

A Review of the Dermatologic Symptoms of Idiopathic Mast Cell Activation Syndrome

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ABSTRACT

Since the first reported cases in 2007, idiopathic mast cell activation syndrome has been increasingly recognized. Understanding of the cutaneous manifestations of this condition is imperative for dermatologists given the substantial clinical heterogeneity in its presentation and high estimated prevalence. A review of PubMed® and SCOPUS® databases was performed in order to investigate the most common dermatologic manifestations of idiopathic mast cell activation syndrome. Evidence to date suggests that flushing, pruritus, and clotting dysfunction or bleeding disorder are the most frequently observed dermatologic symptoms in idiopathic mast cell activation syndrome, while dermatographism has been identified as a common finding in patients as well. Mast cell activation syndromes have also been linked to connective tissue disorders, including an Ehlers-Danlos Syndrome-like phenotype possibly mediated by matrix metalloproteinases and tryptase released by mast cells. Current literature regarding dermatologic manifestations of idiopathic mast cell activation syndrome is limited by the heterogeneity of studies including clinical descriptions, inconsistency of diagnostic criteria implemented, and a paucity of literature available. This work provides a guide for dermatologists to strengthen diagnostic acuity for idiopathic mast cell activation syndrome, therefore contributing toward a goal of helping patients to receive timely, effective, and targeted therapy.

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INTRODUCTION

Mast cells (MCs) are derived from a hematopoietic origin and are found in all human tissues. Upon activation by either immunologic or non-immunologic mechanisms, the former of which involves an immunoglobulin E-mediated process, MCs undergo degranulation to release a variety of mediator molecules.[1] When active, MCs serve as guardians of homeostasis by releasing bioactive substances including histamine, heparin, serotonin, enzymes, cytokines, growth factors, and lipid metabolites which serve to influence local and distant tissue in response to environmental change or bodily insults.[2–4]

Disorders of mast cell activation (MCAD) may arise from primary, secondary, or idiopathic origin.[5] Primary entities include cutaneous mastocytosis, systemic mastocytosis, and monoclonal MC activation syndrome (MMAS).[6] Secondary causes include allergic, inflammatory, or neoplastic origins, along with physical or autoimmune urticaria.[6] Idiopathic entities include idiopathic anaphylaxis, angioedema, or urticaria.[6] Since the first suggestion of MC disorders existing in the absence of MC proliferation was published in 2007, the entity of idiopathic MC activation syndrome (iMCAS) has also been differentiated as an additional subset of idiopathic, non-proliferative MCAD.[6,7] Diagnostic criteria have evolved since its initial description, partly due to an increased appreciation of the inter-relatedness of MC diseases.[5,6,8,9] Diagnostic criteria, initially proposed by Akin et al and subsequently modified, include: 1) Episodic symptoms of MC activation, 2) Increased markers of MC activity, and 3) Exclusion of primary or secondary causes of MC activation.[5,6,8,10]

Sparse epidemiologic data suggest an iMCAS prevalence in the general population as high as 17% and a predilection for females.[9,11] It is thought that iMCAS is more common than its proliferative MCAD counterparts including systemic mastocytosis (SM), which has been estimated to occur at a prevalence of 1 in 364,000, and MC leukemia, which occurs at a rate two orders of magnitude lower.[11,12]

Given considerable overlap in MC-mediator induced symptomatology and biomarkers of MC-activation among all MCAD, previous work has investigated the genetics and epigenetics of MCAD seeking to elucidate a common genetic underpinning of disease.[9] Molderings et al found variable alterations in *KIT*, a tyrosine kinase with well-characterized somatic mutations (including KITD816V) shown to contribute to SM, within all three families studied with co-occurrence of iMCAS or SM.[9,11] Furthermore, authors noted increased prevalence of a specific *KIT* isoform in individuals with severe MCAD.[9] This finding builds upon findings from Haenisch et al, who suggested that a predominance of this particular isoform may contribute to tumorigenicity, increased MCs, and/or increased MC activation.[9,11] In a subsequent study, Haenisch et al found epigenetic differences between 21 MCAD (predominantly iMCAS) patients and a group of healthy controls. Although these studies sug-

gest that MCAD may comprise a spectrum of similar disease including both iMCAS and SM, a lack of sufficient sampling and adequate comparison groups leave the validity of these findings in question.[9]

The clinical presentation of iMCAS is characterized by symptomatic heterogeneity.[13] Most commonly, symptoms of iMCAS include fatigue, fibromyalgia-like pain, presyncope or syncope, headache, pruritus, urticaria, paresthesias, nausea, vomiting, chills, migratory edema, eye irritation, dyspnea, and gastroesophageal reflux.[14] Abdominal pain and flushing are also prominent symptoms.[14] Current validated MC activation markers include serum tryptase along with urine histamine metabolites, prostaglandin (PG) D2, PG metabolites, or leukotriene E4.[15–17] Interestingly, tryptase has been shown to be a non-specific and unreliable marker of iMCAS, as levels are often normal or only mildly elevated.[6,18,19] The utility of serum tryptase in iMCAS differs from its utility in SM, as tryptase levels have been shown to be associated with quantified burden of MCs in the body as opposed to the level of overall MC activation.[20–24]

Understanding of iMCAS is pivotal for dermatologists due to its occasionally equivocal laboratory findings, seemingly non-specific multi-systemic symptoms, and association with comorbidities. In terms of laboratory work, the iMCAS clinical picture may include normal or only mild elevations of serum tryptase.[6,8,10,19] The presentation is further confounded by heterogeneity of symptoms, underlying co-morbidities, and possible MC-mediated connective tissue (CT) effects resulting in an EDS-like phenotype.[25–28] This article delivers a concise review of the dermatologic symptoms of iMCAS while exploring the association between iMCAS and CT disorders (CTDs) with the objective of providing dermatologists with a higher acuity of recognition of this multifaceted disorder.

METHODS

Review of PubMed® and SCOPUS® databases was performed using search terms including "mast cell activation syndrome" and "mast cell activation disorder." Articles published in English from January 1, 1990 through February 8, 2018 were included. Furthermore, included studies featured at least 1 patient meeting diagnostic criteria presented in Table 1, which combines elements from iterations of proposed diagnostic criteria of iMCAS.[5,6,29] Criterion of response to medications targeting MC activation was not included due to several studies including iMCAS patients without explicitly commenting on therapy or response to therapy. Dermatologic descriptions of only the individual patients meeting the aforementioned criteria shown in Table 1 were included. Only 16 primary articles meeting inclusion criteria mentioned dermatologic manifestations of iMCAS.

A separate literature review regarding iMCAS association with CTDs was also performed. Due to the paucity of literature available, aforementioned diagnostic criteria implemented for the previous search were relaxed to include studies with patient(s) who may not have had a diagnostic workup to rule out other forms of MCAD.

TABLE 1.

Inclusion Criteria for iMCAS Descriptions in the Literature Review Characterizing Dermatologic Manifestations of iMCAS.	
Studies included in the present review featured at least 1 patient meeting the following criteria:	
1)	Episodic symptoms suggesting MC activator release
2)	Increased markers of MC-activation in serum or urine
3)	Absence of other proven defined causes (including primary or secondary causes of MC activation or other well-defined idiopathic entities)

Criteria adapted from Akin et al 2010, Molderings et al 2011, Valent et al 2012, and Afrin et al 2014.[5,6,8,29] Abbreviations: iMCAS; idiopathic mast cell activation syndrome, MC; mast cell, SM; systemic mastocystosis.

RESULTS

Early Descriptions of iMCAS

Studies including dermatologic descriptions of patients with iMCAS are summarized in Table 2. In total, 562 patients with dermatologic manifestations of iMCAS, as defined in the present review, were identified in 16 published reports (Table 2).

The first descriptions of iMCAS, prior to proposed diagnostic criteria in 2010, emerged in 2007.[6,7] Molderings et al studied a 17-patient cohort, which included 7 patients with SM and 4 patients not meeting criteria for SM, who also lacked evidence of bone marrow involvement after assessment.[7] In the 4 patients with an iMCAS-like picture, dermatologic symptoms were prevalent, including flushing and anal pruritus in 3 of the 4 patients, clotting dysfunction in all 4 of the patients, and unspecified "skin signs" in half of the patients. In the following year, Butterfield and Weiler published a case series of 4 patients presenting with various symptoms of MC activation from selective release of PGD2.[30] Authors noted pruritus, flushing, urticaria, and angioedema were symptoms noted in at least half the patients examined.[30] One patient experienced periorbital swelling.[30]

Since the initial evidence of non-proliferative MC disease, multiple case reports and series focusing on iMCAS disease associations and treatments have emerged and mentioned dermatologic manifestations. Afrin presented a case series describing iMCAS associated with sclerosing mediastinitis in 2 patients, both of whom noted migratory pruritus.[31] One patient experienced a diffuse migratory rash following a waxing and waning course.[31] Multiple case reports surfaced in the same year detailing iMCAS patients diagnosed per criteria proposed by Akin et al and suffering from symptoms including flushing, urticaria, and dermatographism.[6,32,33] In a case report, Afrin et al described iMCAS involving symptoms of flushing, migratory pruritic rash, edema, hives, dermatographism, dys-

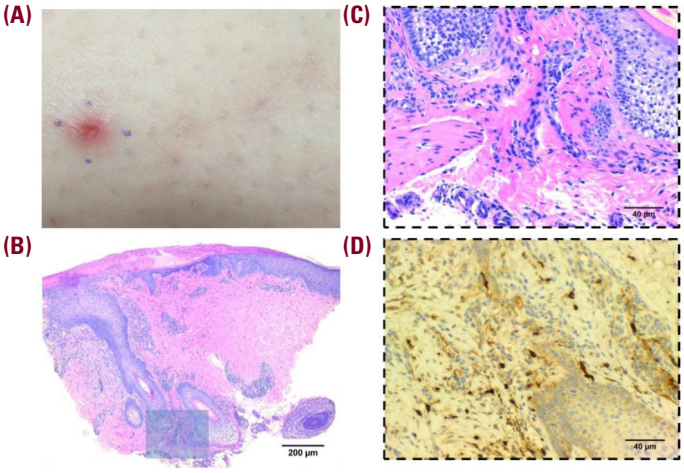
TABLE 2.

Summary of All 16 Studies Meeting Inclusion and Exclusion Criteria.

Study	Study Type	Number of MCAS Patients	Dermatologic Manifestations
Molderings et al 2007[7]	Cross-sectional Study	4 of 17 total	Clotting dysfunction (4/4) Flushing (3/4) Anal pruritus (3/4) "Skin signs" (2/4)
Butterfield and Weiler 2008[30]	Case Series	4	Pruritus (3/4) Flushing (3/4) Angioedema (2/4) Food/antibiotic-induced urticaria (1/4) Hives (1/4) Periorbital swelling (1/4)
Alvarez-Twose et al 2010[41]	Cross-sectional Study	32 of 83 total	Pruritus (11/32, 34%) Flushing (10/32, 31%)
Afrin 2011[67]	Case Series	3	Flushing (2/3) Migratory edema (2/3) Dermatographism (2/3) Xerostomia (1/3) Migratory abdominal wall cellulitis (1/3) Pruritus (1/3) Shingles (1/3) Lichen planus (1/3)
Seidel et al 2011[42]	Cross-sectional Study	60 of 68 total	Mild bleeding diathesis (28/60, 47%)
Afrin 2012[68]	Case Report	1	Xerostomia, mucositis, rash (unspecified), edema, hives, abscess, shingles, cellulitis*
Mönkemüller et al 2012[33]	Case Report	1	Dermatographism
Bell and Jackson 2012[32]	Case Report	1	Flushing, urticaria
Afrin et al 2012[31]	Case Series	2	Migratory pruritus (2/2) Migratory, waxing/waning rash (1/2)
Schafer et al 2014[13]	Prospective Cohort	12 of 22 total	Bleeding tendency (10/12) Flushing (8/12) Pruritus (7/12) Telangiectasia (6/12) Rosacea-like folliculitis (5/12) Angioedema (4/12) Urticaria (4/12), Urticaria pigmentosa (2/12)
Ravi et al 2014[17]	Retrospective Review	25	Flushing (21/25, 84%) Pruritus (17/25, 68%) Urticaria (12/25, 48%)
Afrin et al 2014[26]	Case Report	1	Migratory pruritus, Flushing, Vasomotor instability
Afrin et al 2015[34]	Case Report	1	Flushing, migratory pruritic rash, edema, hives, dermatographism, dyshydrotic eczema, Reynaud's
Asawa et al 2015[69]	Case Report	1	Erythema, pruritus, and swelling (at site of bite) Flushing, erythema (not associated bite)
Richter et al 2017[70]	Case Report	1	Edema, flushing, pruritus (worsened with physical exertion)
Afrin et al 2017[14]	Cross-sectional Study	413	Dermatographism (76%) Pruritus or urticaria (63%) Edema (up to 56%) Rash-unspecified (up to 49%) Sweats (up to 47%) Bruising (up to 39%) Flushing (up to 31%) Poor healing (23%) Alopecia (15%) Pallor (13%) Onychodystrophy (13%)

A total of 562 iMCAS patients were identified. Each study is presented along with its corresponding number of iMCAS patients and dermatologic manifestations. Abbreviations: iMCAS; idiopathic mast cell activation syndrome. *Patient was neutropenic

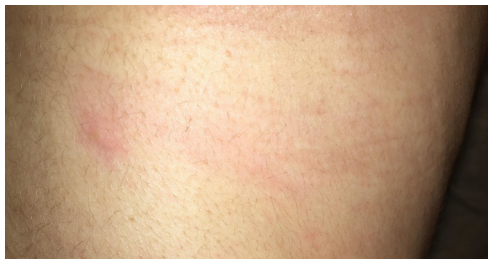
FIGURE 1. Gross and histopathological findings of an intermittent and pruritic leg rash in a patient with MCAD, EDS, and POTS. Gross appearance of an excoriated erythematous papule on the anterior right lower leg **(A)**. Low-power view at 4x magnification of histopathological findings with hematoxylin and eosin stain. Scale bar shows 200 microns and transparent blue rectangle shows the area selected for high-power view **(B)**. High-power view at 20x magnification of histopathological findings with hematoxylin and eosin stain. Scale bar shows 40 microns **(C)**. High-power view at 20x magnification of tryptase immunohistochemistry demonstrates numerous MCs in the dermis. Scale bar shows 40 microns **(D)**.



hydrotic eczema, and Raynaud's.[34] More recently, Afrin et al reported two cases of iMCAS involving symptoms of flushing, diffuse migrating pruritus and edema, diaphoresis, alopecia, poor healing, longitudinal nail ridging, brittle nails, and loss of nail growth plates.[35] One patient also experienced a diffusely migrating, patchy, macular, and erythematous rash.[35] Molderings et al published a case report describing a iMCAS patient with symptoms including Raynaud's syndrome, easy bruising and bleeding, alopecia, dermatographism, diffuse edema, and longitudinal nail ridging.[36] Lastly, Simpson reports a suspected iMCAS patient with diaphoresis, pruritus, erythema, facial swelling, and pressure-induced urticaria, similar to symptoms seen in patients described in other recent case reports and smaller published samples of iMCAS patients.[37–40]

Larger samples of iMCAS patients have also been characterized, including six studies with 10 or more iMCAS patients in which pruritus, flushing, urticaria, and bleeding tendency have all shown to be prominent features (Table 2).[13,14,17,41,42] Seidel et al found bleeding diathesis to be prevalent (47%) in a cohort of 60 iMCAS patients.[42] Flushing and pruritus were commonly noted by Alvarez-Twose in 32 patients with iMCAS (31 and 34%, respectively).[41] In a sample of 12 patients, Schafer et al also noted symptoms of telangiectasia, rosacea-like folliculitis, angioedema, and urticaria pigmentosa.[13]

FIGURE 2. Urticarial skin manifestation in pubic area of patient with MCAD and co-morbid EDS-like CTD.



Cutaneous Manifestations of iMCAS: Bringing Together the Evidence

Notably, 413 of 562 patients included in cited reports were from a single study.[14] Excluding this single large study, the most common dermatologic sequelae described included flushing in 34.9% of patients (52/149), pruritus in 32.2% of patients (48/149), clotting dysfunction or bleeding disorder in 28.2% of patients (42/149), and urticaria or hives in 14.1% (21/149) patients. Recently, in the aforementioned largest study of iMCAS patients to date, Afrin et al reported pruritus and urticaria to affect as many as 63% of the 413-patient sample.[14] Results also conveyed that the other most common dermatologic findings in iMCAS include dermatographism (76% of patients), edema (up to 56%), unspecified rash (up to 49%), sweats (up to 47%), bruising (up to 39%), and flushing (up to 31%) (Table 2).[14] Alopecia and onychodystrophy were symptoms in 15% and 13% of patients, respectively (Table 2).[14]

MCAD, iMCAS, and CTD

Familial hypertryptasemia and MCAD variants, including iMCAS, have been observed in association with CTDs.[27,28,43–45] Lyons et al studied 33 atopic patients with persistently elevated serum tryptase and found an initially found a high prevalence of CT abnormalities (23 patients).[45] Flushing and episodic urticaria, as shown in Figure 1, was noted in 26 patients.[45] Further, 17 patients had history of itch, while 5 patients had history of angioedema.[45] In a subsequent study investigating the genetic basis for CT abnormalities in patients with familial hypertryptasemia, Lyons et al discovered that increased copy number of *TPSAB1*, a gene encoding for α-tryptase, coincides with inherited increased basal serum tryptase levels.[44] Although familial hypertryptasemia is likely a distinct entity from MCAD, these findings are highly relevant as they demonstrate a potential etiology of CTDs occurring in iMCAS and MCAD, which may also be mediated by products of MC degranulation.[27,28,44] Indeed, in the author's own experience, histopathological examination of an erythematous papule from a patient with MCAD and EDS symptoms demonstrates prominent staining with tryptase immunohistochemistry (Figure 2).

MMPs are also released from MCs and are tryptase-activated enzymes directly involved in breaking down extracellular ma-

trix components (ECM) such as collagen and proteoglycans.[46,47] Abundant release of MMPs may act alone or in conjunction with increased tryptase to alter the ECM architecture in the CT of patients with iMCAS directly, thereby contributing to an HT EDS-like phenotype. Evidence has shown that increased activity of MMPs has been associated with a HT EDS-like phenotype in the absence of collagen gene mutations.[48,49] Lyons et al suggest that activation of protease-activated receptor 2 (PAR2)-dependent pathways may also be responsible for tryptase-mediated CT changes.[44] PAR2 is a G protein-coupled protease-activated receptor involved in pathways relevant to both acute and chronic inflammation, inflammatory pain, and allergy.[50–53] Proteases, such as tryptase and matrix metalloproteinase (MMP)-1, cleave a portion of this receptor, initiating events leading to transmembrane signaling.[54–57] PAR2 is up-regulated by mediators of inflammation, including TNF-α and interleukin (IL)-1α, and overstimulation of PAR2 can lead to increased tissue permeability, granulocyte infiltration, tissue damage, and edema.[51,58,59]

Practical Pearls

Although there are no large scale trials to support treatments in iMCAS patients, conventional pharmacologic therapy involves H1 and H2 histamine receptor antagonists, leukotriene-altering agents, glucocorticoids, cromolyn sodium, and omalizumab.[5,60] In the author's experience with MCAD patients, off-label treatment with low dose doxycycline 40mg daily along with topical stabilized hypochlorous acid as needed has demonstrated benefit in improving pruritus and controlling cutaneous rash when used in conjunction with topical super-potent steroids and oral anti-histamine therapy. Hypochlorous acid has been shown to contribute to reduced histamine levels in skin, and in addition to doxycycline, has previously been shown to inhibit MMPs.[61–64] Within a few weeks of initiating treatment, a 23 year old female patient with a three year history of MCAD symptoms experienced improvement of her erythematous, excoriated, and papular rash.

As the differentiation of iMCAS from secondary MCAD may not be obvious at the time of presentation, avoidance of possible triggers is paramount in management.[29] Medications are triggers of particular interest, and may hold the key for furthering understanding of the underlying genetic basis for MCAD, possibly found in mutations in drug-metabolizing enzymes of the cytochrome P450 (CYP450) system.[65] Although there is a lack of literature attributing CYP450 mutations with MCAD, further investigation is needed in order to both enhance patient ability to avoid triggers and provide the basis for more targeted therapy.

DISCUSSION

The iMCAS subtype of MCAD is a disorder characterized by chronic multisystem inflammation triggered by non-neoplastic MC over-activity and is a diagnosis of exclusion after ruling out primary or secondary causes of MC activation.[5,6,29] Although proposed to be on the same spectrum of disease as other MCAD, such as SM and MMAS, iMCAS has been previously differentiated from other members of the MCAD family on the basis of having no underlying cause (including a lack of clonal proliferation of MCs) and often being associated with lower tryptase elevations.[6–8,10,19] A paucity of literature has sought to characterize the dermatologic clinical presentation of iMCAS, which is classically described as having similar symptomatology to other MCADs. Current literature suggests that the most common cutaneous findings include flushing, pruritus, clotting or bleeding disorders, dermatographism, and urticaria. The most robust characterization of iMCAS clinical presentation confirms the highly sensitive finding of dermatographism, while providing evidence that flushing may be a finding of lower sensitivity than pruritus or urticaria, unspecified rashes, diaphoresis, and easy bleeding and bruising.[14] This review also highlights the prominence of bleeding disorders in iMCAS, which is an underappreciated characteristic of the disease also shared with SM but without a direct neoplastic cause.[66] An emerging association between patients with MCAD, iMCAS, and familial hypertryptasemia having CT abnormalities also implicates tryptase and/or MMPs as potential mediators of CTD and joint hypermobility.

Limitations of the current review include the heterogeneity of studies featuring iMCAS clinical descriptions, inconsistency of diagnostic criteria implemented in the literature, and small volume of studies available. The adapted diagnostic criteria utilized for inclusion into the present review also presents a limitation, in that the criteria used did not account for response to therapy targeting MC activation. Nonetheless, the chosen inclusion criteria for the present review afforded specificity for iMCAS while allowing for reasonable sensitivity by including various aspects of previously proposed diagnostic criteria, justified by advances in iMCAS understanding gained in recent years. This observation underscores the need for more appropriate implementation of diagnostic criteria for iMCAS in the literature. Furthermore, this review highlights the importance of recognizing this highly prevalent syndrome in patients by possibly more subtle dermatologic findings, as increases in plasma tryptase are less extreme and less common in this disorder in comparison to other MCAD.[6,10,19] Reports suggest that iMCAS is largely treatment-responsive, and there has been evidence suggesting that treatment can even result in improvement of other co-morbidities, such as metastatic uterine cancer and sickle cell disease.[25,26] Due to a lack of testing for iMCAS markers in routine labs, serum tryptase levels not always being helpful, and iMCAS patients tending to have good response to treatment, it is imperative for clinicians to have a suspicion for iMCAS when the clinical presentation is relevant.[6,8,19]

CONCLUSIONS

Knowledge of the cutaneous manifestations of iMCAS is vital

because of its high estimated prevalence and the diagnostic challenge it presents.[9,11,12] Review of the literature conveys that flushing, pruritus, clotting or bleeding disorders, and dermatographism are the most prominent dermatologic symptoms in iMCAS. Future work should seek to continue to stratify analyses in such a way to compare patients with iMCAS to those with SM and other forms of MCAD in order to determine differences in underlying genetics and clinical presentation. Future studies of iMCAS patients with EDS-like phenotypes are also needed in order to gain further insight regarding the biochemical basis of co-occurring CT abnormalities. As iMCAS is identified with higher acuity, increased understanding of comorbidities and underlying pathophysiology will result and may contribute to the development of improved management of patients suffering.

DISCLOSURE

The authors have no relevant conflicts of interest.

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