Summarizing the Clinical Findings of SM, Classified Into B-Findings and C-Findings (Adapted From Valent et al [1, 9])

B-findings	C-finding
Increased mast cell burden: ≥ 30% by histology on BM and/or serum tryptase ≥ 200 ng/mL and/or *KIT* D816V VAF ≥ 10% in BM or PB white blood cells	Cytopenia/s (one or more of the following): ANC < 1×10^9/L, Hb < 10 g/dL, Plt < 100×10^9/L
Features suggestive of MPN and/or MDS	Hepatopathy: hepatomegaly or cirrhosis ± ascites and elevated liver enzymes ± portal HTN
Organomegaly: palpable hepatomegaly or/and splenomegaly without systemic effects (i.e., no ascites or signs of organ damage and no hypersplenism, weight loss, and/or lymphadenopathy or visceral LN enlargement (> 2 cm) on imaging	Spleen: palpable splenomegaly with hypersplenism ± weight loss ± hypoalbuminemia
	GIT: malabsorption and hypoalbuminemia ± weight loss
	Bone: large-sized osteolysis (≥ 2 cm) with pathologic fracture ± bone pain

WHO: World Health Organization; BM: bone marrow; VAF: variant allele frequency; PB: peripheral blood; MPN: myeloproliferative neoplasm; MDS: myelodysplastic syndrome; LN: lymph node; ANC: absolute neutrophil count; Plt: platelet; Hb: hemoglobin; HTN: hypertension; GIT: gastrointestinal tract.

ent with SM. Immunostaining was positive for CD117, CD68, and tryptase, while molecular testing from the peripheral blood using polymerase chain reaction (PCR) to amplify exons 8, 9, 11, 13, and 17 of c-KIT was negative. Attempts to get a sample for the bone marrow were unsuccessful as they resulted in a dry tap. There was no evidence of other concomitant hematological malignancy on bone marrow examination. Positron emission tomography (PET)/CT scan illustrated fluorodeoxyglucose (FDG)-avid generalized skeletal sclerosis attributable to the underlying SM. The patient was started on imatinib along with symptomatic treatment such as topical clobetasol, famotidine, and loratadine, which led to improvement in the skin lesions, although she reported muscle aches, which were attributed to medication-related adverse effects. The patient is presently well maintained on a regimen of 300 mg of imatinib daily 2 years from the initial presentation.

Case 2

A 40-year-old male, known to have bronchial asthma, sought medical attention for recurrent anaphylactic episodes marked by syncope, skin manifestations, respiratory distress, and gastrointestinal symptoms. The clinical presentation, initially triggered by physical exertion and later associated with specific dietary factors, prompted comprehensive diagnostic investigations. These episodes started at the age of 30 years and manifested as sudden-onset headaches, palpitations, and flushing, followed by an episode of brief loss of consciousness. The evaluation revealed eosinophilia, prompting bone marrow biopsy, which revealed indolent SM, demonstrating multifocal infiltration by atypical mast cells expressing tryptase, CD117, and CD25. Cytogenetic studies were negative for PDGFR alpha and beta rearrangements, and molecular testing from the bone marrow sample using PCR to amplify exons 8, 9, 11, 13, and 17 of c-KIT was negative, as well as testing of the *KIT* mutation through the myeloid next-generation sequencing (NGS) panel on the bone marrow samples, returned negative results. There was no evidence of an associated myeloid neoplasm on bone marrow review. Therapy with midostaurin was started, while continuing on supportive therapy which included montelukast, cetirizine, and inhaled intranasal and systemic steroids (prednisolone 5 mg daily), resulting in a significant reduction in symptom frequency. However, subsequent challenges in medication availability led to sequential transitions to dasatinib, which was changed later to imatinib due to poor response, and ultimately avapritinib after developing another anaphylactic reaction 9 months after starting imatinib. The patient is well managed with avapritinib and has a complete clinical response; however, he developed hair and skin depigmentation, attributed to avapritinib treatment (Fig. 1).

Discussion

SM represents a rare and aggressive entity within the spectrum of mast cell disorders, featuring further subclassifications according to the ICC that vary in severity, including indolent SM (incorporating bone marrow mastocytosis), smoldering SM, aggressive SM, SM with an associated hematologic neoplasm (AHN-SM), and mast cell leukemia (MCL) (Table 1) [1, 8-10].

Mastocytosis is often linked to somatic gain-of-function point mutations in the *KIT* gene, namely at the D816V domain, where aspartic acid is replaced by valine, resulting in unregulated proliferation, amplified growth, and increased survival of mast cells [14, 15]. Various cellular entities, including mast cells, hematopoietic progenitor cells, germ cells, melanocytes, and interstitial cells of Cajal within the gastrointestinal tract, manifest the expression of KIT, a type III receptor belonging to the tyrosine kinase family encoded by a 21-exon containing gene located on chromosome 4q12 [9, 16-19]. In normal circumstances, the *KIT* gene is downregulated upon the maturation of all hematopoietic progenitor cells, except for mast cells. Mast cell surfaces express *KIT* genes at high levels. However, the stem cell factor, a ligand for KIT, controls the mast cell activity [9, 15]. Other less common mutations observed in advanced SM encompass, yet are not confined to, *TET2*, *SRSF2*, *ASXL1*, *RUNX1*, *JAK2*, *N/KRAS*, *CBL*, and *EZH2* [13, 20-22].

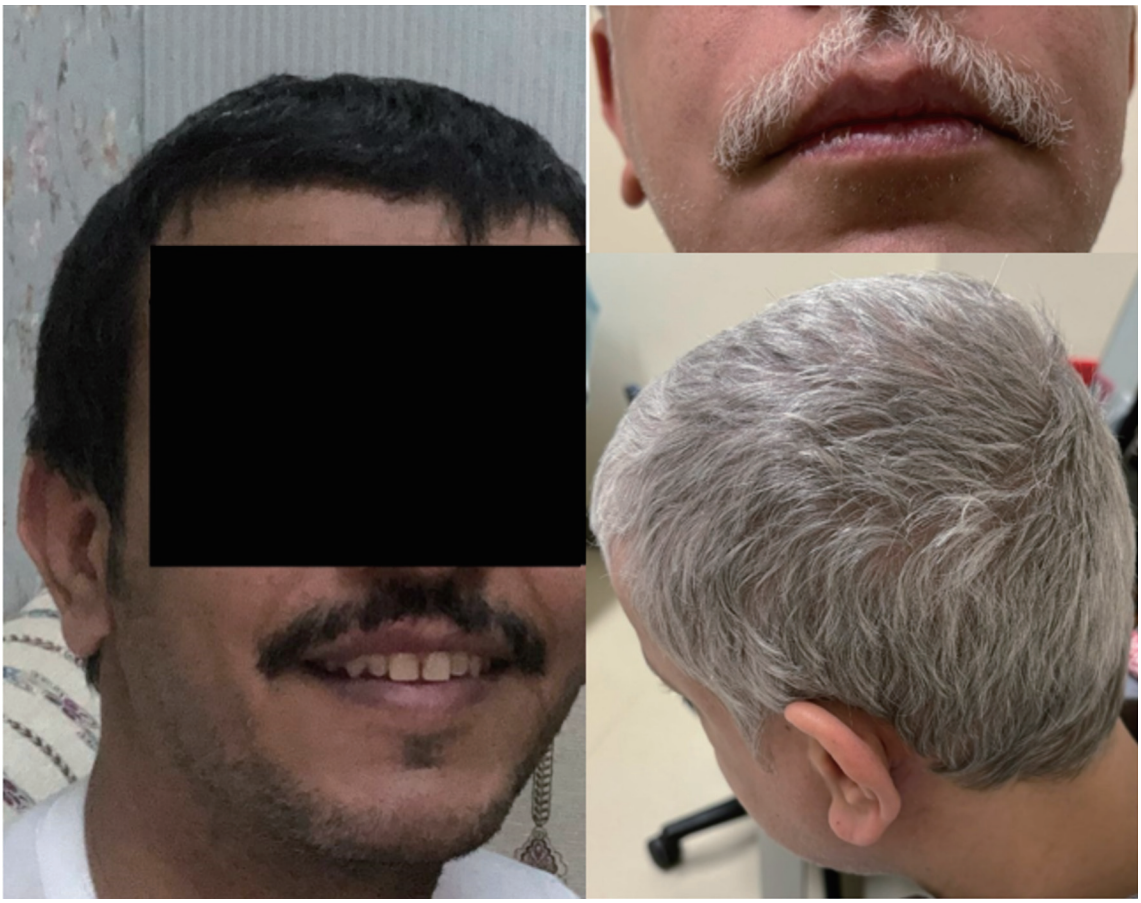

Figure 1. Case 2: skin and hair color pre (left) and post (right) avapritinib treatment. Wild-type KIT signaling is involved in melanogenesis and hair pigmentation, and inhibition can result in hair depigmentation and lightning of the skin through a temporary melanocyte dysfunction. Avapritinib skin and hair changes were reported in 6% to 21% of treated patients.

Although *KIT* mutations are prevalent, occurring in > 95% of SM cases, their uniform presence is not ubiquitous [12, 23]. The occurrence of *KIT*-negative cases of SM is notably rare [9, 24]. However, their prevalence has gained increased recognition over the years, as evidenced by the cases reported in the literature (Table 4) [14, 25-28] and those presented in this paper. Research is still being done to understand better the complex interactions between different mutations, their capacity to change mast cells, and their influence on clinical manifestations and treatment of mastocytosis [9]. Individuals with SM manifest symptoms primarily related to the infiltration of different tissues by mast cells and their activation, which leads to the release of vasoactive mediators and cytokines [3]. The clinical manifestations include episodic flushing, diarrhea, hypotension, osteoporosis, and abdominal pain [4, 14]. In the context of *KIT*-negative SM, there is not enough evidence on the specific features seen in this entity; however, there is evidence expressing its association with advanced SM subtypes, such as MCL and MSC [12, 29]. According to the cases we have reported and reviewed in the literature, the clinical symptoms seem similar to those of *KIT*-positive SM (Table 3) [1, 9]. Additional features reported in the sparse cases available in the literature include dizziness, nausea, vomiting, headache, fatigue, weight loss, memory problems, insomnia, exertional dyspnea, joint pain, lower gastrointestinal bleeding, and compression fractures [14, 25-28]. By assessing both our reported *KIT*-negative SM cases and those documented in the literature, we can see that there appears to be a noticeable diversity in clinical manifestations. This spectrum includes a range of symptom types and varying degrees of severity, collectively emphasizing the notable variability in this condition (Table 3) [1, 9].

Detecting *KIT*-activating point mutations is typically done using molecular biology techniques, precisely PCR in conjunction with DNA sequencing [9, 15, 30]. The ability to detect the *KIT*-D816V mutation relies on the sensitivity of the test used and the concentration of mast cells in the sample [31]. *KIT*-D816V testing from whole blood has been reported to have high specificity but limited sensitivity [32]. To enhance the sensitivity of this testing, it has been recommended that the test be performed on purified cell groups, including abnormal mast cells, eosinophils, basophils, and monocytes [32]. However, targeting the affected mast cells or other cell groups makes testing challenging, and this is further complicated by the inconsistency of mast cell infiltration in cases of SM. Several attempts have been made to enhance the sensitivity of de-

Table 4. Clinical and Pathologic Comparison of Our SM Cases and Cases in the Literature

	Sex	Age (years)	SM subtype	Presenting symptoms	Management	Response
Case 1	F	49	Aggressive SM	Skin rashes, dizziness, nausea, vomiting	Imatinib 300 mg	Clinical response
Case 2	M	40	Indolent SM	Recurrent anaphylactic episodes	Avapritinib 150 mg/day	Clinical response
Azad et al, 2023 [25]	M	53	Aggressive SM	Headache, fatigue, weight loss, cognitive impairment, insomnia, exertional dyspnea, abdominal pain, bone and joint pain, diarrhea, bloody stools, and a pruritic rash localized in the torso and extremities	Failed imatinib, cladribine, nilotinib, hydroxyurea, and midostaurin	Clinical and biochemical response to avapritinib.
					Avapritinib 200 mg/day	
Conde-Fernandes et al, 2017 [27]	M	15	Indolent SM	Recurrent flushing, hypotension, and syncope, preceded by skin lesions	Oral disodium cromoglycate	Clinical and biochemical response
Caceres-Nazario et al, 2016 [14]	M	78	Aggressive SM	Incidental discovery of normocytic anemia with thrombocytopenia	Imatinib to interferon-α	Death
					Prednisone	
Savini et al, 2015 [28][a]	F	65	Mast cell leukemia	Flushing and hypotension	Antihistamine	Death
					Imatinib 400 mg to dasatinib 100 mg	
Sakane-Ishikawa et al, 2013 [26][b]	F	43	Aggressive SM	Vertebral compression fracture, multiple lytic bone lesions with epidural mass, and eosinophils	Emergent laminectomy and subsequent irradiation of the tumor	Death
					Interferon-α to dasatinib to cladribine	

[a]The patient died of hemorrhagic stroke and disseminated intravascular coagulation. [b]The patient initially responded to interferon-α, however, it was changed due to myelosuppression. Cladribine resulted in improvement in eosinophilia. The patient died from sepsis. SM: systemic mastocytosis.

tecting *KIT* mutations in SM [30]. Kristensen et al developed a quantitative and sensitive allele-specific real-time quantitative polymerase chain reaction (qPCR) assay to detect the *KIT*-D816V mutation [30]. This test detected the mutation in 19 out of 20 SM patients at low levels, as low as 0.03% in bone marrow mononuclear cells [30]. In cases of a negative *KIT* testing result, applying refined methodologies becomes essential for assessing the results' reliability, particularly when the mutation detection limit exceeds the proportion of mast cells within the sample, often due to the island-like aggregation of mast cells in the bone marrow [30]. Nevertheless, the genuinely negative *KIT* mutation is believed to occur in some patients with SM. Further refinement and advancement of methodologies and investigations are needed to improve *KIT* mutation detection and accurately diagnose *KIT*-negative SM. NGS can enhance the ability to detect *KIT* and non-*KIT* mutations and quantify the variant allele frequency (VAF) of the *KIT*-D816V mutation [33, 34]. A limitation of our study is the unavailability of the most advanced tools for detecting *KIT* mutations, which may have led to false-negative results in the cases we reported.

The therapeutic approach to SM depends on the severity of symptoms. Therapy can range from vigilant monitoring to cytoreductive therapy and, in rare and more aggressive cases, stem cell transplantation [9, 34]. Treatment modalities include symptom alleviation, mast cell reduction strategies for disease modification, and the implementation of supportive measures [9].

Symptomatic control involves the regulation of vasoactive mediators and cytokines, achieved through administration of H1 and H2 antihistamines, anti-leukotrienes, and nonsteroidal anti-inflammatory drugs (nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin) [9, 34, 35]. Omalizumab, a recombinant humanized monoclonal antibody, improves mastocytosis symptoms by inhibiting immunoglobulin E (IgE) binding to the high-affinity IgE receptor (RI) on mast cells' surface. Its efficacy is particularly seen in patients experiencing recurrent anaphylaxis [9, 34, 36]. Despite its symptomatic benefits, the Food and Drug Administration (FDA) has not yet approved omalizumab for mastocytosis [9, 36]. Disodium cromoglycate is an organic sodium salt used to treat asthma. It has improved tryptase levels and symptoms in *KIT*-D816V-negative SM cases [27]. It functions as a mast cell stabilizer and has an anti-inflammatory effect. In the report by Conde-Fernandes et al, the patient turned out to have a different type of *KIT* mutation,

known as the *KIT*-V560G mutation [27].

Advanced cases require additional interventions, including cytoreductive agents, for example, hydroxyurea, which causes non-targeted myelosuppression, purine analogs such as cladribine, and interferon-α [4, 9, 37-39]. Cladribine has demonstrated efficacy across all the subtypes of SM, with the additional advantage being time-constrained [9, 38]. Interferon-α is less frequently used but may be valuable in areas with modest resources [9, 39]. However, with the rapid evolution in the medical field, advancements in targeted therapies have emerged, which has increased their appeal. The high prevalence of *KIT* mutations in SM makes it an attractive therapeutic target [40, 41]. Examples of kinase inhibitors that selectively target *KIT* mutations include avapritinib, approved as first-line therapy for indolent and advanced SM [42-45]. Regarding cases of true *KIT*-negative SM, it is theorized that therapies that selectively target *KIT* mutations are less effective when compared to their impact in cases of *KIT*-positive SM. Therefore, pursuing treatments with alternative mechanisms of action beyond *KIT* mutation targeting is considered a viable therapeutic strategy when managing such cases. That being said, there is evidence demonstrating the efficacy of avapritinib in cases of *KIT*-negative SM [25]. This observation is highlighted in some of the cases reported, including one of ours (Table 3) [1, 9]. Gotlib et al explored the efficacy of midostaurin, a potent multi-kinase inhibitor, in cases of advanced SM and reported a response rate of up to 60%, irrespective of *KIT*-mutation status [46, 47]. Alternatively, tyrosine kinase inhibitors (TKIs) such as imatinib, nilotinib, and dasatinib are used in cases of *KIT*-negative SM. Interestingly, *KIT*-positive SM patients respond poorly to various TKIs, especially to imatinib, as *KIT*-D816V mutations result in primary resistance [48-51]. Nonetheless, there has been significant heterogeneity in the responsiveness to different TKIs across the reported cases of *KIT*-negative SM (Table 3) [1, 9].

Multiple medications are being investigated for efficacy in SM, including bezuclastinib, an orally administered potent and selective type I TKI targeting multiple loci, including D816V [52-54]. BLU-263 is an orally administered selective inhibitor targeting *KIT* D816V [55, 56]. Masitinib is a TKI exhibiting activity against wild-type KIT, Lyn, and Fyn kinases [57].

Supportive interventions are vital to managing SM. These measures include avoiding triggers such as aspirin, contrast dyes, anesthesia, narcotics, and alcohol, as well as preventing and managing osteopenia/osteoporosis [9, 34].

The prognosis of SM depends on different factors, including age, cytopenias, the WHO classification-defined subtype of SM, biochemical markers, and mutational profile [58-60]. Multiple prognostic scoring systems are used for advanced and non-advanced SM, e.g., REMA, IPSM, GPS, MARS, and MAPS scoring systems. These scoring systems rely on parameters such as age, blood counts, serum tryptase, β2-microglobulin, alkaline phosphatase, and the mutational profile [20, 21, 34, 61, 62]. The presence of non-*KIT* mutations, such as *SRSF2*, *ASXL1*, *RUNX1*, and *EZH2*, has been associated with advanced SM subtypes and inferior prognosis [12, 20-22, 34]. Although a *KIT*-D816V VAF of > 10% has been linked with a higher tumor burden [63, 64], the prognosis of patients with negative *KIT*-D816V mutations remains vague. In cases of *KIT*-D816V-negative SM, these prognostic scores are controversial.

A report by Naumann et al concluded that the conventional scoring systems used in SM cannot be applied in cases of *KIT*-negative SM and have linked the negativity of KIT in SM with an inferior response to treatment and overall survival [12]. However, in AHN-SM, patients with *KIT*-D816V-negative mutation had a lower burden of mast cells with the domination of the AHN, which resulted in a better overall survival [12]. In this review, we have reported a case of *KIT*-D816V-negative SM with an excellent response to avapritinib, along with the reported case by Azad et al (Table 3) [1, 9, 25], which can serve as an initiation point for further comprehensive cohort studies to assess the effect of avapritinib on *KIT*-D816V-negative SM. The prognostic implications of the *KIT* D816V mutation require additional investigations to thoroughly establish its influence on overall survival, disease-free survival, and quality of life [14, 60].

Conclusions

SM is a rare disease, and the *KIT*-D816V-negative SM subset accounts for less than 5% of all cases. This exceedingly rare entity's specific clinical manifestations, treatment, and prognosis are poorly understood. Further and more comprehensive research is needed to expand our understanding of *KIT*-D816V-negative SM and determine the most appropriate management and prognosis.

Acknowledgments

None to declare.

Financial Disclosure

This report is not funded by a specific grant.

Conflict of Interest

Mansour Alfayez: Honoraria: Johnson & Johnson, Pfizer, Astellas, Novartis, Amgen, AstraZeneca, AbbVie; Advisory board: Johnson & Johnson, Biologix, Eli Lilly; Research support: Abbvie, AstraZeneca. Other authors declare no conflict of interest with this manuscript.

Informed Consent

Informed consents were obtained.

Author Contributions

RA, CAA, SA, AH, and SKA compiled and summarized the

data. RA, SOA and MA treated the patient and wrote the article. All authors contributed, reviewed, and edited the manuscript.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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