

Controversies in Allergy: Is a Bone Marrow Biopsy Optional or Essential in the Evaluation of the Patient with a Suspected Mast Cell Disorder?



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INTRODUCTION

In diagnosing or caring for a patient with a suspected or known mast cell disorder, the allergist-immunologist, hematologist, or other health care professional may have to decide whether a bone marrow examination is indicated, and whether it is essential (indispensable or crucial) or optional (discretionary or elective). Some of the various scenarios in which a bone marrow biopsy and examination of the aspirated marrow smear might be considered indicated include in (1) securing the diagnosis of indolent systemic mastocytosis (ISM), also sometimes referred to as “systemic mastocytosis [SM]”; (2) identifying whether a patient with serum tryptase concentrations of greater than or equal to 15 ng/mL has ISM, monoclonal mast cell activation syndrome (MMCAS), or perhaps familial hypertryptasemia; (3) determining whether maculopapular cutaneous mastocytosis (MPCM, aka urticaria pigmentosa) in an adult patient is associated with underlying ISM; (4) exploring whether patients with a working diagnosis of idiopathic anaphylaxis (IA), mast cell activation syndrome (MCAS), or symptoms of mast cell activation have undiagnosed ISM; and (5) excluding ISM in patients who have survived anaphylaxis from a Hymenoptera sting and are found to have a basal serum tryptase concentration of more than 11.4 ng/mL. The purpose of this article was to explore the essentiality or discretionary approaches to bone marrow biopsy and aspiration for analysis in these 5 clinical settings.

GENERAL COMMENTS

The diagnostic criteria for ISM are presented in Table I.¹⁻⁷ Because there is no single blood test to secure the diagnosis of ISM, the diagnosis can be confirmed by the astute clinician and the presence of the major criterion and 1 minor criterion or 3 of the 4 minor criteria.^{1,4,6} Clinical signs and symptoms include episodes of flushing, pruritus, abdominal pain (cramping), diarrhea, heartburn, hypotension, and in some patients, urticaria. There may be a history of Hymenoptera-induced or unexplained episodes of anaphylaxis, as well as osteoporosis and nontraumatic

fractures. Chronic spontaneous (idiopathic) urticaria typically is not present. Lesions of MPCM are fixed, red-brown macules or papules less than or equal to 5 mm in diameter in adults and usually are present on the thighs and trunk.^{1,2,4,6} In children, lesions can be present on the head, trunk, and extremities and may be uniform in size and resemble the monomorphic variant of adult MPCM or may be larger in size and variable in appearance as the polymorphic variant. With mild stroking of the lesions, the mast cells degranulate, which produces a wheal/erythema (Darier's sign). Maculopapular cutaneous mastocytosis is present in approximately 80% of adults with ISM.⁶ Some patients with ISM may have hepatomegaly, splenomegaly, and lymphadenopathy, although these findings are more common in more aggressive forms of mastocytosis. Laboratory testing in patients with mastocytosis generally reveals a serum tryptase concentration of greater than or equal to 20 ng/mL, although milder forms of ISM may have tryptase concentration below this cutoff. Indeed, from 26 patients with ISM who had cutaneous lesions, just 9 (34.6%) patients had a serum tryptase concentration of more than 20 ng/mL.⁸ This finding emphasizes the reality that the serum tryptase concentration is a minor, not major, criterion of ISM. The activating KIT D816V mutation can be identified from peripheral blood, bone marrow, or tissue if the clonal mast cells population has expanded sufficiently for this mutation to be identified.^{1,8-10} In 1 series, 43 of 48 (90%) patients with ISM were KIT D816V positive by testing peripheral blood, consistent with a high sensitivity test.⁸

The purported value of a bone marrow examination (biopsy, aspiration of marrow; often with flow cytometry on the aspirate) must be considered in light of patient experiences such as procedure-related pain, which with local anesthesia occurs in up to 70% of patients, from which 35% report pain as “severe.”¹¹ The aspiration results in about 15 seconds of stinging pain, which may be followed by a feeling of painful pressure or discomfort. A common approach to minimize pain is infiltration with lidocaine 1% into the skin for local anesthesia followed by lidocaine 2% administered into the periosteum. Another

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Abbreviations used

IA- idiopathic anaphylaxis
ISM- indolent systemic mastocytosis
MCAS- mast cell activation syndrome
MMCAS- monoclonal mast cell activation syndrome
MPCM- maculopapular cutaneous mastocytosis
SM- systemic mastocytosis

approach is to use conscious sedation (midazolam) and opioids (orally or intravenously) to help reduce morbidity and may be appropriate for some patients. Hemorrhage is rare. Family members and friends generally should not be in the procedure area; indeed, one of us (P.G.) has had a friend of the patient undergoing bone marrow biopsy faint, while the hematologist was performing the procedure. This point emphasizes that some patients or their partners may be quite fearful of the bone marrow biopsy/aspiration or because the procedure will lead to the diagnosis of ISM.

SECURING THE DIAGNOSIS OF ISM

When clinical findings such as frequent flushing, abdominal cramping, pruritus, and episodes of anaphylaxis with documented hypotension, possibly from Hymenoptera stings, are accompanied by a basal serum tryptase concentration generally greater than or equal to 20 ng/mL, the possibility of ISM is high and confirming and securing the diagnosis is important for prognosis and management.^{1,6,10} Approximately 80% of patients with ISM will have cutaneous findings of MPCM.⁶ ISM is a variant of SM and has a variable course.¹ SM and its subtypes, including ISM, are incurable but can be treated. It is essential to secure the diagnosis, and this currently requires a bone marrow examination (see Table I and Figure 1). Perhaps, genetic testing or peripheral blood assays will one day eliminate the need for a bone marrow biopsy and examination, but this ideal is not the case now. Hopefully, in the near future, specific mast cell treatments that target mast cells carrying the KIT D816V mutation (which imatinib does not) with few and minimal side effects will become available and safe enough for the treatment of mild-to-moderate ISM. Studies are needed, for example, to see whether ISM may be managed without significant long-term risk using such pharmacologic agents including midostaurine, where initial reports are intriguing.¹² Thus, knowing the mast cell burden will be informative because it could direct therapy. If the patient with elevated serum tryptase concentration, such as 40 to 200 ng/mL, has episodes of flushing and splenomegaly or lytic bone lesions are identified, a bone marrow examination would be essential to search for other subtypes of SM such as aggressive SM or SM with an associated hematologic neoplasm.

IDENTIFYING WHETHER THE PATIENT WITH SERUM TRYPTASE CONCENTRATIONS OF GREATER THAN OR EQUAL TO 15 ng/mL HAS ISM, MMCAS, OR HEREDITARY ALPHA TRYPTASEMIA

The sensitivity of serum tryptase as a screening test for ISM is not high. In a series of 22 patients with ISM with diagnostic

bone marrow examinations, serum tryptase concentrations were less than or equal to 20 ng/mL in 16 patients and less than or equal to 11.4 ng/mL in 12 patients.⁸ However, in this report, 15 of 16 patients with serum tryptase concentrations of less than or equal to 20 ng/mL were D816V positive.⁸ Presumably, this dichotomy suggests that these patients have a lower burden of abnormal KIT D816V-positive mast cells. However, without a bone marrow examination, the diagnosis of ISM would have been missed or in other patients, MMCAS would not have been identified.

There are reports of hereditary alpha tryptasemia, involving 3 consecutive generations in which the median serum tryptase concentration was 37 ng/mL, with a range from 25.5 to 62.7 ng/mL.¹³ Some people have concomitant MCAS.¹³ One patient had a basal serum tryptase concentration of 37 ng/mL, a KIT A816V mutation in the bone marrow, and a history of abdominal cramps and diarrhea.¹³ Splenomegaly was present. This patient did not have other criteria of ISM. A bone marrow examination would be essential in such patients, although aggregates of abnormal mast cells may not be present. This patient's bone marrow examination did not reveal evidence compatible with ISM, but a KIT mutation was detected.¹³ More information is needed because experience is limited.^{13,14} But, it is our approach that a bone marrow examination would be essential and not discretionary, especially in patients with splenomegaly.

Other causes of persistently elevated basal tryptase concentrations are renal failure, myelodysplastic syndromes, and hypereosinophilic syndrome. A bone marrow examination would be essential in the latter 2 syndromes and presumably, discretionary in the case of renal failure.

DETERMINING WHETHER MPCM IN AN ADULT IS ASSOCIATED WITH ISM

In patients with MPCM, there should be a consideration of concomitant ISM, whether latent or manifest.^{1,2,6} The serum tryptase concentration should be measured even if patients do not describe symptoms of mast cell activation. If the serum tryptase concentration is less than 11.4 ng/mL, for nearly all patients, a bone marrow examination would not be indicated. However, patients should be examined and evaluated at regular intervals for development of evidence of SM including attention to splenomegaly and osteoporosis. For patients with an elevated serum tryptase concentration (≥ 11.4 ng/mL) and MPCM, consideration for the criteria of ISM should be reviewed periodically. Bone marrow examination would be discretionary in the absence of any additional evidence of ISM. However, should the patient with MPCM experience episodes of anaphylaxis, whether from Hymenoptera stings or if apparently idiopathic, the indication for bone marrow examination increases substantially. We believe that the bone marrow examination becomes essential in those settings. As testing for alleles of KIT expands and our understanding increases, we hope that bone marrow examinations will not be essential, but that is a goal and not current reality. It is important to explain to patients the necessity of identifying or ruling out either latent or previously overlooked ISM because most patients with MPCM will have KIT D816V-positive mast cells that are detectable in the bone marrow.²

TABLE I. Criteria for the diagnosis of ISM and related disorders of mast cell activation

Disorder	Diagnostic criteria/observations
ISM	Major criterion Multifocal accumulation with compact clusters of ≥ 15 mast cells in the bone marrow or another organ
	Minor criteria 1. In mast cell infiltrates in the bone marrow or other organ, $>25\%$ of mast cells are spindle shaped or atypical in the bone marrow 2. Presence of an activating KIT mutation at codon 816 in bone marrow, blood, or an extracutaneous organ 3. Kit+ mast cells in bone marrow, blood, or other extracutaneous organ(s) express CD25 with or without CD2 4. Serum total tryptase concentration persistently ≥ 20 ng/mL
MMCAS ("low-burden" SM)*	1-2 minor criteria of ISM Bone marrow shows sparse infiltrates of mast cells, not clusters, and mast cell burden is 1%-5% (mast cells likely have the KIT D816V mutation or are CD25 ⁺ in the bone marrow) Basal serum tryptase concentration usually is ≤ 11.4 ng/mL but may exceed 20 ng/mL during a symptomatic episode
MCAS†	1. Episodic multisystem symptoms consistent with activation of mast cells 2. Appropriate response to medications to reduce/suppress signs and symptoms of mast cell activation 3. Elevated serum tryptase at least once or at least twice with urine determinants of mast cell activation during symptomatic episodes‡
IA	1. Episodic signs and symptoms of anaphylaxis, with severity implying a potential risk of death 2. Subclassified as generalized (acute urticaria and/or angioedema with at least 1 of acute abdominal pain/diarrhea, hypotension, or wheezing dyspnea) or angioedema (acute urticaria plus marked tongue enlargement, voice hoarseness, or laryngeal or oropharyngeal swelling) 3. Basal serum tryptase concentration is normal and the acute phase may be elevated 4. Prednisone/H1 antihistamine empiric treatment reduces the frequency and severity of episodes

*Note that there is no evidence of an associated hematological neoplasm and mast cell burden is low. For classification of other variants of mastocytosis, see Valent et al.¹

†The patient should have 4 of 6 of the following: abdominal pain, dermatographism, diarrhea, flushing, headache, and memory and concentration difficulties.

‡Elevated serum tryptase concentration is present when the acute-phase serum tryptase concentration is $1.2 \times (\text{basal serum tryptase}) + 2$ ng/mL. For example, from 10 ng/mL to at least 14 ng/mL; or from 30 ng/mL to at least 38 ng/mL within a 4-h window after the reaction.

EXPLORING WHETHER PATIENTS WITH A WORKING DIAGNOSIS OF IA, MMCAS, OR SYMPTOMS OF MAST CELL ACTIVATION HAVE UNDIAGNOSED ISM

It has been reported that some patients referred with a diagnosis of IA or unexplained anaphylaxis have undiagnosed ISM or aberrant clones of mast cells.¹⁵⁻¹⁷ Clearly, when patients presenting with IA are found to have a basal serum tryptase concentration of greater than or equal to 11.4 ng/mL, the diagnosis of IA has to be reconsidered.⁷ Alternatively, in a series of 335 patients with IA, none was found to have evolved into or was identified over time as having ISM.¹⁸ In IA, a prototypical patient will have multiple basal serum tryptase concentrations of less than 10 ng/mL only to have a significant elevation (see Table I) during an anaphylactic episode. Thus, using clinical judgment in patients with IA and no evidence of MPCM with basal serum tryptase concentrations of less than 11.4 ng/mL, a bone marrow examination would not generally be indicated. However, as noted above, especially if basal serum tryptase concentrations are elevated, a bone marrow examination would

be either discretionary or essential. Some flexibility in decision making is advised. One of us (P.G.) had a patient present with several episodes of Hymenoptera anaphylaxis, and the episodes resulted in syncope. The patient was skin test positive to yellow jacket, and his initial basal serum tryptase concentration was normal. He was treated with venom immunotherapy. In 3 years, a routine laboratory test showed elevated total protein and hyperglobulinemia and then paraprotein. A hematology consultation, which included a bone marrow examination, led to the diagnosis of monoclonal gammopathy of unknown significance but not ISM or multiple myeloma. Whether this case is a coincidence or not, it suggests the value of careful follow-up. There were never any elevated basal, serum tryptase concentrations, but his episodes of anaphylaxis had been sudden in onset and especially severe.

MCAS has clinical criteria-signs and symptoms for use in diagnosis (Table I).^{3,19} At a minimum, the patient should have 4 of 6 of the following criteria: abdominal pain, dermatographism, diarrhea, flushing, headache, memory, and concentration difficulties ("ADDFHM"), along with laboratory evidence of mast

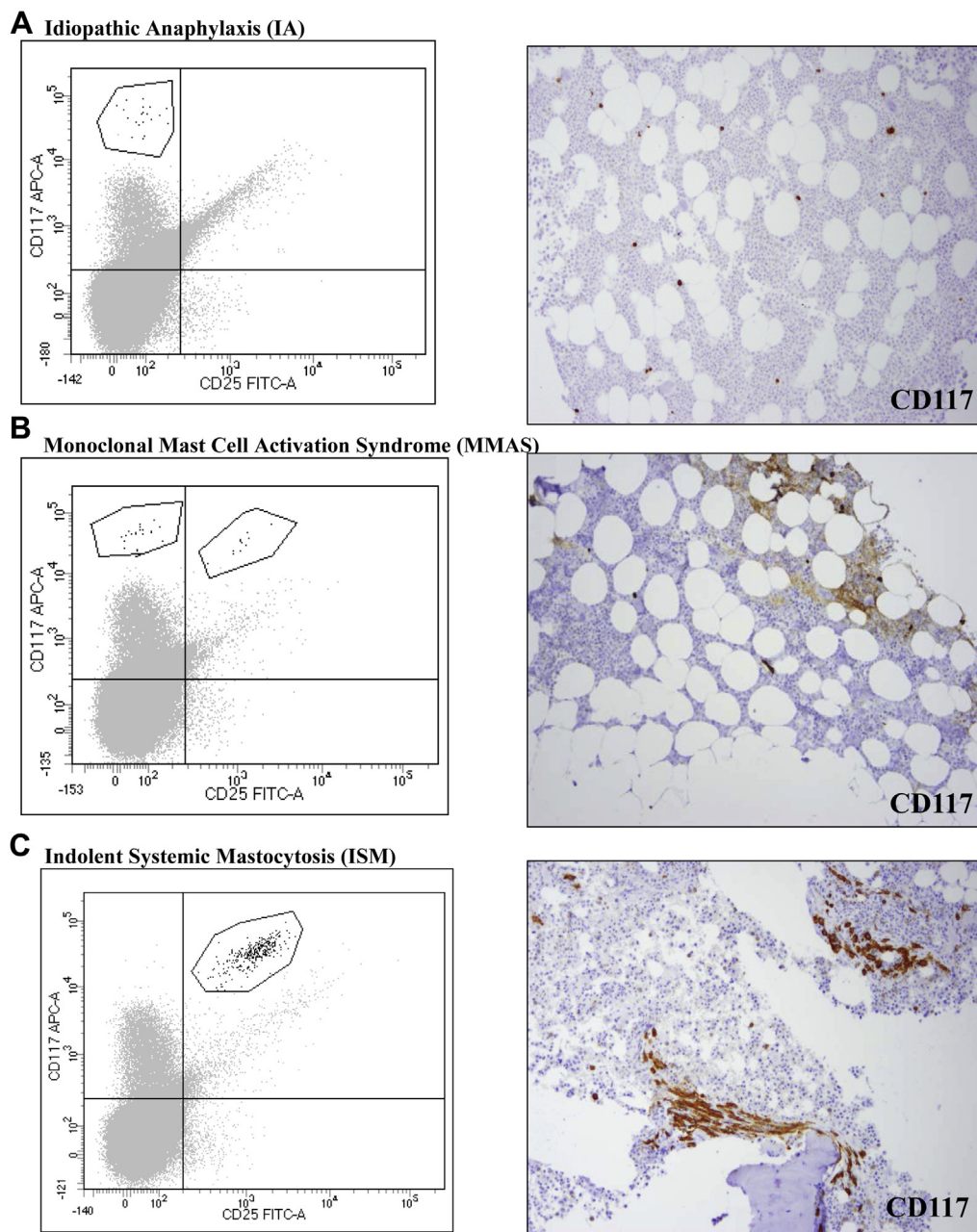


FIGURE 1. Bone marrow mast cell flow cytometry and immunohistochemistry in patients with IA (A), patients with MMAS (MMCAS) (B), and patients with ISM (C). Flow cytometric results show that CD117⁺ mast cells gain CD25 surface expression in patients with clonal disease, as shown by no abnormal CD25⁺ mast cells in patients with IA (Figure 1, A), 2 populations of mast cells in patients with MMAS (CD25⁺ and CD25⁻ cells; Figure 1, B), and abnormal CD25⁺ mast cells in patients with ISM (Figure 1, C). Bone marrow biopsy specimens showed no mast cell clusters in patients with IA and in those with MMAS, with multiple clusters in patients with ISM. APC, Allophycocyanin; FITC, fluorescein isothiocyanate. Reproduced with permission from Carter et al.¹⁵

cell activation and response to mediator blockade or mast cell-stabilizing therapies.^{3,19} Unfortunately, some patients receive the diagnosis incorrectly or self-diagnose themselves and become persuaded that their symptoms are explained by MCAS. A bone marrow examination is not indicated unless there are associated physical findings and laboratory studies suggestive of a clonal mast cell disorder as discussed previously.

EXCLUDING ISM IN A PATIENT WHO HAS SURVIVED AN EPISODE OF HYMENOPTERA ANAPHYLAXIS AND IS FOUND TO HAVE A SERUM TRYPTASE CONCENTRATION OF GREATER THAN OR EQUAL TO 11.4 ng/mL

The practice parameters on anaphylaxis²⁰ and stinging insects²¹ of the American Academy of Allergy, Asthma &

Immunology, the American College of Allergy, Asthma, and Immunology, and the Joint Council of Allergy, Asthma and Immunology suggest at least considering obtaining a basal serum tryptase in all patients who have experienced an episode of anaphylaxis from a Hymenoptera sting.^{20,21} We believe that there should be a workup for MPCM and ISM in such patients on the initial consultation. With a history of *severe* anaphylaxis from a Hymenoptera sting in 22 adult patients, a diagnosis of ISM was made in 16 patients and MMCAS was established in 1 patient.²² Severe anaphylaxis meant documented hypotension, loss of consciousness, or both.²² Basal serum tryptase concentrations were less than 11.4 ng/mL, and none of the 22 patients had examination findings of MPCM.²² Furthermore, in a series of 379 patients who had presented for evaluation after anaphylaxis from Hymenoptera species, 44 (11.6%) patients had basal serum tryptase concentrations of more than 11.4 ng/mL.²³ The diagnosis of ISM was established in 21 of 379 (5.5%) patients, of which 14 patients fulfilled the major/minor criteria and 7 patients had 3 minor criteria.²³ In addition, there were 2 patients with an established diagnosis of MPCM. Two of 5 other patients with suspicious cutaneous lesions had skin biopsies that confirmed MPCM. MMCAS was identified in 9 of 379 (2.4%) patients. Although most patients who present after recovering from an episode of anaphylaxis after an insect sting do not have ISM, MPCM, or MMCAS, the eventual indication for a bone marrow examination is considered either discretionary or essential as the workup proceeds. It is worth noting that 31 of 124 (25%) patients presenting with grade IV anaphylactic reactions (hypotensive shock) had basal serum tryptase concentrations of more than 11.4 ng/mL.²³

SUMMARY

A bone marrow biopsy/examination can be essential, optional, or not indicated in patients who present with evidence suggestive of ISM or IA. There should be a careful examination of the skin searching for crops of hyperpigmented (salmon-red) macules that are consistent with MPCM. Should the skin biopsy confirm the diagnosis of MPCM in an adult and peripheral blood testing identify the KIT D816V mutation, a bone marrow biopsy/examination will be indicated to confirm the diagnosis of ISM and gauge the burden of mast cells. Alternatively, about 20% of patients with ISM do not have MPCM. Thus, physicians and health care professionals have to consider when to pursue the workup for ISM or MMCAS and inquire about anaphylactic reactions from stinging insects, unexplained osteoporosis or fractures, and search for splenomegaly, hepatomegaly, and lymphadenopathy. It remains unknown why some patients with repeated attacks of IA also have concomitant chronic spontaneous urticaria, whereas other patients with IA never have activation of mast cells aside from isolated episodes of anaphylaxis. But, persistently elevated basal serum tryptase concentrations should indicate ISM or other disorders of SM and not IA.

In the final analysis, a physician working with a patient must take into consideration the patient's history and concerns, as well as physical and laboratory findings when deciding on when to recommend a bone marrow biopsy and aspirate. It is hoped that the situations discussed above will aid in guiding such decisions, and there is always reason for differences in judgment based on

published information and recommendations, as well as experience and circumstances.

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