

Mastocytosis and Hymenoptera allergy

Anthony E.J. Dubois

Purpose of review

Mastocytosis is a rare disease with associations with anaphylactic reactions to Hymenoptera stings. The purpose of this review is to examine these associations with regard to prevalence, diagnosis, treatment and prognosis in the insect-venom-allergic population.

Recent findings

Systemic mastocytosis is overrepresented in the Hymenoptera-allergic population and is associated with an increased risk of more-severe reactions following field stings or sting challenges, lack of sensitization to venoms by skin test or radioallergosorbent test, increased side effects to venom immunotherapy, reduced efficacy of venom immunotherapy and treatment failures. Serum tryptase determinations are a simple and reliable screening procedure for systemic mastocytosis. Patients with elevated values should be referred to specialized centers for confirmatory diagnosis including bone marrow histology.

Summary

The diagnosis of systemic mastocytosis should be considered in Hymenoptera-allergic patients showing any of the management problems associated with this disease. Patients with mastocytosis and Hymenoptera allergy require special attention, mainly because of reduced safety and efficacy of venom immunotherapy. Whether or not venom immunotherapy is given, such patients should continue to carry an Epipen[®] indefinitely.

Keywords

Epipen[®], Hymenoptera, insect venom allergy, mastocytosis, venom immunotherapy

Curr Opin Allergy Clin Immunol 4:291–295. © 2004 Lippincott Williams & Wilkins.

Department of Allergology, University Hospital Groningen, Groningen, The Netherlands

Correspondence to A.E.J. Dubois, University Hospital Groningen, Dept of Allergology, PB 30.001, 9700 RB Groningen, The Netherlands
Tel: +31 50 3612976; fax: +31 50 3121576; e-mail: a.e.j.dubois@int.azg.nl

Current Opinion in Allergy and Clinical Immunology 2004, 4:291–295

Abbreviations

MIMA N-methylimidazole acetic acid
RAST radioallergosorbent test

© 2004 Lippincott Williams & Wilkins
1528-4050

Introduction

Although mastocytosis is a relatively uncommon disorder, it is a significant co-morbid condition in patients with anaphylactic sensitivity to insect stings, affecting their diagnosis, treatment and prognosis. Recent developments in the diagnosis of mastocytosis have improved our understanding of this disease and these advances may now be applied to identifying affected individuals presenting with Hymenoptera allergy. In this review, the key features of mastocytosis will be discussed briefly, and the significance of this disease in the venom allergic patient population will be examined. Finally, the impact of mastocytosis on the management of Hymenoptera-allergic patients will be reviewed.

Mastocytosis: clinical presentation, classification and diagnosis

Mastocytosis is characterized by increased numbers of mast cells in the skin, or in bone marrow, liver, spleen, lymph nodes and other tissues, or both. These accumulations of mast cells are caused by mutations in the *c-kit* gene with alteration of the c-Kit receptor (the receptor for stem cell factor, or c-Kit ligand, which is a growth factor for mast cells), resulting in ligand-independent activation of the c-Kit receptor and proliferation of mast cells. Different clinical forms of the disease may be classified using the World Health Organization criteria [1]. Although aggressive and malignant forms of the disease occur, the most common association with Hymenoptera allergy is indolent systemic mastocytosis. Isolated cutaneous mastocytosis is common in early childhood, whereas in adulthood there is often coexistent systemic disease. The usual cutaneous presentation is urticaria pigmentosa, consisting of multiple pigmented, small (<0.5 cm) lesions which urticate when rubbed (Darier's sign). Although biopsy of lesional skin may reveal accumulations of mast cells, the gold standard for the diagnosis of systemic mastocytosis is histologically confirmed bone marrow involvement in most cases. In the absence of classic dense mast cell infiltrates in bone marrow, current criteria allow for the diagnosis of systemic mastocytosis on the basis of at least three of four possible minor criteria: (1) spindle-shaped mast cell morphology; (2) detection of a codon 816 *c-kit* mutation; (3) bone marrow mast cell expression of CD117, CD2 and CD25; and (4) serum tryptase of >20 ng/ml [1]. For a recent review of this topic, see [2••].

Prevalence of mastocytosis in patients presenting with Hymenoptera allergy

Although it has been recognized for over a decade that mastocytosis may present with an anaphylactic reaction to an insect sting [3], there have been no data published on the prevalence of mastocytosis in the insect-allergic population. At our center, patients suspected of Hymenoptera allergic reactions are screened for mastocytosis using a mass-spectrometric urinary *N*-methylhistamine/*N*-methylimidazole acetic acid (MIMA) determination [4]. It should be noted that our patient population consists almost entirely of individuals allergic to yellow jackets (*Vespulae* species). Between 1985 and 2003, approximately 2375 patients suspected of Hymenoptera allergy were screened. Of these, 39 patients had elevated urinary histamine metabolite levels. A full diagnostic work up, including bone marrow biopsy, was carried out in 32 of these patients. Of these 32, 22 (69%) had histologically confirmed systemic mastocytosis. The estimated prevalence calculated from 69% of the 39 of 2375 patients with positive biochemical screening results thus yields a prevalence of approximately 1%. By comparison, between 1 in 1000 to 1 in 8000 patients visiting a dermatology clinic are diagnosed as having cutaneous mastocytosis [5], while prevalence estimates of systemic disease in these patients varies between 10 and 70% [6], for an overall prevalence of 0.07 to 0.00125%. Despite the limitations of this comparison, it seems clear that systemic mastocytosis is overrepresented in patients presenting with anaphylactic reactions to Hymenoptera venom, with a prevalence of about 1%.

Studies on the frequency of elevated tryptase levels in Hymenoptera allergic patients show even higher numbers, ranging from 7.3 to 10.5% [7,8**]. In the study by Haeberli *et al.* [8**] abnormally elevated basal tryptase levels were significantly more frequent amongst vespid-allergic patients than individuals allergic to honey bees. Bone marrow histology was not obtained in either of these studies.

Impact of mastocytosis on severe/fatal insect sting reactions

Although the prevalence of mastocytosis in Hymenoptera-allergic patients may be quantitatively modest, there are now several reports which suggest that these patients may be at risk for more-severe reactions following stings. In a study of 114 patients with reactions to Hymenoptera stings, 12 patients with elevated levels of serum tryptase ($> 13.5 \mu\text{g/l}$) reported severe reactions significantly more frequently (75%) than 102 patients with normal tryptase values (28%) [7]. Although systemic mastocytosis was not histologically confirmed in these patients and risk in isolated cutaneous mastocytosis has not been studied, reports have suggested that both elevated serum tryptase [6,9] and elevated urinary *N*-methylhistamine levels [10]

are indicative of systemic disease in patients with cutaneous mastocytosis. Taken together, these data thus suggest that systemic mastocytosis is associated with more-severe insect sting reactions. This was confirmed in the study by Haeberli *et al.* [8**], which also showed a significant association between elevated tryptase levels and severity of the field sting reaction: elevated values were seen in 0% of Grade I and II reactions, 4% of Grade III and 14% of Grade IV reactions. In vespid-allergic patients, the severity score of the reaction to a sting challenge carried out during venom immunotherapy was significantly higher in patients with an elevated basal tryptase value than in those with normal values [8**].

We have previously reported two patients who had been treated with venom immunotherapy and developed systemic mastocytosis (one after treatment, one during treatment resulting in intolerable side effects and cessation of immunotherapy) and subsequently died following a yellow jacket sting. Neither patient had significant co-morbidity and both had received prompt and adequate emergency treatment [11]. We subsequently examined an asylum seeker found dead after an insect sting in which a post-mortem bone marrow examination revealed mastocytosis (Dubois AEJ, van Doormaal JJ, de Monchy JGR, unpublished observations). In a recent survey by Pumphrey and Roberts [12] of fatal anaphylactic reactions, a patient with systemic mastocytosis who died as a result of an anaphylactic reaction to a honey bee sting is described. These cases, which demonstrate the coincidence of two rare conditions (systemic mastocytosis and death following an insect sting) raise the possibility that a subset of patients with mastocytosis has a poor prognosis.

Mastocytosis and negative venom skin tests and radioallergosorbent test determinations

Mastocytosis has been thought to contribute to anaphylactic reactions to insect stings in both IgE-dependent and IgE-independent ways. The IgE-independent pathway is thought to result from the direct action of mast cell-activating substances present in venom on the large numbers of mast cells associated with mastocytosis. Several reports suggest that the absence of sensitization is more frequent amongst patients with mastocytosis than in those without the disease. Müller *et al.* [13] reported three patients with cutaneous mastocytosis and anaphylactic reactions to honey bee stings who all had negative radioallergosorbent tests (RASTs) to honey bee venom. One of these patients also had a negative skin test to honey bee venom [13]. A later report described five patients with cutaneous mastocytosis of which one had a negative skin test and four a negative RAST to venoms [14]. Fricker *et al.* [15] subsequently reported 10 patients with cutaneous mastocytosis and anaphylactic reactions following insect stings of whom eight had

elevated serum tryptase levels. Five of these patients had negative RASTs, whereas two had both negative RASTs and skin tests to venoms [15]. These results were partially confirmed in a subsequent study [8**] in which negative RAST results to venoms were found in four of 239 (1.7%) patients with normal tryptase levels, but in three of 19 (15.8%) of patients with elevated tryptase levels. No differences were seen in skin test results. Other recent reports confirm the association of mastocytosis or elevated tryptase levels with venom skin test or RAST negativity, or both, in patients with anaphylactic reactions to insect stings [16,17].

In our own patient population we were able to compare patients with elevated urinary *N*-methylhistamine levels in which the diagnosis of systemic mastocytosis was either confirmed or excluded by bone marrow examination. While all of 10 patients without histological evidence of mastocytosis were sensitized to venom by either skin test or RAST, 4 of 19 patients (21%) with systemic mastocytosis had no evidence of sensitization to venom by either test. These data suggest that systemic mastocytosis may be associated with anaphylactic responses to insect stings in the absence of demonstrable sensitization to venoms, and may explain some but certainly not all of such cases [18].

Mastocytosis and venom immunotherapy: safety and side effects

Systemic side effects to venom immunotherapy have been noted in case reports of patients with systemic mastocytosis [11,19]. By contrast, studies of patients with cutaneous disease and/or elevated tryptase levels showed no increased propensity for side effects from venom immunotherapy [8**,15]. We treated 12 patients with venom immunotherapy who had increased urinary *N*-methylhistamine levels. Based on bone marrow histology, systemic mastocytosis was confirmed in seven of these patients and excluded in the remaining five patients. Of the seven patients with systemic disease, six had systemic side effects to venom immunotherapy causing discontinuation of the treatment in four cases. Of the five patients with normal bone marrow, three had systemic side effects to venom immunotherapy causing discontinuation of treatment in two patients. Our experience thus suggests that patients with elevated urinary *N*-methylhistamine levels have a greater than expected rate of adverse reactions to venom immunotherapy and that the majority of patients with histologically confirmed disease are unable to undergo this treatment because of intolerable side effects. In the study by Haeberli *et al.* [8**], patients with elevated serum tryptase levels experienced systemic side effects in only 10% of cases. This difference with our experience is unexplained, but may be due in part to differences in diagnostic criteria or treatment schedules.

Mastocytosis and venom immunotherapy: efficacy and treatment failures

Following our dramatic experience with two treatment failures (one partial) with fatal outcome [11], we examined systemic reactions to field stings during or after venom immunotherapy in the 12 patients with elevated urinary *N*-methylhistamine values described above. Reactions to stings occurred in six of seven patients with positive bone marrow histology and in three of five patients with normal bone marrows. In the study by Fricker *et al.* [15], six patients with cutaneous mastocytosis had field stings or sting challenges with only one mild reaction. However, only two patients had clearly elevated serum tryptase levels and a third patient had histologically confirmed systemic mastocytosis. None of these three patients reacted to a single exposure to the culprit insect. In a subsequent study, reactions to sting challenge during venom immunotherapy were studied [8**]. Elevated tryptase levels were seen more frequently in patients reacting to the challenge. Reactions were more severe in patients with elevated tryptase levels. These differences reached statistical significance for vespid-allergic patients. Thus these data suggest that the efficacy of venom immunotherapy is reduced in patients with mastocytosis, particularly in vespid-allergic patients.

Testing for mastocytosis in venom-allergic patients: when and how

While centers such as ours screen all patients suspected of Hymenoptera allergy for mastocytosis, this is not common practice in many clinics. Although such screening may not be strictly necessary, testing for the disease may be helpful in venom-allergic patients with management problems which suggest mastocytosis may be present. Signs and symptoms of systemic mastocytosis associated with Hymenoptera allergy include unexplained anaphylaxis in addition to Hymenoptera allergy, lack of sensitization to venom(s), systemic reactions to skin tests, frequent or severe systemic side effects to venom immunotherapy, treatment failure and refractory anaphylaxis following insect stings. Because of the relatively high frequency of mastocytosis in the Hymenoptera-allergic population, it may also be useful to consider the diagnosis if general signs or symptoms of the disease are present, such as unexplained flushing, dyspepsia, hepatosplenomegaly, lymphadenopathy or osteoporosis. It should be noted that while typical lesions of urticaria pigmentosa are associated with systemic mastocytosis in the majority of adult patients, insect-allergic patients with systemic mastocytosis may have no demonstrable skin lesions. In our series, nine of 17 (53%) patients with histologically confirmed systemic mastocytosis had no skin abnormalities. Similarly, Haeberli *et al.* [8**] found that only 18.8% of 16

patients with elevated tryptase values had cutaneous involvement.

In patients in whom testing for mastocytosis is indicated, measurement of serum tryptase levels is the most widely available. Assays using the B12 monoclonal antibody recognizing α - and β -tryptase are well standardized with well-defined normal values and can be run in any laboratory capable of performing commercial specific IgE (CAP RAST, Pharmacia Diagnostics) determinations. The sensitivity of serum tryptase has been estimated as being approximately 83% as compared to bone marrow histology, with a specificity of 98% [9,20]. In our center, we also use the much less widely available urinary *N*-methylhistamine/MIMA determination utilizing mass spectrometry. This test is also well standardized with well-defined normal values [4]. We compared the diagnostic properties of serum tryptase and urinary MIMA determinations in patients presenting with Hymenoptera allergy and elevated urinary *N*-methylhistamine values. These results were compared to the bone marrow histology as well as to each other. In patients with elevated urinary *N*-methylhistamine and positive bone marrow histology, 21 out of 22 had an elevated urinary MIMA level and 15 out of 18 had an elevated serum tryptase determination ($>13.5 \mu\text{g/l}$). In patients with elevated urinary *N*-methylhistamine but normal bone marrow results, four out of 11 had an elevated urinary MIMA level, and three out of 10 had an increased serum tryptase value. Thus, in Hymenoptera-allergic patients selected on the basis of urinary *N*-methylhistamine, serum tryptase determinations show excellent sensitivity and specificity as compared to bone marrow histology in the diagnosis of systemic mastocytosis. In patients with positive biochemical screening test results, bone marrow testing is recommended to confirm or rule out the diagnosis and rule out associated hematological disorders. This should take place in centers where special staining and detection of CD markers and *c-kit* mutations may be carried out [2••].

Management of Hymenoptera allergy in patients with systemic mastocytosis

There are a number of general medical measures which may benefit patients with indolent systemic mastocytosis whether they have had allergic reactions to Hymenoptera stings or not. These include treatment of pruritis, flushing, dyspepsia or diarrhea as well as prevention of osteoporosis [2••]. In patients with coexisting Hymenoptera allergy, however, management of their allergy will require special care and attention. Moreover, some management issues are somewhat controversial because of conflicting data or experience.

Systemic reactions to venom skin tests have been reported in patients with systemic mastocytosis [11], although the frequency of this phenomenon is unknown. Skin testing should probably be performed with caution in these patients. Diagnostic sting challenge testing, particularly in untreated patients, should be avoided. We currently view mastocytosis as a contraindication for this test [21].

The treatment of patients with systemic mastocytosis with venom immunotherapy is controversial because of doubts about the tolerability and efficacy of this treatment. Some authorities recommend lifelong treatment [8••] while others offer standard but not lifelong therapy [22]. Currently, we do not offer venom immunotherapy to patients with documented systemic mastocytosis because of concerns about lack of efficacy in these patients who might be less vigilant as a result of the (in this case, false) sense of security venom immunotherapy provides [23]. If venom immunotherapy is given, it is necessary to caution patients regarding the diminished efficacy of this treatment. In most European centers, patients are generally encouraged to relinquish their Epipen on reaching the venom immunotherapy maintenance dose. This is recommended because the Epipen is known to have a negative influence on health-related quality of life [23]. However, in view of the concerns about efficacy of venom immunotherapy in patients with systemic mastocytosis, it would seem prudent to advise patients to continue carrying their Epipen despite undergoing venom immunotherapy.

Conclusion

Systemic mastocytosis should be considered in insect-allergic patients with management problems suggestive of the disease, such as lack of sensitization to venoms, systemic reactions to venom immunotherapy (and possibly to venom skin tests) and treatment failure. Serum tryptase determinations are reliable in screening for the disease. Patients with consistently elevated values should have the diagnosis confirmed with additional diagnostic determinations including bone marrow histology. Patients with Hymenoptera allergy and systemic mastocytosis require special attention, including counseling on the increased risks and diminished efficacy of venom immunotherapy if this treatment is offered. Patients should continue to carry their Epipen at all times, even while receiving venom immunotherapy. A subset of patients with systemic mastocytosis seems to have a bad prognosis with an increased risk of fatal reactions to insect stings. Unfortunately, we are presently unable to identify this subset of patients. The contribution of mastocytosis to insect sting mortality is one of the most important unanswered questions in this area and further studies of this relationship are needed.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

- 1 Valent P, Horny HP, Li CY, *et al*. Mastocytosis. In: Jaffe ES, Harris NL, Stein H, Vardiman JW, editors. World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Hematopoietic and Lymphoid Tissues. Lyon: IARC Press; 2001. pp. 291–302.
- 2 Akin C, Metcalf DD. Systemic mastocytosis. *Annu Rev Med* 2004; 55:419–432.
- A comprehensive and recent review of mastocytosis.
- 3 Kors JW, van Doormaal JJ, de Monchy JG. Anaphylactoid shock following Hymenoptera sting as a presenting symptom of systemic mastocytosis. *J Intern Med* 1993; 233:255–258.
- 4 Oosting E, Keyzer JJ, Wolthers BG, Scholtis RJ. Age dependent normal values of histamine and histamine metabolites in human urine. *Agents Actions* 1988; 23:307–310.
- 5 Fine J. Mastocytosis. *Int J Dermatol* 1980; 19:117–123.
- 6 Soter NA. Mastocytosis and the skin. *Hematol Oncol Clin North Am* 2000; 14:537–555.
- 7 Ludolph-Hauser D, Rueff F, Fries C, *et al*. Constitutively raised concentrations of mast-cell tryptase and severe anaphylactic reactions to Hymenoptera stings. *Lancet* 2001; 357:361–362.
- 8 Haeberli G, Brönnimann M, Hunziker T, Müller U. Elevated basal serum tryptase and hymenoptera venom allergy: relation to severity of sting reactions and to safety and efficacy of venom immunotherapy. *Clin Exp Allergy* 2003; 33:1216–1220.
- A landmark paper studying many of the issues in this review on a significant number of patients for the first time.
- 9 Schwartz LB. Clinical utility of tryptase levels in systemic mastocytosis and associated hematologic disorders. *Leuk Res* 2001; 25:553–562.
- 10 Keyzer JJ, de Monchy JG, van Doormaal JJ, van Voorst Vader PC. Improved diagnosis of mastocytosis by measurement of urinary histamine metabolites. *N Engl J Med* 1983; 309:1603–1605.
- 11 Oude Elberink JN, de Monchy JG, Kors JW, *et al*. Fatal anaphylaxis after a yellow jacket sting, despite venom immunotherapy, in two patients with mastocytosis. *J Allergy Clin Immunol* 1997; 99:153–154.
- 12 Pumphrey RS, Roberts IS. Postmortem findings after fatal anaphylactic reactions. *J Clin Pathol* 2000; 53:273–276.
- 13 Müller UR, Horat W, Wutrich B, *et al*. Anaphylaxis after Hymenoptera stings in three patients with urticaria pigmentosa. *J Allergy Clin Immunol* 1983; 72:685–689.
- 14 Müller U, Helbling A, Hunziker T, *et al*. Mastocytosis and atopy: a study of 33 patients with urticaria pigmentosa. *Allergy* 1990; 45:597–603.
- 15 Fricker M, Helbling A, Schwartz L, Müller U. Hymenoptera sting anaphylaxis and urticaria pigmentosa: Clinical findings and results of venom immunotherapy in ten patients. *J Allergy Clin Immunol* 1997; 100:11–15.
- 16 Krauke B, Sturm G, Aberer W. Negative venom skin test results and mastocytosis. *J Allergy Clin Immunol* 2004; 113:180–181.
- 17 Kontou-Fili K. IgE negative venom anaphylaxis. In: Proceedings of the International Symposium Allergia al veleno d'insetti; 22–23 September 2000; Ancona. JGCS.r.l.–Via Quagliariello, Napoli; pp.45–58.
- 18 Golden DB, Tracy JM, Freeman TM, Hoffman DR. Insect Committee of the American Academy of Allergy, Asthma and Immunology. *J Allergy Clin Immunol* 2003; 112:495–498.
- 19 Engler RJ, Davis WS. Rush hymenoptera venom immunotherapy: successful treatment in a patient with systemic mast cell disease. *J Allergy Clin Immunol* 1994; 94:556–559.
- 20 Schwartz LB, Irani AM. Serum tryptase and the laboratory diagnosis of systemic mastocytosis. *Hematol Oncol Clin North Am* 2000; 14:641–657.
- 21 Dubois AE. Investigational and clinical use of the sting challenge. *Curr Opin Allergy Clin Immunol* 2003; 3:283–285.
- 22 Krishna MT, Fearby S, Annala I, Frew A. Hymenoptera stings and serum tryptase. *Lancet* 2001; 357:1527–1528.
- 23 Oude Elberink JN, de Monchy JG, van der Heide S, *et al*. Venom immunotherapy improves health-related quality of life in patients with yellow jacket allergy. *J Allergy Clin Immunol* 2002; 110:174–182.