Systemic Mastocytosis: Classification, Pathogenesis, Diagnosis, and Treatment

Olga Bunimovich, MD; Marcelle Grassi, MD; Maria R. Baer, MD

GOAL

To understand systemic mastocytosis (SM) to better manage patients with the condition

LEARNING OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Describe classifications of cutaneous mastocytosis and SM.
2. List c-*kit* mutations associated with SM variants.
3. Outline methods to diagnose and treat patients with SM.

INTENDED AUDIENCE

This CME activity is designed for dermatologists and generalists.

CME Test on page 28.

This article has been peer reviewed and approved by Michael Fisher, MD, Professor of Medicine, Albert Einstein College of Medicine. Review date: December 2008.

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of Albert Einstein College of Medicine and Quadrant HealthCom, Inc. Albert Einstein College of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

Albert Einstein College of Medicine designates this educational activity for a maximum of *1 AMA PRA Category 1 Credit*™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

This activity has been planned and produced in accordance with ACCME Essentials.

Drs. Bunimovich, Grassi, and Baer report no conflict of interest. The authors discuss off-label use of dasatinib for systemic mastocytosis. Dr. Fisher reports no conflict of interest. The staff of CCME of Albert Einstein College of Medicine and *Cutis*® have no conflicts of interest with commercial interest related directly or indirectly to this educational activity.

Mastocytosis is a heterogeneous entity that may present as either a cutaneous or systemic disease. Progression of pediatric cutaneous mastocytosis (CM) is uncommon, but in adults, this condition persists and often progresses to systemic disease. Mast cell proliferation and differentiation from stem cell precursors depend on a number of factors, including a mast cell tyrosine kinase receptor (kit) *and its ligand (the stromal cell–derived cytokine stem cell factor). A gain-of-function mutation in codon 816 of c-*kit *is frequently present in mast cells of patients with systemic mastocytosis (SM). The diagnostic approach for a patient with suspected mast cell disease includes a thorough skin examination, a skin biopsy, a serum tryptase level, and bone marrow aspiration and biopsy. The treatment is*

Accepted for publication November 14, 2007.

Dr. Bunimovich is a resident, Department of Dermatology, State University of New York, Buffalo School of Medicine. Dr. Grassi is Assistant Clinical Professor, Department of Dermatology, and Dr. Baer was Professor, Department of Medicine, both from Roswell Park Cancer Institute, Buffalo. Dr. Baer currently is Professor of Medicine, Greenebaum Cancer Center, University of Maryland, Baltimore.

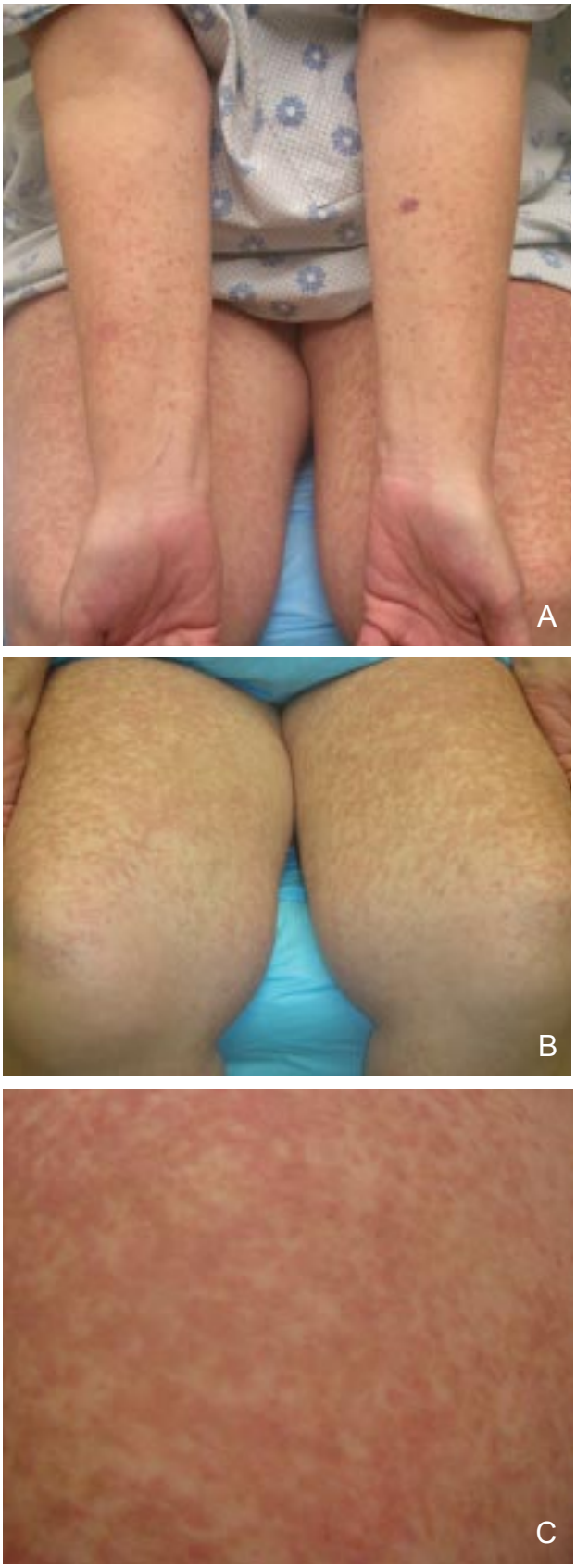
Correspondence: Olga Bunimovich, MD, Roswell Park Cancer Institute, Department of Dermatology, Elm & Carlton St, Buffalo, NY 14263 (olgabunimovich@yahoo.com).

directed toward avoidance of triggers of mast cell mediator release and management of symptoms. Aggressive cases are managed with cytoreductive therapies, such as interferon alfa-2b and cladribine. Research has been directed at more specific treatment modalities, including specific kit *tyrosine kinase inhibitors.*

Cutis. 2009;83:29-36.

Case Report

A 46-year-old woman presented with a rash that had been present for more than 20 years but had progressed over the past 6 years and was associated with pruritus, burning, and blistering precipitated by temperature changes or anxiety. In addition, she had watery diarrhea for 5 years and also had been found to have osteopenia. She was a healthy-appearing woman with prominent facial erythema. Vital signs were normal. Skin examination revealed facial telangiectases as well as erythema and 2- to 4-mm reddish brown papules and macules on the extensor surfaces of the arms and thighs, chest, abdomen, and back, coalescing into plaques on the thighs (Figure). She had bilateral axillary lymphadenopathy. Liver and spleen were not palpable. Her hemoglobin level was 12.7 g/dL (reference range, 14.0–17.5 g/dL); white blood cell count was 5.2×10^9/L (reference range, 4.5–11.0×10^9/L) with 63 neutrophils, 36 lymphocytes, and 1 monocyte; and platelet count was 301×10^9/L (reference range, 150–350×10^9/L). Chemistries were within reference range, except for an alkaline phosphatase level of 136 U/L (reference range, 38–126 U/L). Biopsy of a forearm skin lesion showed an unremarkable epidermal layer overlying a dermis without vasculitis but with a mild increase in perivascular and focally interstitial mononuclear cells staining with mast cell tryptase and CD117. Serum tryptase level was greater than 200 ng/mL (reference, <11.4 ng/mL). A 24-hour urine collection showed increased histamine levels. Computed tomography of the chest, abdomen, and pelvis demonstrated axillary, subcarinal, posterior mediastinal, retrocrural, porta hepatis, retroperitoneal, mesenteric, and external iliac lymphadenopathy with a maximum size of 2.2 cm, mild splenomegaly (16 cm), and extensive diffuse sclerosis throughout the bones, as well as several small areas of lucency. The bone marrow could not be aspirated, and the bone marrow biopsy was 85% cellular with diffuse reticulin and focal collagen fibrosis and with multiple sheets of spindle and oval mononuclear cells. Immunoassays demonstrated cells staining with tryptase and CD68, consistent with mast cells, that occupied 60% of the biopsy sections, establishing the diagnosis of systemic mastocytosis (SM). Testing for a c-*kit*



Numerous reddish brown papules and macules on the upper extremities and thighs (A–C).

codon 816 mutation could not be performed because of a lack of available tumor tissue.

The patient was treated with hydroxyzine hydrochloride, with some amelioration of pruritus, and with cromolyn sodium, which she was unable to tolerate because of bloating. She was subsequently initiated on the tyrosine kinase inhibitor dasatinib (70 mg orally twice daily) but developed dyspnea, anxiety, and skin pain following the initial dose, which responded to intravenous corticosteroid administration. She was initiated on prednisone 30 mg daily 5 days prior to reinitiating dasatinib, with a subsequent 2-week prednisone taper, and also was premedicated with hydroxyzine 25 mg orally before each dasatinib dose and tolerated dasatinib without difficulty. After 2 weeks of dasatinib treatment, she had substantial improvement of both pruritus and diarrhea and reduction in the extent of her rash. Nevertheless, at 6 months she still had a serum tryptase level greater than 200 ng/mL and extensive marrow mast cell infiltration. Given the lack of information regarding the c-*kit* codon 816 mutation in this patient, she was switched from dasatinib to imatinib mesylate in hopes of improving her response.

Comment

Mast cells are hematopoietic cells that function as effector cells in innate immunity and as immunoregulatory cells in adaptive immunity.[1] They also participate in wound healing[2] and angiogenesis[3] in both tissue regeneration and pathologic neoplastic states. Mast cell proliferation and differentiation from stem cell precursors depend on a number of factors, including a mast cell tyrosine kinase receptor (*kit)* and its ligand (the stromal cell–derived cytokine stem cell factor).[4] A gain-of-function mutation in codon 816 of c-*kit* is frequently present in mast cells of patients with SM.

Classification—Mastocytosis is a heterogeneous entity that may present as either a cutaneous or systemic disease.[5]

Cutaneous mastocytosis (CM) is divided into 3 groups based on clinical presentation: urticaria pigmentosa (UP)/maculopapular CM, diffuse CM, and solitary mastocytoma. The maculopapular variant includes 4 subsets: typical UP, plaque form, nodular form, and telangiectasia macularis eruptiva perstans.[6] Progression of pediatric CM is uncommon, but in adults, this condition persists and often progresses to systemic disease.[4]

Systemic mastocytosis is subclassified into indolent SM (ISM), SM with an associated clonal hematologic non–mast cell lineage disease (SM-AHNMD), aggressive SM (ASM), mast cell leukemia, and mast cell sarcoma (Table).[7] To establish the diagnosis of SM, either the major criterion and 1 or more minor criteria or 3 or more minor criteria must be fulfilled. The major criterion is a multifocal dense infiltrate of mast cells in the bone marrow or other extracutaneous organ, with at least 15 mast cells per aggregate. Minor criteria include abnormal mast cell morphology, expression of CD2 and/or CD25, serum tryptase level greater than 20 ng/mL, and presence of mutation in codon 816 of c-*kit*. Indolent SM is the most common presentation of SM and is associated with cutaneous findings without clinically significant organomegaly or organopathy. These patients may have systemic symptoms from mast cell mediator release, but their prognosis is good.[8] In patients with SM-AHNMD, AHNMDs may include idiopathic myelofibrosis, hypereosinophilic syndrome, acute myeloid leukemia, and myelodysplastic syndromes. In these patients, treatment of SM and AHNMD should be approached separately.[4] In patients with ASM, UP-like skin findings are rare. Usually, these patients have mast cell infiltration of various organs and resultant organ dysfunction,[4] but their bone marrow aspirates contain less than 20% mast cells. In contrast, mast cell leukemia is defined by the presence of 20% or more mast cells in the bone marrow and circulating mast cells. These patients have rapidly progressive disease, with progressive organopathy and a poor prognosis.[4] Mast cell sarcoma is very rare, presents as a rapidly growing destructive tumor composed of highly atypical mast cells, and has a grave prognosis.[9]

Pathogenesis—The common finding in mastocytosis is clustering of mast cells in various organs. The pathogenesis of the numerous variants of mastocytosis remains unclear. The c-*kit* point mutation D816V (aspartic acid at residue 816 replaced by valine) is found in more than 80% of cases of SM. This mutation is likely responsible for ISM, but activation of additional proliferation-enhancing oncogenes is likely required for genesis of the more aggressive variants.[4] Other mutations have been found, some correlating with specific variants of mastocytosis and some associated with AHNMDs in SM-AHNMD; c-*kit* D816G (aspartic acid at residue 816 replaced by glycine) is associated with ASM, c-*kit* K509I (lysine at residue 509 replaced by isoleucine) with SM (familial type), c-*kit* D816H (aspartic acid at residue 816 replaced by histidine) with SM-AHNMD, c-*kit* V530I (valine at residue 530 replaced by isoleucine) with SM–acute myelogenous leukemia, and FIPL1 (FIP1-like-1)/PDGFRA (platelet-derived growth factor α-polypeptide) with SM with eosinophilia.[4]

Spectrum of Systemic Mastocytosis and Treatment

Type	Clinical Findings	Hematologic Abnormalities	Cause	Prognosis	Therapy	Most Common Side Effects
ISM	UP/MPCM, diffuse cutaneous mastocytosis	None	Unknown	Good	Avoid triggers: exposure to cold, strenuous exercise, alcohol, NSAIDs	N/A
	No clinically significant organomegaly or organopathy				Aspirin to control flushing, if not a trigger	Hemorrhage, gastritis, tinnitus, renal abnormalities
	Systemic symptoms from mast cell mediator release: hypotension, flushing, chest discomfort, dyspnea				Epinephrine-filled syringes for anaphylactic episodes	Sudden death, angina, arrhythmia, dyspnea, wheezing
					H_1 blockers (aimed at flushing and pruritus)	Headache, somnolence
					H_2 blockers (aimed at gastrointestinal symptoms)	Anemia, leukopenia, thrombocytopenia, hypersensitivity reaction, headache, somnolence
					Cromolyn sodium	Unpleasant taste in mouth, sneezing, nasal burning, stinging, irritation
					Topical corticosteroids	Skin atrophy
					PUVA	Increased risk for skin cancer
					No cytoreductive treatment necessary unless severe osteoporosis is present	N/A
SM-AHNMD	See clinical findings for ISM and ASM	Idiopathic, myelofibrosis hypereosinophilic, syndrome, acute myeloid leukemia, myelodysplastic syndromes	Unknown	Same as associated non–mast cell disorder	Treat SM as if no AHNMD found and treat AHNMD as if no SM present	Varies depending on treatment

Type	Clinical Findings	Hematologic Abnormalities	Cause	Prognosis	Therapy	Most Common Side Effects
SM-AHNMD (cont'd)	Clinical findings associated with the particular AHNMD				Splenectomy (if splenomegaly inhibits treatment)	Infection with encapsulated organisms
ASM	UP-like skin findings are rare	Bone marrow aspirate: <20% mast cells	Unknown	Poor	Interferon alfa-2b	Fatigue, anorexia, nausea, myalgia, arthralgia, myelosuppression, depression, dyspnea, cough, alopecia
	Organ dysfunction: bone marrow failure, liver dysfunction with ascites, splenomegaly with hypersplenism, skeletal osteolytes with pathologic fractures, gastrointestinal abnormalities with malabsorption and weight loss				Glucocorticoids	Hypertension, hyperglycemia, gastritis, peptic ulcer disease, muscle weakness, psychosis, osteoporosis, glaucoma, atherosclerosis
	Systemic symptoms from mast cell mediator release (see above)				Cladribine	Myelosuppression, infection, nausea/vomiting
					Tyrosine kinase inhibitors (imatinib mesylate, dasatinib)	Nausea, diarrhea, rash, fluid retention, myelosuppression, musculoskeletal pain, cough, dyspnea
					Splenectomy	See above
Mast cell leukemia	Progressive organopathy (see ASM)	Bone marrow aspirate: ≥20% mast cells	Unknown	Poor	Interferon alfa-2b	See above
	Systemic symptoms from mast cell mediator release (see above)				Cladribine	See above
					Tyrosine kinase inhibitors	See above
					Hematopoietic stem cell transplant	GVHD, infection, renal abnormalities, hepatotoxicity, pulmonary complications

TABLE CONTINUED ON PAGE 34

Table. (continued)

Type	Clinical Findings	Hematologic Abnormalities	Cause	Prognosis	Therapy	Most Common Side Effects
Mast cell leukemia (cont'd)					Splenectomy	See above
					Hydroxyurea	Myelosuppression, nausea/vomiting, mucositis

Abbreviations: ISM, indolent systemic mastocytosis; UP, urticaria pigmentosa; MPCM, maculopapular cutaneous mastocytosis; NSAIDs, nonsteroidal anti-inflammatory drugs; PUVA, psoralen plus UVA; N/A, not applicable; SM-AHNMD, systemic mastocytosis with an associated clonal hematologic non–mast cell lineage disease; ASM, aggressive systemic mastocytosis; GVHD, graft-vs-host disease.

Of further interest is the abnormal expression of surface adhesion antigens on neoplastic mast cells, particularly CD2 (LFA-2 [lymphocyte function–associated antigen 2]). It has been hypothesized that a mast cell surface adhesion molecule, CD58, which is a ligand for CD2, acts together with CD2 to promote mast cell aggregation and clustering.[10]

Systemic and Local Disease—The clinical manifestations of mastocytosis can be divided into systemic and local effects (Table). Systemic effects include hypotension; flushing; chest discomfort; and dyspnea caused by release of mast cell mediators, including histamine, heparin, tryptase, interleukins, prostaglandin D_2, platelet-activating factor, leukotrienes, chymase, cathepsin G, and carboxypeptidase. Local effects result from aggregation of mast cells in particular organ systems; the bone marrow is involved in more than 90% of cases of SM. The most common hematologic abnormality is anemia, which is present in one-third to one-half of patients.[11] Gastrointestinal symptoms occur in 70% to 80% of patients and include abdominal pain, nausea, vomiting, diarrhea, and peptic ulcer disease.[12,13] The liver is frequently involved, with hepatomegaly in 72% of patients, periportal fibrosis in 14%, and cirrhosis in 4%.[14] Splenomegaly is present in 50% of cases.[15] Lymphadenopathy also is common but is usually clinically insignificant.[11] Diffuse osteopenia also may be present, along with both lytic and sclerotic lesions. Of note, the extent of radiographic disease correlates with the prognosis of patients with SM.[16]

Diagnosis—A patient with suspected mast cell disease should undergo a thorough skin examination, a skin biopsy, a serum tryptase level, and bone marrow aspiration and biopsy.[11] The diagnosis of SM requires either the major criterion and 1 or more minor criteria or 3 or more minor criteria. The major criterion is a multifocal dense infiltrate of mast cells (aggregates of 15 cells or more) in sections of bone marrow and/or other extracutaneous organs. Minor criteria include abnormal mast cell morphology, expression of CD2 and/or CD25 on bone marrow mast cells, serum tryptase level greater than 20 ng/mL, and presence of a c-*kit* codon 816 mutation.[11] Urinary *N*-methylhistamine levels have been used to measure the extent of disease, but serum tryptase levels discriminate better between patients with and without mast cell aggregates.[17] Of note, increased levels of tryptase, histamine, or histamine metabolite may be present in other disease states, such as anaphylaxis.

Treatment—A practical first step in treating patients with SM is to counsel them to avoid triggering factors such as temperature extremes, physical exertion, ingestion of ethanol, and use of nonsteroidal anti-inflammatory drugs or opiates (Table).[11] In addition, Hymenoptera stings and exposure to iodinated contrast materials may cause hypotension,[11] which should be treated with epinephrine. Patients with SM and episodes of hypotension should carry epinephrine-filled syringes. Histamine blockers, including proton pump inhibitors, may be used to decrease pruritus and to treat gastritis and peptic ulcer disease. Patients can be started on hydroxyzine hydrochloride (10–25 mg up to 4 doses daily) titrated to symptoms and sedative effects. Cromolyn sodium decreases gastrointestinal symptoms at dosages of 200 mg 4 times daily taken 30 minutes prior to meals.[18] Topical corticosteroids and psoralen plus UVA have been effective in treating cutaneous manifestations of SM. Glucocorticoids have been used to reduce ascites and malabsorption in patients with SM, but ascites frequently recurs upon discontinuation of treatment.[11,12] Splenectomy has been used to improve cytopenia in patients with ASM and has prolonged survival by an average of 8 months.[19]

Patients with ISM require only symptomatic treatment with a mast cell stabilizer, such as cromolyn

sodium, and histamine antagonists, and do not require cytoreductive therapy unless severe osteoporosis is present. In patients with SM-AHNMD, separate treatment should be directed toward each disease process.[4] Aggressive SM should be treated with interferon alfa-2b and glucocorticoids because of the rapid progression of this disease. Prednisone may be initiated at 50 to 75 mg daily several days prior to starting treatment with interferon. Interferon alfa-2b is initiated at 3 million IU subcutaneously 3 times weekly and, after careful monitoring during the first several weeks of treatment, can be increased to 3 to 5 million IU daily with a maintenance dose of prednisone (12.5 mg/d or less).[4] Although these agents can reduce disease load considerably, prognosis remains unchanged.[20,21] Those patients who fail to respond to these treatments are candidates for chemotherapeutic agents, including cladribine (0.13 mg/kg 5 days weekly in 2-hour infusions, repeated after 4–6 weeks), though toxicities of treatment must be heavily weighed.[22]

kit Tyrosine kinase inhibitors recently have been developed and are now being used in the treatment of SM. Imatinib mesylate is a potent inhibitor of tyrosine kinases, including *kit*, in addition to Abl and PDGFRs, but it is ineffective in halting the proliferation of cells bearing the D816V mutation, which is found in more than 80% of cases of SM. Nevertheless, a subset of patients with SM responds to this therapy, particularly those patients with FIPL1/PDGFRA, an oncogene that is found in patients with SM and concomitant eosinophilia.[20] In a phase 2 trial, patients received imatinib mesylate 400 mg daily with prednisone 15 mg twice daily for 2 weeks to avert potential allergic reactions.[23] Imatinib mesylate received US Food and Drug Administration approval in 2006 for treatment of adults with ASM without the D816V c-*kit* mutation or with unknown c-*kit* mutation status. The recommended dosage is 400 mg daily for patients without the D816V c-*kit* mutation or with unknown c-*kit* mutation status but is 100 mg daily for patients with ASM associated with eosinophilia.

Dasatinib is a novel kinase inhibitor that targets *kit*, in addition to Abl, Src, PDGFR, and other tyrosine kinases. Dasatinib is structurally unrelated to imatinib mesylate, is a substantially more potent inhibitor, and has demonstrated efficacy in treating chronic myeloid leukemia (CML) that is resistant to imatinib mesylate.[24] Dasatinib is well-tolerated in patients with CML, possibly because of its short biologic half-life (3–5 hours) compared with imatinib mesylate and its active metabolite (18 hours and 40 hours, respectively). It remains to be seen if the optimal dosage of dasatinib for treatment of SM will be the same as the dosage currently used in patients with CML (70 mg twice daily) and if the medication will be as well-tolerated if higher doses are required. Dasatinib is approved for the treatment of CML but has not yet been approved for use in SM. Nilotinib, another tyrosine kinase inhibitor that overcomes *bcr-abl* mutations associated with imatinib mesylate resistance in CML and also is a *kit* inhibitor, is not yet approved by the US Food and Drug Administration.[25] Additional *kit* inhibitors are becoming available. Optimal drugs and strategies for *kit* tyrosine kinase inhibition in mastocytosis remain to be identified.

REFERENCES

1. Mekori YA, Metcalfe DD. Mast cell-T cell interactions. *J Allergy Clin Immunol*. 1999;104(3, pt 1):517-523.
2. Weller K, Foitzik K, Paus R, et al. Mast cells are required for normal healing of skin wounds in mice. *FASEB J*. 2006;20:2366-2368. Epub September 11, 2006.
3. Nienartowicz A, Sobaniec-Łotowska ME, Jarocka-Cyrta E, et al. Mast cells in neoangiogenesis. *Med Sci Monit*. 2006;12:RA53-56. Epub February 23, 2006.
4. Valent P, Akin C, Sperr WR, et al. Mastocytosis: pathology, genetics, and current options for therapy. *Leuk Lymphoma*. 2005;46:35-48.
5. The World Health Organization. Mastocytosis. In: Jaffe ES, Harris NL, Stein H, et al, eds. *WHO Classification of Tumours: Pathology and Genetics of Tumours of Haematopoetic and Lymphoid Tissues*. Vol 3. IARC Press: Lyon, France; 2001: 293-302.
6. Wolff K, Komar M, Petzelbauer P. Clinical and histopathological aspects of cutaneous mastocytosis. *Leuk Res*. 2001;25:519-528.
7. Valent P, Akin C, Sperr WR, et al. Mast cell proliferative disorders: current view on variants recognized by the World Health Organization. *Hematol Oncol Clin North Am*. 2003;17:1227-1241.
8. Stankovic K, Sarrot-Reynauld F, Puget M, et al. Systemic mastocytosis: predictable factors of poor prognosis present at the onset of the disease. *Eur J Intern Med*. 2005;16: 387-390.
9. Chott A, Guenther P, Huebner A, et al. Morphologic and immunophenotypic properties of neoplastic cells in a case of mast cell sarcoma. *Am J Surg Pathol*. 2003;27: 1013-1019.
10. Schernthaner GH, Jordan JH, Ghannadan M, et al. Expression, epitope analysis, and functional role of the LFA-2 antigen detectable on neoplastic mast cells. *Blood*. 2001;98:3784-3792.
11. Metcalfe DD. Regulation of normal and neoplastic human mast cell development in mastocytosis. *Trans Am Clin Climatol Assoc*. 2005;116:185-203.
12. Mickys U, Barakauskiene A, Wolf-Peeters D, et al. Aggressive systemic mastocytosis complicated by

protein-losing enteropathy. *Dig Liver Dis*. 2007;39:693-697. Epub July 14, 2006.
13. Jensen RT. Gastrointestinal abnormalities and involvement in systemic mastocytosis. *Hematol Oncol Clin North Am*. 2000;14:579-623.
14. Horny HP, Kaiserling E, Campbell M, et al. Liver findings in generalized mastocytosis. a clinicopathologic study. *Cancer*. 1989;63:532-538.
15. Webb TA, Li CY, Yam LT. Systemic mast cell disease: a clinical and hematopathologic study of 26 cases. *Cancer*. 1982;49:927-938.
16. Chen CC, Andrich MP, Mican JM, et al. A retrospective analysis of bone scan abnormalities in mastocytosis: correlation with disease category and prognosis. *J Nucl Med*. 1994;35:1471-1475.
17. van Toorenenbergen AW, Oranje AP. Comparison of serum tryptase and urine *N*-methylhistamine in patients with suspected mastocytosis. *Clin Chim Acta*. 2005;359(1-2):72-77.
18. Horan RF, Sheffer AL, Austen KF. Cromolyn sodium in the management of systemic mastocytosis. *J Allergy Clin Immunol*. 1990;85:852-855.
19. Friedman B, Darling G, Norton J, et al. Splenectomy in the management of systemic mast cell disease. *Surgery*. 1990;107:94-100.
20. Quintas-Cardama A, Aribi A, Cortes J, et al. Novel approaches in the treatment of systemic mastocytosis. *Cancer*. 2006;107:1429-1439.
21. Casassus P, Caillat-Vigneron N, Martin A, et al. Treatment of adult systemic mastocytosis with interferon-alpha: results of a multicentre phase II trial on 20 patients. *Br J Haematol*. 2002;119:1090-1097.
22. Kluin-Nelemans HC, Oldhoff JM, Van Doormaal JJ, et al. Cladribine therapy for systemic mastocytosis. *Blood*. 2003;102:4270-4276. Epub August 21, 2003.
23. Droogendijk HJ, Kluin-Nelemans HJ, van Doormaal JJ, et al. Imatinib mesylate in the treatment of systemic mastocytosis: a phase II trial. *Cancer*. 2006;107:345-351.
24. Shah NP, Lee FY, Luo R, et al. Dasatinib (BMS-354825) inhibits KITD816V, an imatinib-activating mutation that triggers neoplastic growth in most patients with systemic mastocytosis. *Blood*. 2006;108:286-291.
25. Weisberg E, Manley P, Mestan J, et al. AMN107 (nilotinib): a novel and selective inhibitor of BCR-ABL. *Br J Cancer*. 2006;94:1765-1769.