Cardiovascular symptoms in patients with systemic mast cell activation disease

ULRICH W. KOLCK, BRITTA HAENISCH, and GERHARD J. MOLDERINGS

BONN, GERMANY

Traditionally, mast cell activation disease (MCAD) has been considered as just one rare (neoplastic) disease, mastocytosis, focused on the mast cell (MC) mediators tryptase and histamine and the suggestive, blatant symptoms of flushing and anaphylaxis. Recently another form of MCAD, the MC activation syndrome, has been recognized featuring inappropriate MC activation with little to no neoplasia and likely much more heterogeneously clonal and far more prevalent than mastocytosis. Increasing expertise and appreciation has been established for the truly very large menagerie of MC mediators and their complex patterns of release, engendering complex, nebulous presentations of chronic and acute illness best characterized as multisystem polymorbidity of generally inflammatory ± allergic theme. We describe the pathogenesis of MCAD with a particular focus on clinical cardiovascular symptoms and the therapeutic options for MC mediator-induced cardiovascular symptoms. (Translational Research 2016;174:23–32)

Abbreviations: H_1R = histamine H_1 receptor; H_2R = histamine H_2 receptor; MC = mast cell; MCAD = mast cell activation disease; MCAS = mast cell activation syndrome; MMP = matrix metalloproteinase; NE = norepinephrine; SM = systemic mastocytosis

MAST CELLS: BASIC BIOLOGY

Mast cells (MCs) are immune cells of hematopoietic origin found in all human tissues, especially at the environmental interfaces, that secrete prestored mediators, such as histamine and tryptase, as well as numerous de novo synthesized chemokines and cytokines in response to allergic or nonimmune triggers. MCs act as both effector and regulatory cells and play a central role in adaptive and innate immunity.[1] This versatility is reflected in numerous activation stimuli with intracellular pathways that intersect to modulate the quality and magnitude of the MC response. The best characterized mechanism of MC activation is cross-linking of immunoglobulin E (IgE) bound to the high affinity IgE receptor (FcεRI) on MCs by antigen contact. In addition, human MCs express a multiplicity of G protein–coupled receptors and other recognition sites on their surface,[2] which are IgE-independently involved in MC activation under physiological and pathophysiological conditions.

Apart from being prominently involved in allergic reactions, their ubiquitous distribution places MCs in a privileged position to act not only as guardians of the immune system, but also to contribute to many biological processes and in the maintenance of homeostasis. Their important role in immunologic and nonimmunologic processes is reflected by the large number of mediators (>200) by which MCs may influence other cells.[3,4] The profile of mediators and cytokines stored or produced de novo in MCs can markedly differ between and even within organs and tissues depending on a wide array of macroenvironmental and

From the Johanniter-Kliniken Bonn, Waldkrankenhaus, Innere Medizin II, Bonn, Germany; German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany; Institute of Human Genetics, University Hospital of Bonn, Bonn, Germany.

Submitted for publication October 5, 2015; revision submitted December 11, 2015; accepted for publication December 18, 2015.

Reprint requests: Gerhard J. Molderings, Institute of Human Genetics, University Hospital of Bonn, Sigmund-Freud-Strasse 25, D-53127 Bonn, Germany; e-mail: molderings@uni-bonn.de.

1931-5244/$ - see front matter

http://dx.doi.org/10.1016/j.trsl.2015.12.012

microenvironmental factors including antigenic and physical stimuli. Their mediators allow MCs to regulate local tissue functions and host defense by acting as innate immune cells, by interacting with the specific immune system, and by inducing and regulating inflammation. Because MCs tend to site themselves at the body's environmental interfaces, they are perfectly equipped with their mediators to significantly contribute to orchestrating the immune system. They can recruit other immune cells to the site of injury and control the function of various cells such as granulocytes and T and B lymphocytes, thereby acting to protect the organism against bacterial, parasitic, and viral infections. MC actions can be targeted very precisely, as apart from their ability to release prestored mediators via classic nonselective whole-MC degranulation (as in anaphylaxis), MCs also selectively release specific patterns of mediators by morphologically distinct secretory pathways referred to as piecemeal or differential degranulation.[3] In addition, MCs are essential to the regulation of homeostasis. In this respect, they contribute to wound healing and tissue remodeling, for example in hair follicles and bones.[3] MCs also promote homeostasis by degrading certain endogenous toxic compounds such as endothelin 1 or neurotensin released in response to bacterial infection and bacterial toxins via their potent proteases.

PHYSIOLOGICAL AND PATHOPHYSIOLOGICAL ROLES OF MCS IN THE CARDIOVASCULAR SYSTEM

The presence of MCs has been documented in the human heart.[5-8] MCs generally reside in the interstitial space between the cardiomyocytes and are often in close proximity to nerves,[5,9,10] which may be relevant to the generation and progression of arrhythmias. Activated cardiac MCs release a variety of potent proinflammatory and profibrotic mediators.[5,9-12] In humans, MCs have been classified on the basis of the presence of the proteases tryptase, chymase, or both chymase and tryptase.[13,14] Ninety percent of the MCs in the human heart are of both chymase and tryptase types.[15]

Cardiac MCs participate in various physiological functions, such as angiogenesis,[16] formation of atrial natriuretic peptide,[17] and local production of angiotensin II (ANG II) by renin[9] (for review, see Reid et al[5]) and independently of angiotensin-converting enzyme (ACE) by chymase, thereby being unaffected by ACE inhibitors.[9,18-20] MC chymase also participates in the activation of big endothelin to endothelin 1.[21] Other mediators such as cytokines and the growth factors tumor necrosis factor α and transforming growth factor, histamine, the chymase and tryptase, chemokines, and leukotrienes play an important role in the tissue repair.

The perineuronal location of cardiac MCs in addition to their accumulation in pathologic conditions may promote the development of myocardial dysfunction. In fact, cardiac MCs have been implicated in various pathophysiological processes (for review, see references[22-24]), such as cardiac remodeling (ie, changes in size, shape, structure, and physiology of the heart after injury to the myocardium because of myocardial infarction [via atherosclerosis or vasospasm]), volume overload, chronic hypertension or myocarditis,[25-31] arrhythmias,[10-12] graft rejection after heart transplant,[32,33] dilated cardiomyopathy,[34] cardiac hypertrophy and heart failure,[35-40] Takotsubo cardiomyopathy,[41,42] atherosclerosis[43] (for review, see Bot et al[44]), acute coronary artery syndromes,[6,45-47] and formation of abdominal aortic aneurysm.[48,49]

SYSTEMIC MC ACTIVATION DISEASE

The umbrella term of *systemic mast cell activation disease* (MCAD) has been proposed[50] to describe the full spectrum of systemic MC disease, that is *systemic mastocytosis* (SM), which is further divided into several subtypes,[51] primary *systemic mast cell activation syndrome* (MCAS) and *MC leukemia*.[52-54] Pathogenetically MCAD denotes a group of primary polygenic MC disorders[55] characterized by aberrant release of variable subsets of MC mediators and also an accumulation of morphologically altered and immunohistochemically identifiable mutated MCs because of MC proliferation (SM and MC leukemia) or by an accumulation of morphologically ordinary MCs because of decreased apoptosis (MCAS).[56-58] SM is characterized by immunohistochemical and biochemical findings known as the World Health Organization criteria[51,59] (Supplementary Table 1), which are due to the presence of a pathologic mutation at amino acid position 816 in the tyrosine kinase KIT (most frequently KIT^{D816V}). MCAS seemingly is dominantly driven by sets of mutations in all domains of KIT but not affecting codon 816 (for review, see Molderings[55]) and the diagnosis can be made according to the current international provisional definition criteria (Supplementary Table 1). Because of both the widespread distribution of MCs and the great heterogeneity of aberrant mediator expression patterns, symptoms can occur in virtually all organs and tissues; hence, the clinical presentation of MCAD is very diverse, sometimes to the even further confounding point of presenting opposite abnormalities in different patients. However, according to the recent molecular genetic findings,[55,60,61] the subclasses and clinical subtypes of MCAD do not represent distinct disease

entities but should be more accurately regarded as varying compositions of a common MC dysfunction.[50,62-64] Although the prevalence for SM in Europeans ranges between 0.3 and 13:100,000,[65-67] the prevalence for MCAS may be as high as 17% (in Germany).[68]

CARDIOVASCULAR ASPECTS OF MCAD

Importantly for the clinician (and the patient), although MCAS may lack hallmark histologic and biochemical features of SM (eg, marked proliferation, aggregation and spindling of MCs, and tryptase overexpression), these 2 major subclasses of MCAD have largely equivalent potentials for wreaking multisystem havoc including the cardiovascular system (Table I) via aberrant mediator production and release.[52,64,69-71] Accordingly, in the following the main cardiovascular symptoms are described and discussed in the broader context of MCAD and not separately for SM and MCAS.

Supraventricular tachycardia, palpitations, and cardiac arrest. Palpitations and episodes of supraventricular tachycardia are frequently reported by both SM (29%)[70] and MCAS patients (at least 20%).[52,69,72-75] MCAS patients often present with a hyperadrenergic postural tachycardia syndrome[76] (own unpublished observation 2015), and hence in patients with postural tachycardia syndrome, MCAD should be considered as a potential underlying cause. In addition, MCAD can present as cardiac emergency with cardiac arrest or ventricular fibrillation.[77]

Pathogenesis. Release of pathologic amounts of norepinephrine (NE) from cardiac sympathetic nerves can result in arrhythmias and sudden cardiac death. MCs can modulate NE release by targeting sympathetic nerves by 2 ways: one is represented by ANG II, which is in the heart formed locally both by MC-derived renin[9] (or review, see Reid et al[5]) and independent of ACE by the proteases cathepsin-D[78] and chymase,[9,18-20] and functions as a positive modulator of NE release. Renin released by activated MCs initiates the activation of a local renin-angiotensin system, which culminates in the formation of ANG II. ANG II then binds to facilitatory presynaptic angiotensin AT_1 receptors on the sympathetic nerve endings.[79] Aside from facilitating NE release and its arrhythmogenic effects, ANG II can also directly elicit cardiac arrhythmias without sympathetic involvement.[80] The other way of modulation of NE release comprises MC-derived histamine, which functions as a negative modulator of NE release by stimulation of inhibitory histamine H_3-receptors on sympathetic nerve terminals.[81-83] Because presynaptic AT_1 receptors and H_3-receptors have opposing effects on NE release, the ratio of renin and histamine release from MCs may determine the risk and the extent of tachycardia in MCAD. In addition, histamine is known to act as a direct stimulator of the H_1- and H_2-receptors on the cardiomyocytes. H_2-receptors cause an increase in heart rate and contractility, whereas H_1-receptors mediate negative chronotropic effects. However, the activation thresholds of H_1- and H_2-receptors are much greater (micromolar) than that of H_3-receptors (nanomolar),[84] suggesting that H_3-receptors may become activated at a lower concentration of histamine release from MCs. Finally, prostaglandin (PG) D_2, which is also a major mediator released from MCs, has been shown to induce tachycardia in humans.[85]

Table I. Cardiovascular symptoms and findings in mast cell activation disease (MCAD)[52,64,69,70]

Possible cardiovascular symptoms of MCAD
• Dysrhythmias
• Palpitations
• Cardiac arrest
• Pericarditis
• Presyncope, syncope
• Hypotension
• Arterial hypertension (systemic and pulmonary arterial hypertension)
• Heart failure (classic and atypical heart failure, for example Takotsubo cardiomyopathy)
• Artery dissection/aneurysm
• Raynaud syndrome
• Vasculitis
• Coronary syndromes (associated with rupture of an atherosclerotic plaque, partial or complete thrombosis, arterial embolism, allergic coronary spasm)
• Peripheral arterial atherosclerosis
• Aberrant angiogenesis (hemangiomas, arteriovenous malformations, telangiectasias)
• Livedo reticularis
• Hemorrhoids
• Varicosities
• Flush
• Hot flashes
• Clotting and bleeding abnormalities

Therapeutic options. The MC mediator-induced supraventricular tachycardia and tachyarrhythmia should be treated when it is extremely distressing the patients and when the heart rate permanently exceeds 100–120 beats/min. As first step the doses of MC activity reducing drugs such as H_1-antihistamines should be optimized. If this action is not sufficient to normalize heart rate and rhythm, further medical treatment should be considered. As a result of its pathophysiology, supraventricular tachycardia because of MC activation should be sensitive to treatment with direct renin inhibitors and AT_1 receptor blockers. Drugs of these classes can only be used in patients who do not have

hypotension, because the drugs can induce a further decrease in blood pressure. In those patients and in case of missing response to these drugs, the calcium channel blocker verapamil can be tried. If verapamil is ineffective as is frequently the case,[86] the funny current (I_f) blocker ivabradine,[87] which reduces heart rate in patients with sinus rhythm (but not in those with atrial fibrillation) without altering blood pressure,[88] can be used next if available (as in Europe).[86,89] β-Adrenoceptor antagonists are contraindicated in MCAD patients. β-Adrenoceptors play an important inhibitory role in the control of MC mediator release.[90,91] Hence, β-adrenoceptor antagonists disinhibit MC mediator release leading to aggravation of the symptoms of the MCAD.[92,93] Finally, it should be noted that epinephrine should be used in tachycardic MCAD patients with caution because it has been reported to precipitate ventricular fibrillation.[75] Antagonists of the two PGD_2 receptors, *PGD_2 receptor 1* (DP_1) and *chemoattractant homologous receptor expressed on Th2 cells* ($CRTH_2$), may be a future approach to the treatment of tachycardia in MCAD.

Blood pressure regulation irregularities. MCAD can present in different hemodynamic variants. Many patients experience a significant and sometimes dramatic decrease in blood pressure, whereas on the other hand, other patients exhibit a marked increase in blood pressure. Some MCAD patients demonstrate both hypotension and hypertension, sometimes fluctuating rapidly from one to the other.

Hypotension up to syncope. Episodes of hypotension with lightheadedness or syncope as the most dramatic acute manifestation of MCAD are reported by 22%–55% of the MCAD patients[68-70,94,95] in contrast to a prevalence of 5% in the control group.[68] The severity and frequency of the episodes of syncope can vary from as frequently as daily to as rarely as once per year or never.

Pathogenesis. MC can produce and release a number of mediators, which induce vasodilatation (Table II), and thereby induce hypotension up to vascular collapse.

Therapeutic options. MC activity reducing drugs such as H_1-antihistamines should be the first-line therapy. Acetylsalicylic acid (81–325 mg orally once or twice daily in adults) may be beneficial in some patients who have high levels of vasodilating PGs,[95-97] if the patient's ability to use nonsteroidal anti-inflammatory drugs without adverse effects is known. Alternatively, PG formation can be reduced by selective inhibition of cyclooxygenase 2 such as with etoricoxib in Europe or celecoxib in the US, although the potential cardiovascular risks of cyclooxygenase 2–selective nonsteroidal anti-inflammatory drugs need to be acknowledged.[98] Preliminary data from SM patients suggest an efficacy of omalizumab, a humanized monoclonal antibody against IgE, in the prevention of spontaneous episodes of systemic hypotension.[99-103] In case of recurrent anaphylactic syncopes, acute treatment with epinephrine and corticosteroids should be considered. Antagonists of the PGD_2 receptors DP_1 and $CRTH_2$ may be a future approach to the treatment of vascular symptoms in MCAD.

Arterial hypertension. In up to 31% of the MCAD patients marked recurrent or sustained increase in arterial blood pressure because of MC activation has been observed.[68,69,104,105]

Pathogenesis. MCs can produce and release a number of mediators, which induce vasoconstriction (Table II), and thereby induce hypertension. In particular, ANG II is a potent vasoconstrictor. Another major mediator released in MCAD patients is PGD_2,[106,107] which is a vasodilator. However, PGD_2 can be metabolized by 11-ketoreductase to its biologically active metabolite $9\alpha,11\beta$-PGF_2, which is a vasopressor substance.[104] Thus, arterial hypertension in MCAD patients may be linked to the metabolism of PGD_2 in the individual patient.

Therapeutic options. As first step the doses of MC activity reducing drugs such as H_1-antihistamines should be optimized. As a result of its pathophysiology hypertension in MCAD patients may be especially sensitive to treatment with direct renin inhibitors and AT_1 receptor blockers. From the standard medication for the treatment of high blood pressure β-adrenoceptor antagonists (see aforementioned details) and ACE inhibitors are contraindicated in MCAD patients. ACE also degrades bradykinin that is an activator of MCs.[93] Therefore, inhibition of ACE increases MC mediator releasability and hence autocrine MC activation with MCAD symptoms through stabilization of bradykinin.[93] Antagonists of the PGD_2 receptors DP_1 and $CRTH_2$ may be a future approach to the treatment of arterial hypertension in MCAD patients.

Chronic heart failure. Despite the evidence for a role of MCs in the evolution of congestive heart failure obtained in animal models[35-40] case reports of heart failure in SM patients are scarce.[108-110] In a Danish retrospective cohort study of 548 adults with SM only 12 patients had a congestive heart failure.[66] In a prospective study with 18 MCAS patients performed to investigate the suspected cardiac impact of an increased systemic MC activation no pathologic alterations in systolic left ventricular function, systolic and diastolic left ventricular diameter, and shortening fraction were recorded.[111] However, in 12 of the 18

Table II. Selected mast cell (MC) mediators and mechanisms through which activated MCs can induce cardiovascular symptoms

Mediators	Physiological/pathophysiological effects	Cardiovascular symptoms
Preformed (stored) mediators		
Biogenic amines		
Histamine	Vasodilation/vasoconstriction, vascular permeability ↑, PG production ↑, reduced myocardial contractility (histamine H_1 receptor, H_1R), increased myocardial contractility (histamine H_2 receptor, H_2R), positive chronotropic (H_2R), tissue factor expression ↑	Hypotension, hypertension, tachycardia, heart failure
Serotonin	Vasoconstriction	Coronary syndromes
Enzymes		
Tryptase	Bradykinin formation with vasodilation, fibroblast proliferation, and fibrosis ↑, increased intraplaque hemorrhage, high density lipoprotein degradation	Hypotension, heart failure, atherosclerosis
Chymase	Angiotensin II synthesis, vasodilation because of bradykinin formation, conversion of pro-MMPs to MMPs	Hypotension, hypertension, heart failure
Carboxypeptidase A	Angiotensin II synthesis, cleavage of bradykinin	Hypertension
Phospholipases	Arachidonic acid generation	Hypotension, hypertension
MMPs	Matrix degradation	Tachycardia, aneurysm
Renin	Angiotensin I synthesis	Hypertension
Proteoglycans		
Heparin	Stabilization of tryptase and histamine, initiation of bradykinin formation, enhanced lipid uptake	Hypotension, atherosclerosis
Chemokines		
IL-8	Attraction of leukocytes to the atherosclerotic lesion and activation of immune cells, histamine and serotonin release from MCs	Atherosclerosis, aneurysm, coronary syndromes
CCL-5 (RANTES)	Attraction of leukocytes to the atherosclerotic lesion and activation of immune cells, histamine and serotonin release from MCs	Atherosclerosis, aneurysm, coronary syndromes
Polypeptides		
Vasoactive intestinal polypeptide	Vasodilation	Hypotension
Endothelin 1 and 3	Vasoconstriction, positive chronotropic	Hypertension, tachycardia, coronary syndromes
De novo formed mediators		
Phospholipid metabolites		
PGD_2	Vasodilation, vascular permeability ↑	Hypotension, hypertension (by metabolite)
PGE_2	Vasodilation	Hypotension
Thromboxane A_2	Vasoconstriction	Hypertension
Leukotrienes	Vasoconstriction	Hypertension, coronary syndromes
Platelet activating factor	Vasodilation, platelet activation, negative chronotropic, reduced myocardial contractility	Hypotension, heart failure
Cytokines and chemokines		
IL-1β	Arachidonic acid metabolite formation	Atherosclerosis, aneurysm
IL-4	Fibroblast proliferation ↑, chemotaxis, and matrix protein production	Atherosclerosis, heart failure
IL-6	Proinflammatory, hypotensive	Hypotension, atherosclerosis, heart failure
IL-10	Regulation of tissue remodeling	Heart failure
CCL2 (MCP-1)	Attraction of leukocytes to the atherosclerotic lesion and activation of immune cells, histamine and serotonin release from MCs, synthesis of leukotriene C4	Atherosclerosis, coronary syndromes
CCL3, CCL4 (MIP-1α and 1β)	Attraction of leukocytes to the atherosclerotic lesion and activation of immune cells	Atherosclerosis
TNF-α	Adherence and migration of inflammatory cells ↑, fibroblast growth, and chemotaxis	Atherosclerosis, heart failure
Growth factors		
Vascular endothelial growth factor	Vasopermeability ↑, induction of plaque angiogenesis	Atherosclerosis
Fibroblast growth factor-2 and -7	Activates fibroblasts, induction of plaque angiogenesis	Atherosclerosis, heart failure

(*Continued*)

Table II. (*Continued*)

Mediators	Physiological/pathophysiological effects	Cardiovascular symptoms
Transforming growth factor beta	Production of *CC-chemokine ligand 2* in fibroblasts ↑	Heart failure
Other		
Nitric oxide	Vasodilation	Hypotension

Abbreviations: IL, interleukin; *MCP,* monocyte chemoattractant protein; *MIP,* macrophage inflammatory proteins; *MMPs,* matrix metalloproteinases; *PG,* prostaglandin; *TNF-α,* tumor necrosis factor α; *CCL-5,* chemokine (C-C motif) ligand 5; *RANTES,* regulated on activation normal T cell expressed and secreted.

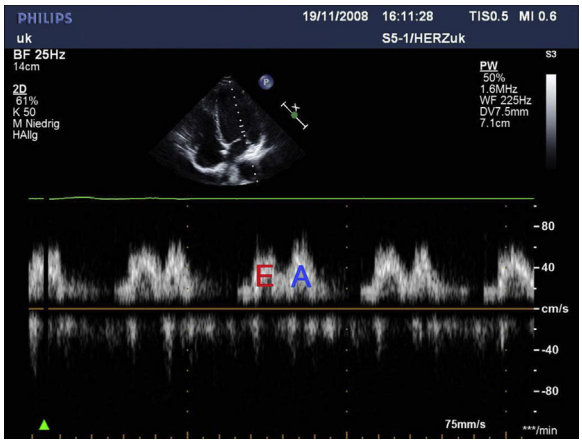

Fig 1. Pulse-wave (PW) Doppler of the diastolic mitral flow profile in the left ventricle in the transthoracic apical 4-chamber view (upper part of the picture). In the lower part of the picture, the E-wave (E) is smaller than the A-wave (A), which suggests a diastolic dysfunction of the left ventricle in terms of a relaxation disturbance. Female mast cell activation syndrome patient, age 61 years. (Figure taken from Kolck).[111]

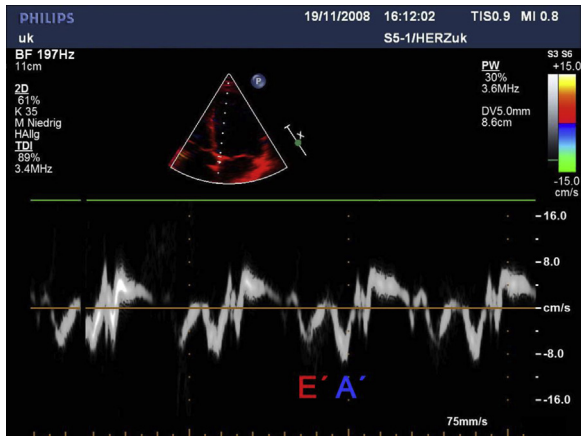

Fig 2. Tissue Doppler imaging (TDI) of the medial mitral annulus in the transthoracic apical 4-chamber view (upper part of the picture). In the lower part of the picture, the E'-wave is clearly smaller than the A'-wave, which is demonstrating a diastolic dysfunction of the left ventricle. Normally the E'-wave is taller than the A'-wave. The same patient as in Fig 1. (Figure take from Kolck).[111]

MCAS patients a diastolic left ventricular dysfunction could be determined by pulse-wave imaging and-or tissue Doppler imaging, which represents the most sensitive sign of a myocardial textural alteration (Figs 1 and 2).[112,113] In 5 of the 12 patients a left ventricular hypertrophy was observed. Thus, although there may be textural signs of heart failure in most MCAD patients, symptomatic chronic heart failure appears to be not more prevalent than in the general population.

Pathogenesis. These alterations are probably due to the remodeling effect of prohypertrophic cytokines and proteases and profibrotic growth factors synthesized and secreted by MCs.[27,37,114,115]

Therapeutic options. The medical treatment options of patients with chronic heart failure (New York Heart Association class II–IV) based on the European guidelines[116] are also valid for MCAD patients with clinically manifest heart failure. The European Society of Cardiology Guidelines recommend a therapy-escalation starting with diuretics to relieve symptoms or signs of congestion, followed by implementation of ANG 1 receptor antagonists. ACE inhibitors are contraindicated in MCAD patients (for reasons, see aforementioned details). The next step in the therapeutic scheme would be the use of β-adrenoceptor blockers, which, however, are also contraindicated in MCAD patients (for reasons, see aforementioned details). Therefore, alternatively calcium channel antagonists of the verapamil-type should be used. As further escalation step of the medical therapy the use of spironolactone or alternatively eplerenone is recommended. In case patients have a sinus rhythm the next therapy step should be the implementation of ivabradine, if the heart rate is >70 beats/min. In the case of atrial fibrillation digoxine or digitoxine could be considered, if an induced cardioversion (medical or electrical) has not been successful.

Coronary syndromes. MCs have been detected at the site of vasospasm in patients with variant angina indicating a role in coronary artery spasm.[6] Numerous case reports of patients with MCAD presenting as Prinzmetal (Variant) angina[117] or allergic acute coronary syndrome ("Kounis syndrome")[71,118] have

been published. We have made similar observations in our patient population (unpublished findings 2015).

Pathogenesis. MCs can form and secrete a plethora of vasoconstrictive mediators such as serotonin, leukotrienes, and endothelin (Table II).

Therapeutic options. The treatment should both dilate coronary vessels and suppress MC mediator release. Vasodilator drugs, including nitrates and calcium channel blockers, should be considered as first-line therapy.

CONCLUSIONS

Cardiovascular symptoms because of released MC mediators are frequent in MCAD. Because a symptom can be caused by several different MC mediators (Table II), knowledge of the mediators increased in an individual patient would allow a personalized therapy. At present only few mediators can be determined in routine laboratory; however, in future more mediators will probably be available for routine investigation.

ACKNOWLEDGMENTS

Conflicts of Interest: All authors have read the journal's policy on disclosure of potential conflicts of interest and have none to declare.

All authors have read the journal's authorship agreement. All authors participated in the writing of the manuscript. The manuscript has been reviewed and approved by all authors. We thank Mr Wolfgang Taumann for his linguistic revision of the manuscript.

REFERENCES

1. Gri G, Frossi B, D'Inca F, et al. Mast cell: an emerging partner in immune interaction. Front Immunol 2012;3:120.
2. Molderings GJ. Mast cell function in physiology and pathophysiology. Biotrend Rev 2010;5:1–9.
3. Lundequist A, Pejler G. Biological implications of preformed mast cell mediators. Cell Mol Life Sci 2011;68:965–75.
4. Ibelgaufts H. "Mast cells" in COPE: cytokines and cells online pathfinder encyclopaedia. Available at: http://www.copewithcytokines.de/cope.cgi?key=mast%20cells; 2015. Accessed February 4, 2015.
5. Reid AC, Silver RB, Levi R. Renin: at the heart of the mast cell. Immunol Rev 2007;217:123–40.
6. Forman MB, Oates JA, Robertson D, Robertson RM, Roberts LJ, Virmani R. Increased adventitial mast cells in a patient with coronary spasm. N Engl J Med 1985;313:1138–41.
7. Dvorak AM. Mast-cell degranulation in human hearts. N Engl J Med 1986;315:969–70.
8. Marone G, De Crescenzo G, Adt M, Patella V, Arbustini E, Genovese A. Immunological characterization and functional importance of human heart mast cells. Immunopharmacology 1995;31:1–18.
9. Silver RB, Reid AC, Mackins CJ, et al. Mast cells: a unique source of renin. Proc Natl Acad Sci U S A 2004;101:13607–12.
10. Morrey C, Brazin J, Seyedi N, Corti F, Silver RB, Levi R. Interaction between sensory C-fibers and cardiac mast cells in ischemia/reperfusion: activation of a local renin-angiotensin system culminating in severe arrhythmic dysfunction. J Pharmacol Exp Ther 2010;335:76–84.
11. Mackins CJ, Kano S, Seyedi N, et al. Cardiac mast cell-derived renin promotes local angiotensin formation, norepinephrine release, and arrhythmias in ischemia/reperfusion. J Clin Invest 2006;116:1063–70.
12. Koda K, Salazar-Rodriguez M, Corti F, et al. Aldehyde dehydrogenase activation prevents reperfusion arrhythmias by inhibiting local renin release from cardiac mast cells. Circulation 2010;122:771–81.
13. Gurish MF, Boyce JA. Mast cells: ontogeny, homing, and recruitment of a unique innate effector cell. J Allergy Clin Immunol 2006;117:1285–91.
14. Prussin C, Metcalfe DD. IgE, mast cells, basophils, and eosinophils. J Allergy Clin Immunol 2006;117:S450–6.
15. Weidner N, Austen KF. Heterogeneity of mast cells at multiple body sites. Fluorescent determination of avidin binding and immunofluorescent determination of chymase, tryptase, and carboxypeptidase content. Pathol Res Pract 1993;189:156–62.
16. Rakusan K, Sarkar K, Turek Z, Wicker P. Mast cells in the rat heart during normal growth and in cardiac hypertrophy. Circ Res 1990;66:511–6.
17. Proctor GB, Chan KM, Garrett JR, Smith RE. Proteinase activities in bovine atrium and the possible role of mast cell tryptase in the processing of atrial natriuretic factor (ANF). Comp Biochem Physiol 1991;99:839–44.
18. Frangogiannis NG, Lindsey ML, Michael LH, et al. Resident cardiac mast cells degranulate and release preformed TNF-α, initiating the cytokine cascade in experimental canine myocardial ischemia/reperfusion. Circulation 1998;98:699–710.
19. Moyazaki M, Takai S, Jin D, Muramatsu M. Pathological roles of angiotensin II produced by mast cell chymase and the effects of chymase inhibition in animal models. Pharmacol Ther 2006;112:668–76.
20. Wei CC, Hase N, Inoue Y, et al. Mast cell chymase limits the cardiac efficacy of Ang I-converting enzyme inhibitor therapy in rodents. J Clin Invest 2010;120:1229–39.
21. Marone G, de Crescenzo G, Patella V, Genovese A. Human cardiac mast cells and their role in severe allergic reactions. In: Marone G, Auslen KF, Holgate ST, Kay AB, Lichtenstein LM, eds. Asthma and allergic diseases. London: Academic Press Ltd, 1998:237–69.
22. Kennedy S, Wu J, Wadsworth RM, Lawrence CE, Maffia P. Mast cells and vascular diseases. Pharmacol Ther 2013;138:53–65.
23. Xu JM, Shi GP. Emerging role of mast cells and macrophages in cardiovascular and metabolic diseases. Endocr Rev 2012;33:71–108.
24. DeBruin EJ, Gold M, Lo BC, et al. Mast cells in human health and disease. Methods Mol Biol 2015;1220:93–119.
25. Gilles S, Zahler S, Welsch U, Sommerhoff CP, Becker BF. Release of TNF-α during myocardial reperfusion depends on oxidative stress and is prevented by mast cell stabilizers. Cardiovasc Res 2003;60:608–16.
26. Palaniyandi SS, Inagaki K, Mochly-Rosen D. Mast cells and epsilonPKC: a role in cardiac remodeling in hypertension-induced heart failure. J Mol Cell Cardiol 2008;45:779–86.
27. Levick SP, Meléndez GC, Plante E, McLarty JL, Brower GL, Janicki JS. Cardiac mast cells: the centrepiece in adverse myocardial remodelling. Cardiovasc Res 2011;89:12–9.
28. Meléndez GC, Li J, Law BA, Janicki JS, Supowit SC, Levick SP. Substance P induces adverse myocardial remodelling via a mechanism involving cardiac mast cells. Cardiovasc Res 2011;92:420–9.

29. Higuchi H, Hara M, Yamamoto K, et al. Mast cells play a critical role in the pathogenesis of viral myocarditis. Circulation 2008; 118:363–72.
30. Brower GL, Janicki JS. Pharmacologic inhibition of mast cell degranulation prevents left ventricular remodeling induced by chronic volume overload in rats. J Card Fail 2005;11:548–56.
31. Huang ZG, Jin Q, Fan M, et al. Myocardial remodeling in diabetic cardiomyopathy associated with cardiac mast cell activation. PLoS One 2013;8:e60827.
32. Li QY, Raza-Ahmad A, MacAulay MA, et al. The relationship of mast cells and their secreted products to the volume of fibrosis in post transplant hearts. Transplantation 1992;53:1047–51.
33. Zweifel M, Hirsiger H, Matozan K, Welle M, Schaffner T, Mohacsi P. Mast cells in ongoing acute rejection: increase in number and expression of a different phenotype in rat heart transplants. Transplantation 2002;73:1707–16.
34. Palaniyandi Selvaraj S, Watanabe K, Ma M, Tachikawa H, Kodama M, Aizawa Y. Involvement of mast cells in the development of fibrosis in rats with postmyocarditis dilated cardiomyopathy. Biol Pharm Bull 2005;28:2128–32.
35. Hara M, Ono K, Hwang MW, et al. Evidence for a role of mast cells in the evolution to congestive heart failure. J Exp Med 2002;195:375–81.
36. Joseph J, Joseph L, Shekhawat NS, et al. Hyperhomocysteinemia leads to pathological ventricular hypertrophy in normotensive rats. Am J Physiol Heart Circ Physiol 2003;285:H679–86.
37. Shiota N, Rysa J, Kovanen PT, Ruskoaho H, Kokkonen JO, Lindstedt KA. A role for cardiac mast cells in the pathogenesis of hypertensive heart disease. J Hypertens 2003;21: 1935–44.
38. Batlle M, Roig E, Perez-Villa F, et al. Increased expression of the renin-angiotensin system and mast cell density but not of angiotensin-converting enzyme II in late stages of human heart failure. J Heart Lung Transplant 2006;25:1117–25.
39. Kim J, Ogai A, Nakatani S, et al. Impact of blockade of histamine H2 receptors on chronic heart failure revealed by retrospective and prospective randomized studies. J Am Coll Cardiol 2006;48:1378–84.
40. Balakumar P, Singh AP, Ganti SS, Krishan P, Ramasamy S, Singh M. Resident cardiac mast cells: are they the major culprit in the pathogenesis of cardiac hypertrophy? Basic Clin Pharmacol Toxicol 2008;102:5–9.
41. Cheng TO, Kounis NG. Takotsubo cardiomyopathy, mental stress and the Kounis syndrome. Int J Cardiol 2012;161:65–7.
42. Vultaggio A, Matucci A, Del Pace S, et al. Tako-Tsubo-like syndrome during anaphylactic reaction. Eur J Heart Fail 2007;9: 209–11.
43. Ramalho LS, Oliveira LF, Cavellani CL, et al. Role of mast cell chymase and tryptase in the progression of atherosclerosis: study in 44 autopsied cases. Ann Diagn Pathol 2013;17:28–31.
44. Bot I, Shi GP, Kovanen PT. Mast cells as effectors in atherosclerosis. Arterioscler Thromb Vasc Biol 2015;35:265–71.
45. Steffel J, Akhmedov A, Greutert H, Lüscher TF, Tanner FC. Histamine induces tissue factor expression. Circulation 2005;112: 341–9.
46. Kervinen H, Kaartinen M, Mäkynen H, Palosuo T, Mänttäri M, Kovanen PT. Serum tryptase levels in acute coronary syndromes. Int J Cardiol 2005;104:138–43.
47. Deliargyris EN, Upadhya B, Sane DC, et al. Mast cell tryptase: a new biomarker in patients with stable coronary artery disease. Atherosclerosis 2005;178:381–6.
48. Wang Y, Shi GP. Mast cell chymase and tryptase in abdominal aortic aneurysm formation. Trends Cardiovasc Med 2012;22: 150–5.
49. Zhang J, Sun J, Lindholt JS, et al. Mast cell tryptase deficiency attenuates mouse abdominal aortic aneurysm formation. Circ Res 2011;108:1316–27.
50. Akin C, Valent P, Metcalfe D. Mast cell activation syndrome: proposed diagnostic criteria. J Allergy Clin Immunol 2010; 126:1099–104.
51. Valent P, Akin C, Escribano L, et al. Standards and standardization in mastocytosis: consensus statements on diagnostics, treatment recommendations and response criteria. Eur J Clin Invest 2007;37:435–53.
52. Molderings GJ, Brettner S, Homann J, Afrin LB. Mast cell activation disease: a concise practical guide for diagnostic workup and therapeutic options. J Hematol Oncol 2011;4:10.
53. Hamilton MJ, Hornick JL, Akin C, Castells MC, Greenberger NJ. Mast cell activation syndrome: a newly recognized disorder with systemic clinical manifestations. J Allergy Clin Immunol 2011;128:147–52.
54. Valent P, Akin C, Arock M, et al. Definitions, criteria and global classification of mast cell disorders with special reference to mast cell activation syndromes: a consensus proposal. Int Arch Allergy Immunol 2012;157:215–25.
55. Molderings GJ. The genetic basis of mast cell activation disease—looking through a glass darkly. Crit Rev Oncol Hematol 2015;93:75–89.
56. Kohno M, Yamasaki S, Tybolewicz VL, Saito T. Rapid and large amount of autocrine IL-3 production is responsible for mast cell survival by IgE in the absence of antigen. Blood 2005;105: 2059–65.
57. Aichberger KJ, Gleixner KV, Mirkina I, et al. Identification of proapoptotic Bim as a tumor suppressor in neoplastic mast cells: role of KIT D816V and effects of various targeted drugs. Blood 2009;114:5342–51.
58. Karlberg M, Ekoff M, Labi V, Strasser A, Huang D, Nilsson G. Pro-apoptotic Bax is the major and Bak an auxiliary effector in cytokine deprivation-induced mast cell apoptosis. Cell Death Dis 2010;1:e43.
59. Valent P, Horny HP, Escribano L, et al. Diagnostic criteria and classification of mastocytosis: a consensus proposal. Leuk Res 2001;25:603–25.
60. Haenisch B, Fröhlich H, Herms S, Molderings GJ. Evidence for contribution of epigenetic mechanisms in the pathogenesis of systemic mast cell activation disease. Immunogenetics 2014; 66:287–97.
61. Lasho T, Finke C, Zblewski D, et al. Concurrent activating KIT mutations in systemic mastocytosis. Br J Haematol 2015. Ahead of print.
62. Molderings GJ, Kolck UW, Scheurlen C, Brüss M, Homann J, Von Kügelgen I. Multiple novel alterations in Kit tyrosine kinase in patients with gastrointestinally pronounced systemic mast cell activation disorder. Scand J Gastroenterol 2007;42:1045–53.
63. Molderings GJ, Meis K, Kolck UW, Homann J, Frieling T. Comparative analysis of mutation of tyrosine kinase kit in mast cells from patients with systemic mast cell activation syndrome and healthy subjects. Immunogenetics 2010;62:721–7.
64. Hermine O, Lortholary O, Leventhal PS, et al. Case-control cohort study of patients' perceptions of disability in mastocytosis. PLoS One 2008;3:e2266.
65. Haenisch B, Nöthen MM, Molderings GJ. Systemic mast cell activation disease: the role of molecular genetic alterations in pathogenesis, heritability and diagnostics. Immunology 2012; 137:197–205.
66. Cohen SS, Skovbo S, Vestergaard H, et al. Epidemiology of systemic mastocytosis in Denmark. Br J Haematol 2014;166:521–8.

67. van Doormaal JJ, Arends S, Brunekreeft KL, et al. Prevalence of indolent systemic mastocytosis in a Dutch region. J Allergy Clin Immunol 2013;131:1429–31.
68. Molderings GJ, Haenisch B, Bogdanow M, Fimmers R, Nöthen MM. Familial occurrence of systemic mast cell activation disease. PLoS One 2013;8:e76241.
69. Alvarez-Twose I, González de Olano D, Sánchez-Muñoz L, et al. Clinical, biological, and molecular characteristics of clonal mast cell disorders presenting with systemic mast cell activation symptoms. J Allergy Clin Immunol 2010;125:1269–78.
70. Horan RF, Austen KF. Systemic mastocytosis: retrospective review of a decade's clinical experience at the Brigham and Women's Hospital. J Invest Dermatol 1991;96(3 suppl): 5S–13S.
71. González-de-Olano D, Matito A, Sánchez-López P, et al. Mast cell-related disorders presenting with Kounis syndrome. Int J Cardiol 2012;161:56–8.
72. Ricciardi L, Saitta S, Isola S, et al. Systemic mastocytosis associated with recurrent paroxysmal atrial fibrillation. Allergy 2005;60:542–3.
73. Bazan-Socha S, Rudzki Z, Maciejewicz J, Witkoś T, Szczeklik A. Clinical variability in two cases of systemic mastocytosis. Pol Arch Med Wewn 2001;105:311–5.
74. Crawhall JC, Wilkinson RD. Systemic mastocytosis: management of an unusual case with histamine (H_1 and H_2) antagonists and cyclooxygenase inhibition. Clin Invest Med 1987;10:1–4.
75. Rohr SM, Rich MW, Silver KH. Shortness of breath, syncope, and cardiac arrest caused by systemic mastocytosis. Ann Emerg Med 2005;45:592–4.
76. Shibao C, Arzubiaga C, Roberts LJ, et al. Hyperadrenergic postural tachycardia syndrome in mast cell activation disorders. Hypertension 2005;45:385–90.
77. Ridolo E, Triggiani M, Montagni M, et al. Mastocytosis presenting as cardiac emergency. Intern Emerg Med 2013;8:749–52.
78. Hackenthal E, Hackenthal R, Hilgenfeldt U. Isorenin, pseudorenin, cathepsin D and renin. A comparative enzymatic study of angiotensin-forming enzymes. Biochim Biophys Acta 1978; 522:574–88.
79. Molderings GJ, Likungu J, Hentrich F, Göthert M. Facilitatory presynaptic angiotensin receptors on the sympathetic nerves of the human saphenous vein and pulmonary artery. Potential involvement in β-adrenoceptor-mediated facilitation of noradrenaline release. Naunyn-Schmiedebergs Arch Pharmacol 1988;338:228–33.
80. Iravanian S, Dudley SC Jr. The renin-angiotensin-aldosterone system (RAAS) and cardiac arrhythmias. Heart Rhythm 2008; 5:S12–7.
81. Cabanié M, Godfraind T. The role of histamine in the cardiovascular system. Drugs Exp Clin Res 1988;14:141–7.
82. Imamura M, Seyedi N, Lander HM, Levi R. Functional identification of histamine H_3-receptors in the human heart. Circ Res 1995;77:206–10.
83. Mackins CJ, Levi R. Therapeutic potential of H_3-receptor agonists in myocardial infarction. Exp Opin Invest Drugs 2000;9:2537–42.
84. Thurmond RL, Gelfand EW, Dunford PJ. The role of histamine H_1 and H_4 receptors in allergic inflammation: the search for new antihistamines. Nat Rev Drug Discov 2008;7:41–53.
85. Heavey DJ, Lumley P, Barrow SE, Murphy MB, Humphrey PP, Dollery CT. Effects of intravenous infusions of prostaglandin D_2 in man. Prostaglandins 1984;28:755–67.
86. Molderings GJ, Homann J, Brettner S, Raithel M, Frieling T. Mast cell activation disease: a concise practical guide for diagnostic workup and therapeutic options. Dtsch Med Wochenschr 2014;139:1523–34.
87. Bucchi A, Baruscotti M, DiFrancesco D. Current-dependent block of rabbit sino-atrial node I(f) channels by ivabradine. J Gen Physiol 2002;120:1–13.
88. Joannides R, Moore N, Iacob M, et al. Comparative effects of ivabradine, a selective heart rate-lowering agent, and propranolol on systemic and cardiac haemodynamics at rest and during exercise. Br J Clin Pharmacol 2006;61:127–37.
89. Zellerhoff S, Hinterseer M, Felix Krull B, et al. Ivabradine in patients with inappropriate sinus tachycardia. Naunyn-Schmiedebergs Arch Pharmacol 2010;382:483–6.
90. Peachell P. Regulation of mast cells by beta-agonists. Clin Rev Allergy Immunol 2006;31:131–41.
91. Wang XS, Lau HY. Beta-adrenoceptor-mediated inhibition of mediator release from human peripheral blood-derived mast cells. Clin Exp Pharmacol Physiol 2006;33:746–50.
92. Alfter K, von Kügelgen I, Kolck UW, et al. Diagnostics and therapy of systemic mastocytosis. Med Welt 2007;58:621–31.
93. Nassiri M, Babina M, Dölle S, Edenharter G, Ruëff F, Worm M. Ramipril and metoprolol intake aggravate human and murine anaphylaxis: evidence for direct mast cell priming. J Allergy Clin Immunol 2015;135:491–9.
94. Travis WD, Li CY, Bergstralh EJ, Yam LT, Swee RG. Systemic mast cell disease. Analysis of 58 cases and literature review. Medicine (Baltimore) 1988;67:345–68.
95. Valabhji J, Robinson S, Johnston D, Bellamy M, Davies W, Bain BJ. Unexplained loss of consciousness: systemic mastocytosis. J R Soc Med 2000;93:141–2.
96. Butterfield JH. Survey of aspirin administration in systemic mastocytosis. Prostaglandins Other Lipid Mediat 2009;88:122–4.
97. Ono E, Taniguchi M, Mita H, et al. Increased production of cysteinyl leukotrienes and prostaglandin D2 during human anaphylaxis. Clin Exp Allergy 2009;39:72–80.
98. De Vecchis R, Baldi C, Di Biase G, et al. Cardiovascular risk associated with celecoxib or etoricoxib: a meta-analysis of randomized controlled trials which adopted comparison with placebo or naproxen. Minerva Cardioangiol 2014;62:437–48.
99. Carter MC, Robyn JA, Bressler PB, Walker JC, Shapiro GG, Metcalfe DD. Omalizumab for the treatment of unprovoked anaphylaxis in patients with systemic mastocytosis. J Allergy Clin Immunol 2007;119:1550–1.
100. Kontou-Fili K, Filis CI, Voulgari C, Panayiotidis PG. Omalizumab monotherapy for bee sting and unprovoked "anaphylaxis" in a patient with systemic mastocytosis and undetectable specific IgE. Ann Allergy Asthma Immunol 2010;104:537–9.
101. Bell MC, Jackson DJ. Prevention of anaphylaxis related to mast cell activation syndrome with omalizumab. Ann Allergy Asthma Immunol 2012;108:383–4.
102. Kibsgaard L, Skjold T, Deleuran M, Vestergaard C. Omalizumab induced remission of idiopathic anaphylaxis in a patient suffering from indolent systemic mastocytosis. Acta Derm Venereol 2014;94:363–4.
103. Jagdis A, Vadas P. Omalizumab effectively prevents recurrent refractory anaphylaxis in a patient with monoclonal mast cell activation syndrome. Ann Allergy Asthma Immunol 2014;113:115–6.
104. Roberts LJ 2nd, Oates JA. Biochemical diagnosis of systemic mast cell disorders. J Invest Dermatol 1991;96(3 suppl): 19S–24S.
105. Jennings S, Russell N, Jennings B, et al. The mastocytosis society survey on mast cell disorders: patient experiences and perceptions. J Allergy Clin Immunol Pract 2014;2:70–6.
106. Roberts LJ 2nd, Sweetman BJ, Lewis RA, Austen KF, Oates JA. Increased production of prostaglandin D_2 in patients with systemic mastocytosis. N Engl J Med 1980;303:1400–4.

107. Schäfer D, Dreßen P, Brettner S, et al. Prostaglandin D2-supplemented "functional eicosanoid testing and typing" assay with peripheral blood leukocytes as a new tool in the diagnosis of systemic mast cell activation disease: an explorative diagnostic study. J Transl Med 2014;12:213.
108. McElroy EA Jr, Phyliky RL, Li CY. Systemic mast cell disease associated with the hypereosinophilic syndrome. Mayo Clin Proc 1998;73:47–50.
109. Sotlar K, Horny HP, Lebherz J, Leser HG, Bültmann B. Association of bone marrow mastocytosis with extremely immature extramedullary mast cell sarcoma. Pathologe 1997;18:252–6.
110. Clarke K. Anaphylaxis in a patient with mastocytosis [abstract]. J Hospital Med 2012;7(suppl 2). abstract #97898.
111. Kolck UW. Investigations on the pathogenesis of the systemic mast cell activation syndrome and its impact on heart function. Bonn: University, medical thesis, 2009; [in German]; URN:nbn:de:hbz:5N-19064. Available at: http://hss.ulb.uni-bonn.de/2009/1906/1906.htm. Accessed December 2015.
112. Kolck UW, Alfter K, Homann J, von Kügelgen I, Molderings GJ. Cardiac mast cells: implications for heart failure. J Am Coll Cardiol 2007;49:1107.
113. Nagueh SF, Appleton CP, Gillebert TC, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. J Am Soc Echocardiogr 2009;22:107–33.
114. Batlle M, Perez-Villa F, Lazaro A, et al. Correlation between mast cell density and myocardial fibrosis in congestive heart failure patients. Transplant Proc 2007;39:2347–9.
115. Levick SP, McLarty JL, Murray DB, Freeman RM, Carver WE, Brower GL. Cardiac mast cells mediate left ventricular fibrosis in the hypertensive rat heart. Hypertension 2009;53:1041–7.
116. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012;33:1787–847.
117. Ward BR, Schwartz LB. Systemic mastocytosis presenting as Prinzmetal (variant) angina. J Allergy Clin Immunol 2011;127(suppl 2):AB188.
118. Fassio F, Almerigogna F. Kounis syndrome (allergic acute coronary syndrome): different views in allergologic and cardiologic literature. Intern Emerg Med 2012;7:489–95.

Appendix

Supplementary Table 1. Criteria proposed to define mast cell (MC) activation disease (for references, see text) when all other diagnoses that could better explain the full range and chronicity of the findings in the case have been excluded

Proposed criteria defining systemic MC activation syndrome	World Health Organization criteria defining systemic mastocytosis
Major criterion Constellation of clinical complaints attributable to pathologically increased MC activity (MC mediator release syndrome)	Major criterion Multifocal dense infiltrates of MCs (ie, aggregates of >15 MCs) in marrow and/or other extracutaneous organ(s)
Minor criteria 1. Multifocal or disseminated dense infiltrates of MCs in marrow and/or extracutaneous organ(s) (eg, gastrointestinal or genitourinary tract) 2. Abnormal spindle-shaped morphology in >25% of MCs in marrow or other extracutaneous organ(s) 3. Abnormal MC expression of CD2 and/or CD25 (ie, coexpression of CD117/CD25 or CD117/CD2) 4. MC genetic changes (eg, activating KIT mutations outside codon 816) shown to increase MC activity 5. Evidence (typically from body fluids such as whole blood, serum, plasma, or urine) of above-normal levels of MC mediators including • tryptase • histamine or its metabolites (eg, *N*-methylhistamine) • heparin • chromogranin A (note potential confounders of cardiac or renal failure, neuroendocrine tumors, or recent proton pump inhibitor use) • other relatively MC-specific mediators (eg, eicosanoids including prostaglandin (PG) D_2, its metabolite 11β-$PGF_{2\alpha}$, or leukotriene E4) 6. Symptomatic response to inhibitors of MC activation or MC mediator production or action	Minor criteria 1. Abnormal spindle-shaped morphology in >25% of MCs in marrow or other extracutaneous organ(s) 2. Abnormal marrow MC expression of CD2 and/or CD25 (ie, coexpression of CD117/CD25 or CD117/CD2) 3. Activating KIT mutation at codon 816 in MCs in extracutaneous organ(s) 4. Serum total tryptase >20 ng/mL (does not apply to patients who have associated hematologic non–mast cell lineage disease)

The diagnosis primary systemic MC activation syndrome is made on fulfillment of the major criterion plus at least 1 minor criterion (modified from Molderings et al[52]). According to the World Health Organization criteria (Valent et al[51]), the diagnosis systemic mastocytosis is established if the major criterion and at least 1 minor criterion or at least 3 minor criteria are fulfilled.