Systemic Mastocytosis With Associated Clonal Hematologic Nonmast Cell Lineage Disease

A Clinicopathologic Review

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- Systemic mastocytosis (SM) is a heterogeneous disease with 6 subtypes, including systemic mastocytosis with associated clonal hematologic nonmast cell lineage disease (SM-AHNMD). Bone marrow biopsy specimens show multifocal aggregates of mast cells with predominantly spindle-shaped morphology associated with a myeloid or, less frequently, a lymphoproliferative neoplasm defined by World Health Organization criteria. Neoplastic mast cells abnormally express CD2 and/or CD25, which may be detected by flow cytometry or immunohistochemistry. The pathogenesis of SM-AHNMD is not well understood; however, combined KIT tyrosine kinase receptor mutations and additional genetic events in myeloid stem cells may have a pathogenic role. Reactive mast cell hyperplasia, monocytic/histiocytic proliferations, SM without sufficient criteria for a diagnosis of AHNMD, atypical mast cells associated with PDGFRα rearrangements, and other tryptase-positive myeloid proliferations should be excluded. Overall, the prognosis is poor and largely related to the AHNMD. Cytoreductive therapies, splenectomy, allogeneic bone marrow transplant, and tyrosine kinase inhibitors, excluding imatinib, may have potential efficacy in the treatment of these diseases.

(Systemic Mastocytosis With AHNMD—Stoecker & Wang)

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ystemic mastocytosis (SM) is a heterogeneous neoplasm characterized by a clonal proliferation of abnormal mast cells that accumulate in 1 or more extracutaneous organs. Subtypes of systemic mastocytosis are defined by the World Health Organization (WHO) according to the distribution of abnormal mast cell infiltrates and the clinical presentation. In SM there is involvement of the bone marrow, liver, spleen, lymph nodes, or gastrointestinal tract with or without cutaneous lesions. In approximately 5% to 40% of systemic mastocytosis cases, an associated hematologic nonmast cell lineage disease (AHNMD) is diagnosed simultaneously with, before, or after the diagnosis of systemic mastocytosis. The AHNMD is diagnosed according to WHO criteria and can be a myeloid, lymphoproliferative, or plasma cell neoplasm. In most cases, a myeloid malignancy, including myelodysplastic syndromes, myeloproliferative neoplasms, myelodysplastic/myeloproliferative neoplasms (e.g., chronic myelomonocytic leukemia), and acute myeloid leukemia, is diagnosed. In some cases, the mast cell aggregates may be obscured by the nonmast cell proliferation and become apparent after therapy-induced aplasia or repopulation of the marrow by normal hematopoietic elements. Because of this, the diagnosis of SM-AHNMD presents challenges to pathologists. Here, we provide a brief review of SM-AHNMD with emphasis on the histopathologic features and relevant ancillary laboratory studies.

CLINICAL FEATURES

Systemic mastocytosis, including SM-AHNMD, is rare in children and usually diagnosed after the second decade of life. In comparison to other subtypes of SM, a greater proportion of patients are male. The clinical presentation of SM may include constitutional symptoms (fatigue, weight loss, headache, pain, nausea), skin lesions (pruritus, urticaria), mediator-related events (abdominal pain, diarrhea, peptic ulcer, flushing, syncope, hypotension, tachycardia, respiratory symptoms), and musculoskeletal complaints (bone pain, osteoporosis, fractures, myalgias, arthralgias). In SM-AHNMD, patients may present with symptoms related to systemic mastocytosis and the associated hematologic malignancy. Constitutional symptoms are reported most frequently in patients with SM-AHNMD owing to the proliferation of neoplastic mast cells and the nonmast cell lineage component in specific organ systems, while skin lesions, mediator-related events, and gastrointestinal symptoms are reported much less frequently.

Physical examination findings in SM may include skin lesions, hepatomegaly, splenomegaly, and lymphadenopathy. Hematologic findings are frequently present, including anemia, leukocytosis, blood eosinophilia, monocytosis, thrombocytopenia, and elevated lactate dehydrogenase levels. Similar findings may be seen in SM-AHNMD, although the physical and hematologic findings may largely be related to the specific AHNMD.

HISTOPATHOLOGY

In hematoxylin-eosin–stained tissue sections, normal and reactive mast cells have round to oval nuclei with...
clumped chromatin, a low nuclear to cytoplasmic ratio, absent or indistinct nucleoli, and abundant eosinophilic cytoplasm. They are scattered throughout the tissue and are only rarely found in dense aggregates. Normal and reactive mast cells in Romanowsky-stained bone marrow aspirate smears have central round to oval nuclei with abundant cytoplasm containing densely packed metachromatic granules.

In cases of SM, hematoxylin-eosin–stained bone marrow biopsy sections demonstrate multifocal or diffuse cohesive infiltrates of mast cells with spindle-shaped morphology or other atypical morphologic features, including immature chromatin or nuclear lobation/multinucleation. In bone marrow biopsy specimens, mast cell aggregates can be found in paratrabecular, perivascular, or interstitial locations and are often associated with reticulin fibrosis, osteosclerotic or osteolytic changes in the trabecular bone, and lymphocytes and/or eosinophils. In some instances, lymphoid aggregates may be surrounded by mast cell proliferations, or oppositely, mast cell aggregates may form the central core surrounded by lymphocytes (Figure 1, A and B). Bone marrow aspirate smears show atypical mast cells with elongated nuclei, immature chromatin, nuclear lobation or multinucleation, hypogranular cytoplasm, and excessive cytoplasmic extensions (Figure 1, C).

Immunohistochemical stains are useful for identifying mast cells in tissue sections. Tryptase (cytoplasm) and CD117 (membrane and cytoplasm) are expressed in normal and neoplastic mast cells. Early myeloid and erythroid precursors can also express CD117, however, the expression is weaker. Neoplastic mast cells, in addition to tryptase and CD117, show aberrant expression of CD2 and/or CD25. This finding is especially helpful when atypical mast cells are present in a diffuse interstitial pattern. Cytochemical stains performed on bone marrow aspirate smears may also be useful when there is atypical nuclear morphology or cytoplasmic hypogranulation. Normal, reactive, and neoplastic mast cells stain with naphthol AS-D chloroacetate esterase (CAE) and are negative for myeloperoxidase expression.

The WHO defines 1 major criterion and 4 minor criteria for the diagnosis of SM. The major criterion is detection of multifocal, dense infiltrates of mast cells (≥15 mast cells in aggregates) in an adequate bone marrow biopsy specimen and/or other extracutaneous organ(s). The minor criteria are as follows: (1) greater than 25% of mast cells in the bone marrow or other extracutaneous organ biopsy specimens are spindle-shaped or have atypical morphology, or greater than 25% of the mast cells in the bone marrow aspirate smear are immature or atypical; (2) an activating point mutation at codon 816 of KIT in bone marrow, blood, or other extracutaneous organs is detected; (3) CD2 and/or CD25, in addition to normal mast cell markers, are expressed on mast cells in the bone marrow, blood, or other extracutaneous organs; and (4) serum total tryptase levels persistently exceed 20 ng/mL.

The diagnosis of SM-AHNMD is established when WHO criteria for SM and a distinct hematologic nonmast cell lineage disease are met. The fourth minor criterion involving elevation of serum total tryptase levels is excluded from the diagnostic criteria in cases of SM-AHNMD. Clues to the morphologic diagnosis of SM-AHNMD include abnormal peripheral blood cell counts and morphology, hypercellularity of the bone marrow, signs of dysplasia or abnormal myelopoiesis, increased number of blasts (Figure 2, A and B), and abnormal lymphoid or plasma aggregates or interstitial infiltrates. In many cases, the bone marrow is often the only documented site of involvement in SM-AHNMD; therefore, close examination for an AHNMD is important in all cases of SM. Alternatively, the SM component of SM-AHNMD is often identified incidentally during the bone marrow evaluation of the associated nonmast cell hematologic disease. In some cases of SM-AHNMD, the SM component can be obscured by the proliferating neoplastic myeloid or lymphoid cells, and the diagnosis of SM may be initially missed. This is especially true when aggregates of atypical mast cells are small or infrequently present within the biopsy specimen. Owing to the reticulin fibrosis frequently associated with the mast cell aggregates, bone marrow aspirate smears may not be helpful in identifying the atypical cytolanic features. Immunohistochemistry, including stains for mast cell tryptase, CD117, CD2, and CD25, as discussed previously, is frequently helpful in identifying the abnormal mast cell aggregates (Figure 3, A and B). After treatment of the nonmast cell malignancy, mast cell aggregates may become more apparent in the setting of marrow aplasia or repopulation with normal hematopoietic elements (Figure 4).

The AHNMD in most cases is a myeloid neoplasm. Among these cases, myeloproliferative neoplasms (MPNs) diagnosed according to WHO criteria, including primary myelofibrosis, essential thrombocytosis, polycythemia vera, chronic myelogenous leukemia, chronic eosinophilic leukemia, and MPN-unclassifiable, have been reported. Cases of MPN-unclassifiable are characterized by hepatosplenomegaly, leukocytosis, thrombocytosis, and megakaryocytic proliferation not fulfilling criteria for another specific MPN. Patients with SM-MPN may present with prominent eosinophilia, and many of these patients may fulfill criteria for chronic eosinophilic leukemia if a clonal molecular or cytogenetic abnormality or increased number of blasts (>5% in the bone marrow) is identified. Cases with an associated myelodyplastic syndrome (SM-MDS) have included refractory anemia with excess blasts types 1 and 2, refractory anemia, refractory anemia with ringed sideroblasts, refractory cytopenia with multilineage dysplasia, and MDS associated with deletion of 5q. Panmyelopenia, a hypercellular bone marrow with dysplasia in 1 or more cell lines, blast counts, and correlation with cytogenetic studies help to establish and further subclassify cases of SM-MDS. Myelodysplastic/myeloproliferative neoplasms, most frequently chronic myelomonocytic leukemia (SM-CMML), are defined by myeloproliferative features (leukocytosis, specifically monocytosis in CMML, or thrombocytosis) and dysplastic features in 1 or more cell lines with or without an associated clonal cytogenetic abnormality. Leukemic transformation of these entities in addition to de novo acute myeloid leukemia (AML), classified according to cytogenetic and molecular and/or morphologic and immunophenotypic features, may also be identified as the AHNMD. Lymphomas, including chronic lymphocytic leukemia/small lymphocytic lymphoma and plasma cell myeloma, are identified much less frequently.

ANCILLARY STUDIES

Identification of the immunophenotypic characteristics of mast cells is helpful to establish the diagnosis of SM and
SM-AHNMD. In addition to immunohistochemical staining performed on tissue sections, flow cytometric analysis is a useful diagnostic tool. In normal bone marrow, mast cells are present in very low quantities (0.002% to 0.08% of cells). Normal mast cells can be identified by their high side-scatter features, bright expression of CD117, and negative expression of CD34. Additionally, positive markers include CD9, CD11c, CD29, CD33, CD43, CD44, CD45, CD49d, CD49e, CD51, CD54, CD71, and the high-affinity immunoglobulin E receptor. Mast cells also variably express CD11b, CD13, CD18, CD22, CD35, CD40, and CD61. While mast cells, in some cases, may have similar CD45 expression and side-scatter features to basophils, bright expression of CD117 on mast cells is helpful in this distinction. Abnormal mast cells, as seen in cases of SM, in addition to the previously identified immunophenotypic characteristics, are identified by aberrant expression of CD2 and/or CD25. Flow cytometric analysis and immunohistochemistry demonstrate this aberrant immunophenotype equally well and have greater sensitivity for detection of aberrant CD25 expression, although the percentage of mast cells detected by flow cytometry is lower. Additionally, aberrantly high levels of expression of CD35, CD63, and CD69 (activation-related antigens) have been identified in patients with SM. In cases of SM-AHNMD, in addition to the detection of abnormal mast cells, immunophenotypic characterization of the nonmast cell lineage component can be performed simultaneously with flow cytometry.

Detection of an activating point mutation at codon 816 of c-kit is important in the diagnosis and pathogenesis of SM. Polymerase chain reaction and direct sequencing of exon 17 of c-KIT is used most frequently to detect a mutation. The most common mutation is substitution of valine for aspartate at codon 816 (D816V). Other reported mutations include the aspartate to tyrosine (D816Y), histidine (D816H), and phenylalanine (D816F) substitutions. Allele-specific polymerase chain reaction has also been shown to be a sensitive and specific way to detect the D816V mutation. Similar to SM without AHNMD, mutation analysis for KIT D816V or other substitutions can be performed and aid in the diagnosis of SM-AHNMD. Concomitant detection of additional cytogenetic or molecular abnormalities by conventional chromosome analysis and/or fluorescence in situ hybridization, and a variety of molecular techniques, can also be used to further support the diagnosis of and characterize the nonmast cell lineage disease. Identification of a JAK2 V617F mutation can aid in the diagnosis of SM-MPN in the setting of SM with an abnormal myeloproliferation. Moreover, identification of additional clonal cytogenetic abnormalities by karyotype analysis and/or fluorescence in situ hybridization studies may also help to establish a diagnosis of or further characterize cases of SM-MPN, SM-MDS, and SM-CMML. For example, deletion of chromosomes 5 or 7 or other complex karyotypic abnormalities, may confirm the morphologic findings of an associated MDS. In cases of SM-AML, a variety of cytogenetic abnormalities may be identified. For instance, the RUNX1-RUNXIT1 fusion gene may be identified in cases of SM associated with AML with the t(8;21)(q22;q22) translocation.

PATHOGENESIS

Mast cells are of hematopoietic origin, deriving from a CD34+ bone marrow progenitor cell population. The pathogenesis of systemic mastocytosis is linked to mutations in the proto-oncogene c-KIT, located on chromosome band 4q12, which encodes a transmembrane tyrosine kinase receptor with intrinsic tyrosine kinase activity. The KIT receptor is present on mature mast cells, hematopoietic stem cells, gametocytes, cells of Cajal, and melanocytes. Normal mast cell proliferation, survival, differentiation, and activation are dependent on binding of stem cell factor or c-KIT ligand to the KIT receptor. Dimerization, transphosphorylation, protein tyrosine kinase activation, and downstream signaling subsequently occur. The most common mutation in SM, including SM-AHNMD, occurs in exon 17 in the tyrosine kinase 2 (Tk2) domain. The TK2 domain is the activation loop of the KIT receptor, and mutations in this domain lead to stem cell factor–independent autophosphorylation due to stabilization of the kinase in the active conformation. Downstream activation, including activation of the STAT5 pathway, leads to increased mast cell proliferation and survival, changes in adhesion and migration of mast cells, and mast cell degranulation and mediator release. Recognition of these mutations in the KIT tyrosine kinase receptor and the role they play in the pathogenesis of SM...
has led to the addition of mastocytosis into the category of myeloproliferative neoplasms.\(^1\)

The pathogenesis of mastocytosis associated with clonal nonmast cell lineage disease is unknown, and the nonmast cell lineage component might or might not show evidence of the same c-KIT mutation seen in the neoplastic mast cells.\(^2\) The association with c-KIT mutations in SM associated with lymphoid neoplasms is even less apparent, as mutations have not been reported in these cases.\(^3,4,17\)

When there is an associated myeloid neoplasm, there are 2 proposed theories for the pathogenesis of SM-AHNMD. The first theory involves an activating c-KIT mutation that occurs with other genetic mutations and events in a myeloid stem cell. The c-KIT mutation could result in a proliferative advantage to the mutated stem cell and lead to mast cell differentiation and proliferation.\(^4\) In cases of t(8;21)(q22;q22) AML (approximately 5% of all AML cases), the fusion of RUNX1 with RUNXIT1 leads to a block in hematopoietic stem cell differentiation. This event by itself is not sufficient for AML to develop, and other genetic events, including activating c-KIT mutations, are required for leukemogenesis.\(^5\) Although c-KIT mutations are not uncommon in cases of t(8;21) AML, cases associated with systemic mastocytosis are extremely rare. This suggests that additional genetic events are necessary to promote mast cell differentiation from myeloid stem cells.\(^6\)

Evidence for the clonal origin of SM-AHNMD from a myeloid stem cell has been shown through targeted fluorescence in situ hybridization analysis for t(8;21) in leukemic myeloblasts and neoplastic mast cells in SM-AML with t(8;21)(q22;q22) translocation, for which the fusion product was detected in both cell types.\(^18\)

Another possible mechanism of SM associated with myeloid malignancies includes transformation of a subclone of the myeloid progenitor cells through an acquired c-KIT mutation resulting in a coexisting mastocytosis.\(^7\) Although not diagnostic of SM-AHNMD or evolving through the same mechanism as an acquired c-KIT mutation, this theory is illustrated in cases of myelomastocytic leukemia, in which there is mast cell differentiation of underlying immature leukemia cells. For instance, in a reported case of chronic myelogenous leukemia in blast phase, extramedullary lesions showed evidence of mast cell differentiation, supporting the idea of transformation of a subclone of a pluripotent hematopoietic stem cell.\(^7\)

**DIFFERENTIAL DIAGNOSIS**

The histologic differential diagnosis for SM-AHNMD includes reactive mast cell hyperplasia, monocyctic/histiocytic proliferations, cases of SM with signs of dysplasia or myeloproliferative insufficiency for the diagnosis of AHNMD (“B findings” of SM), myeloid neoplasms with prominent eosinophilia and abnormalities of PDGFR\(A\) (gene encoding platelet-derived growth factor receptor, \(\alpha\) polypeptide), and other tryptase-positive myeloid malignancies, including certain cases of acute myeloid leukemia and cases with mast cell differentiation of underlying immature leukemic cells (myelomastocytic leukemia). The correct identification of abnormal mast cells in the setting of a clonal myeloid or lymphoproliferative disease is essential owing to the distinct differences in clinical management.

**Reactive Mast Cell Hyperplasia**

Mast cells in cases of hyperplasia can be diffuse, interstitial, or loosely scattered throughout the bone marrow, and most mast cells have round nuclei with densely granular cytoplasm (Figure 5). Mast cell hyperplasia can be seen after toxic or inflammatory exposures, in myeloid neoplasms, and in lymphoid neoplasms, such as lymphoplasmacytic lymphomas, chronic lymphocytic leukemia/small lymphocytic lymphoma, and hairy cell leukemia, and should not be interpreted as a clonal mast cell process.\(^2\) Immunohistochemical stains for the normal mast cell markers CD117 and tryptase in addition to CD2 and CD25 can be helpful in distinguishing reactive mast cells (CD2\(^-\) and CD25\(^+\)) from neoplastic mast cells CD25\(^-\) and/or CD2\(^-\). These mast cell proliferations are not associated with activating c-KIT mutations.

**Monocytic or Histiocytic Proliferations**

Compact mast cell aggregates should also be distinguished from monocytic nodules seen in myelodysplastic/myeloproliferative neoplasms and other histiocytic proliferations such as granulomas, especially when the compact mast cell aggregates are surrounded by lymphocytes. Immunohistochemical stains for CD68 in addition to mast cell markers can be helpful in this differential diagnosis. Langerhans cell histiocytosis may also enter into the differential diagnosis, especially when there are associated eosinophils. Mast cells, however, lack the typical nuclear grooves seen in Langerhans cells and do not react with the Langerhans cell markers S100, CD1a, fascin, and Langerin.

**Systemic Mastocytosis Cases With Features Insufficient for the Diagnosis of AHNMD**

In some cases of SM, the bone marrow may be hypercellular and abnormal maturation may be noted in 1 or more lineages. These signs of myeloproliferation and/or dysplasia (“B findings” in the classification of SM), however, do not meet the required WHO criteria to establish a diagnosis of an associated MPN, MDS, or MDS/MPN.\(^12\) In addition, the peripheral blood cell counts, typically, are not significantly abnormal, and clinically significant or progressive disease is not noted.\(^2\) Molecular and cytogenetic analysis may be helpful to exclude the possibility of a coexisting clonal myeloid neoplasm in these cases of SM. Transformation to a more aggressive disease, including SM-AHNMD, however, is possible in these cases.\(^2\)

**Myeloid Neoplasms With Prominent Eosinophilia and Abnormalities of PDGFR\(A\)**

Cases of chronic eosinophilic leukemia associated with the *FIP1L1-PDGFR\(A\)* fusion protein frequently show increased mast cells, which can have atypical spindle-shaped morphology and aberrant expression of CD25. In most cases, the criteria for SM are not met owing to the lack of compact mast cell aggregates and absent mutations in codon 816 of c-KIT, and these patients are best considered to have a myeloid neoplasm with eosinophilia and rearrangement of *PDGFR\(A*\). Distinction between these 2 disease processes is important, as patients with *PDGFR\(A*\) mutations may respond to imatinib therapy as opposed to patients with SM and the D816V mutation.\(^19\)

**Other Tryptase-Positive Myeloid Proliferations**

Compact tryptase-positive mast cell infiltrates can have, rarely, round cell morphology with hypergranular cytoplasm...
in bone marrow biopsy specimens. Neoplastic basophils and myeloblasts in acute myeloid leukemia can have similar features, complicating the correct identification of the cell lineage. In this setting, immunohistochemical stains for CD117, CD2, and CD25 (positive in abnormal mast cells) and cytochemical analysis for myeloperoxidase (negative in mast cells) and CAE (positive in mast cells) may be helpful in distinguishing abnormal mast cells from basophils. Additionally, evaluation of stem cell markers by immunohistochemistry or flow cytometry may be helpful in the distinction of myeloid blasts from abnormal mast cells. SM-AHNMD must also be distinguished from cases of myelomastocytic leukemia in which there is mast cell differentiation of underlying leukemic cells (CD117+ and tryptase positive). In these cases, the criteria for SM are assessed and are not met, including the major criterion requiring multiple compact clusters of mast cells. A diagnosis of SM is not suggested when there is a diffuse increase in mast cells in the marrow, as is typically seen in these cases. Additionally, cytogenetic and molecular analysis in these cases may be helpful in establishing the correct diagnosis, as illustrated in a case of chronic myelogenous leukemia in blast crisis presenting with extramedullary mast cell neoplasms. In this case, the BCR-ABL1 fusion gene was identified, but the KIT D816V mutation was absent.7

**DISEASE COURSE AND THERAPY**

The disease course in SM-AHNMD relates to the AHNMD and SM, and therapy should be targeted toward both components.25 In general, advanced age, anemia, thrombocytopenia, weight loss, hypoalbuminemia, and excess bone marrow blasts have been shown to be independently associated with shorter survival in patients with SM, including patients with SM-AHNMD. Patients with SM-AHNMD have a shorter median survival (2 years) than patients with indolent SM (life expectancy similar to age-matched controls) and aggressive SM (3.5 years). Patients with mast cell leukemia have the shortest median survival (2 months).3 Among SM-AHNMD cases, patients with SM-MPN have a significantly longer median survival than patients with SM-CMML, SM-MDS, and SM-AML, which has the worst prognosis. Additionally, leukemic transformation is possible in non–SM-AML cases and has been observed most frequently in SM-MDS.8

For these reasons, the choice of therapy is based on the classification of SM, with symptom-related treatments used in indolent cases and more aggressive forms of therapy, including immunomodulating or cytoreductive agents, used in cases in which the systemic mast cell burden is high, such as in cases of aggressive SM and mast cell leukemia.9 In SM-AHNMD, patients are treated with standard regimens for the specific AHNMD, as if the SM were not present, but treatment strategies for the SM component should also be established. Interestingly, successful treatment of the AHNMD may lead to a shift from SM-AHNMD to a different category of SM.9 Immunomodulating/myelosuppressive (interferon α or corticosteroids) or cytoreductive therapies alone or in combination to target the SM component have been used as a treatment strategy in cases of SM-AHNMD, in addition to splenectomy when significant splenomegaly or hypersplenism is present, but remissions are usually partial or short-lived.2,5,11,12 Allogeneic bone marrow transplant has been performed in certain cases of SM-AHNMD; however, there is limited experience with this procedure.22

Cases of AML with t(8;21)(q22;q22) translocation have a favorable outcome when high-dose cytarabine is used in consolidation.23 The poor prognosis seen in a subset of patients with t(8;21) AML may be explained by activating mutations in exon 17 of c-KIT, which confer a higher relapse risk.24 According to 1 study with a very small number of patients (some of which had prior therapy), patients with SM-AML with t(8;21) have a very poor prognosis, with frequent induction chemotherapy failure. For this reason, although data are limited, allogeneic bone marrow transplants may be an early consideration for these patients, given the poor response to standard induction and consolidation chemotherapy.25

Tyrosine kinase inhibitors are also potential therapy for SM and show promise in targeting the SM component in SM-AHNMD. The location of the mutation in the activation loop of the KIT tyrosine kinase receptor precludes use of the tyrosine kinase inhibitor imatinib.26 Other tyrosine kinase inhibitors are capable of inhibiting the mutated D816V KIT receptor. Use of dasatinib, which inhibits the STAT5 downstream pathway, leads to reduced mast cell numbers, decreased clinical symptoms, and undetectable D816V KIT mutations.26,27 Midostaurin (PKC 412), an inhibitor of autophosphorylation of KIT, may have a synergistic effect with dasatinib, and nilotinib (AMN 107), another tyrosine kinase inhibitor, may have potential efficacy in the treatment of SM-AHNMD.28,29,30

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