

# Mastocytosis and insect venom allergy

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## Purpose of review

To analyse the association of systemic allergic hymenoptera sting reactions with mastocytosis and elevated baseline serum tryptase and to discuss diagnosis and treatment in patients with both diseases.

## Recent findings

In recent large studies on patients with mastocytosis a much higher incidence of severe anaphylaxis following hymenoptera stings than in the normal population was documented. In patients with hymenoptera venom allergy, elevated baseline tryptase is strongly associated with severe anaphylaxis. Fatal sting reactions were reported in patients with mastocytosis, notably after stopping venom immunotherapy. During venom immunotherapy most patients with mastocytosis are protected from further sting reactions. Based on these observations immunotherapy for life is recommended for patients with mastocytosis and venom allergy. The incidence of allergic side-effects is increased in patients with mastocytosis and elevated baseline tryptase, especially in those allergic to *Vespula* venom. Premedication with antihistamines, or omalizumab in cases with recurrent severe side-effects, can be helpful.

## Summary

In all patients with anaphylaxis following hymenoptera stings, baseline serum tryptase should be determined. A value above 11.4 µg/l is often due to mastocytosis and indicates a high risk of very severe anaphylaxis following re-stings. Venom immunotherapy is safe and effective in this situation.

## Keywords

hymenoptera venom allergy, mastocytosis, serum tryptase, venom immunotherapy

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## Introduction

Hymenoptera venom allergy (HVA) is an IgE-mediated disease. Its clinical manifestations result from the degranulation of mast cells or basophils, triggered by the binding of allergens to specific IgE on the surface of these cells. The symptoms of HVA range from large local reactions (LLRs) at the sting site to life-threatening anaphylaxis. In recent years, an association of HVA, especially of severe allergic sting reaction (SAR), with mastocytosis was increasingly realized by studies in large numbers of patients with both HVA [1–5] and mastocytosis [6–8,9<sup>••</sup>].

Between 1 and 7.9% of HVA patients have a clonal mast cells disease (CMD) [3–5,9<sup>••</sup>], and patients with CMD or increased baseline serum tryptase (sBT) above 11.4 µg/l and HVA develop more severe SAR than those without [4,5,10]. The association of the two diseases was therefore further investigated from a clinical and therapeutic point of view. Diagnosis and management of patients with HVA and mastocytosis involves special problems. First, pathogenic mechanisms underlying this

association are not clear. Second, the diagnosis of mastocytosis requires an expensive, in part invasive procedure. It is therefore important to define criteria to select patients with HVA who should undergo this procedure. Third, the first therapeutic option for HVA is venom immunotherapy (VIT), but in the case of mastocytosis additional problems emerge such as optimal maintenance dose, duration, choice of the appropriate venom and management of increased allergic side-effects. Finally, in a small subpopulation of patients with both mastocytosis and SAR, specific IgE cannot be detected.

In this article, we will review recent knowledge on the association of HVA and mastocytosis, with special attention to the diagnostic approach and to the use and problems of immunotherapy [11<sup>••</sup>] (F. Ruëff, B. Przybilla, M.B. Biló, *et al.*, manuscript in preparation; European multicenter study including 680 patients on venom immunotherapy showing that elevated baseline serum tryptase is a significant risk factor for increased systemic allergic side-effects only in vespid venom, but not in bee venom allergic patients).

## Hymenoptera venom allergy

The insects responsible for SAR are hymenoptera of the families Apidae, Vespidae and Formicidae. The Apidae comprise honey bees and bumble bees, the Vespidae comprises the subfamilies Vespinae (*Vespa*, *Dolichovespula* and *Vespa*) and Polistinae (*Polistes* species) among which *Polistes dominulus* is widespread especially in Mediterranean areas [12].

HVA is IgE-mediated and due to sensitization to allergens of the venom. It accounts for up to 34% of all cases of anaphylaxis [13]. The diagnostic procedure includes skin tests and serum-specific IgE assays.

Total avoidance of hymenoptera is not feasible. Patients with HVA should therefore carry a self-administration emergency kit, which includes autoinjectable epinephrine, oral antihistamines and corticosteroids. VIT is well tolerated and effective and decreases the risk of SAR to subsequent stings to less than 20% [14]. It is recommended for all patients with a clear history of SAR and positive diagnostic tests.

## Serum tryptase and hymenoptera venom allergy

Tryptase is a mast cell mediator, present in two major forms: alpha and beta. The beta tryptase is stored in mast cell granulae and released during mast cell activation. It can be determined in serum by a Fluorescent Enzyme Immune Assay. The sBT is closely related to the whole body load of mast cells [15]. Normal values (95% percentile) are less than 11.4 µg/l. Released β-tryptase has a half-life of 90–120 min. Therefore, tryptase must be measured within 1–5 h after the onset of allergic symptoms. A significant increase compared to sBT proves a mast cell-mediated allergic reaction. HVA patients who develop severe anaphylaxis to a sting usually display a strong increase of tryptase during the reaction, but they often also have higher average sBT than those with mild allergic symptoms [5,10,16].

A European multicenter study [11\*\*] has recently confirmed a significant nonlinear association between sBT and the incidence of severe SAR: the slope of the odds ratio graph increases sharply above the concentration of approximately 5 µg/l. It is therefore of great importance to identify risk-prone patients. Measuring sBT is a simple and inexpensive test, and routine measurement in patients with SAR to Hymenoptera stings should become part of common medical practice.

## Mastocytosis: diagnosis and classification

Mastocytosis is a heterogeneous disorder characterized by proliferation and accumulation of mast cells in the

**Table 1 WHO diagnostic criteria for systemic mastocytosis and diagnostic work-up in adult patients suspected for systemic mastocytosis**

Major criterion	Presence of multifocal, dense mast cell infiltrates (>15 in aggregates) in bone marrow or other extracutaneous organs
Minor criteria	>25% mast cells spindle-shaped or with abnormal morphology in bone marrow or other extracutaneous organs. Detection of c-Kit point mutation at codon 816 in bone marrow, blood or extracutaneous organs Mast cells that coexpress CD117 with CD2 and/or CD25, in bone marrow, blood or extracutaneous organs Persistent increased serum total tryptase level (>20 ng/ml)
Diagnostic work-up	Physical examination and record of mastocytosis-related symptoms Tryptase serum levels, complete blood cell count and routine biochemistry Peripheral blood smears (May Grunvald–Giemsa staining) bone marrow biopsy (with immunohistochemical staining for tryptase, CD117, CD25) Bone marrow smears (May Grunvald–Giemsa staining) Flow cytometric analysis of bone marrow (the recommended panel includes at least CD2, CD25, CD45, and CD117) Biopsy of the mucosa of the gastrointestinal tract (in patients who have gastro-intestinal symptoms); lymphadenectomy or splenectomy in selected cases Abdominal ultrasonography (or CT scan), bone mineral density (BMD) measurement, radiograph of bones Specialist evaluation of neurologic or psychiatric symptoms

One major and one minor criterion, or three minor criteria confirm the diagnosis [18,19].

skin, bone marrow and other tissues, which is caused by mutations in the c-Kit gene (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 [17].

In 2001, an international consensus conference defined major and minor criteria for diagnosis of systemic mastocytosis as summarized in Table 1 [18,19]. One major and one minor, or three minor criteria establish the diagnosis of systemic mastocytosis. Systemic mastocytosis can be divided into clinical variants: indolent systemic mastocytosis (ISM) that represent the majority of cases; systemic mastocytosis with an associated clonal, haematologic, non-mast cell lineage disease (SM-AHNMD); aggressive systemic mastocytosis (ASM), mast cell leukaemia (MCL), mast cell sarcoma and extracutaneous mastocytoma [18,19]. Cutaneous mastocytosis is limited to the skin and it is divided in three major variants: urticaria pigmentosa, diffuse cutaneous mastocytosis and – mostly in children – solitary cutaneous mastocytoma [18,19]. Cutaneous mastocytosis in children has

generally a favourable prognosis, with most patients experiencing remission by adolescence. In adulthood skin lesions are associated with bone marrow involvement in more than 80% of cases [18,19] and usually persist. There are little data on the prevalence of mastocytosis in the general population: in one study [20], fewer than one new case of urticaria pigmentosa per 100 000 people and year were reported.

Patients in all categories of mastocytosis often experience symptoms due to inappropriate release of mediators after mast cell activation [21]. The severity of systemic symptoms can vary from mild to severe, and include hypotension, recurrent syncope or presyncope, flushing, headache, pruritus, abdominal pain, dyspepsia, diarrhea, or bone and soft tissue pain and cognitive problems [22]. The mediator release from mast cell can occur through an immunologic, mostly IgE-mediated reaction, as in HVA, but also to a non-IgE-mediated mechanism triggered by physical stimuli (e.g. temperature change, pressure, exercise), medications (e.g. opioid analgesics, anaesthetics, contrast media, NSAIDs) or emotional stress [18].

The diagnosis of mastocytosis is easy in patients with urticaria pigmentosa or other forms of cutaneous mastocytosis, but in the absence of typical skin lesions it may be difficult. An absence of skin involvement is described in ASM and MCL [19], but also in isolated bone marrow mastocytosis (BMM), an ISM subvariant. The term of Monoclonal Mast Cell Activation Syndrome (MMAS) is reserved to those patients with unexplained and/or recurrent anaphylaxis, without skin lesion and without the major criterion but with proof of mast cell clonality [23,24,25<sup>••</sup>].

### Clonal mast cell disorders and hymenoptera venom allergy

The term CMD includes, besides systemic mastocytosis, patients whose major and minor criteria do not fulfil the diagnosis of systemic mastocytosis, but in whom mast cell

clonality is proven. Severe anaphylaxis after hymenoptera stings was initially described in case reports or small series of patients with cutaneous mastocytosis or systemic mastocytosis [2,6,26–29].

Two large studies reported 27 and 6% of patients with anaphylactic reactions to hymenoptera venom among 74 and 163 adult mastocytosis, mostly systemic mastocytosis [7,8], demonstrating a higher incidence of HVA in mast cell disease than in the whole population, while hymenoptera stings played no role in eliciting anaphylaxis in children with mastocytosis. Only one case of anaphylaxis to fire ant was reported in a 4-year-old girl with urticaria pigmentosa [30]. In agreement with Brockow [8], 10 of 43 adults with ISM with skin lesions (23%) referred to the Multidisciplinary Mastocytosis outpatient clinic of Verona had SAR to hymenoptera venom (unpublished data).

Assessment of sBT is widely considered a useful screening test for mastocytosis in patients with SAR after hymenoptera stings, although some cases of systemic mastocytosis and especially with only cutaneous mastocytosis may present values less than 11.4 µg/l, and an elevated sBT may be found also in other conditions, for example in chronic urticaria, chronic renal failure, onchocerciasis or haematologic diseases not associated with the mast cell lineage [4].

As detailed in Table 2 [3–5,9<sup>••</sup>,31<sup>•</sup>,32<sup>•</sup>], the frequency of CMD in screened patients with HVA ranged from 1 to 7.9%, and is higher than in the general population [20]. The lower prevalence reported in some studies could be explained by the low sensitivity of tests used for screening [3], by the lack of a bone marrow evaluation [5] or the evaluation of CD25/CD2 mast cell coexpression and/or c-Kit mutation [4,31<sup>•</sup>,32<sup>•</sup>]. The first report on patients with HVA and elevated sBT, which included regular bone marrow evaluation and analysis for minor criteria of mastocytosis, reported a percentage of CMD as high as 7.9% [9<sup>••</sup>]. In this study, 20% of cases of systemic

**Table 2** Prevalence of clonal mast cell disease in patients with systemic reactions to hymenoptera venom, screened on the basis of elevated tryptase

Reference	Patients	Tryptase ≥11.4 ng/ml [n (%)]	CMD	Percentage
Haerberli <i>et al.</i> [5]	259	19 (7.3)	3 cutaneous mastocytosis <sup>a</sup>	1
Dubois [3]	2375	32 <sup>b</sup> (1.3)	22 systemic mastocytosis	1
Rueff <i>et al.</i> [4]	1102	106 (9.6)	21 cutaneous mastocytosis + 8 systemic mastocytosis <sup>d</sup>	2.6
Bonadonna <i>et al.</i> [9 <sup>••</sup> ]	379	44 (11.6)	21 ISM + 9 MMAS	7.9
Potier <i>et al.</i> [31 <sup>•</sup> ]	138	22 (15.9)	1 cutaneous mastocytosis + 5 systemic mastocytosis <sup>d</sup>	4.4
Guenova <i>et al.</i> [32 <sup>•</sup> ]	274	30 (10.9)	1 cutaneous mastocytosis + 3 ISM <sup>c,d</sup>	1.5

CMD, clonal mast cells disease; ISM, indolent systemic mastocytosis; MMAS, Monoclonal Mast Cell Activation Syndrome.

<sup>a</sup> Bone marrow evaluation not performed.

<sup>b</sup> Screening with urinary Histamine metabolite.

<sup>c</sup> Bone marrow evaluation performed if sBT higher than 15 ng/ml.

<sup>d</sup> Evaluation of CD25/CD2 mast cell coexpression and c-Kit mutation not performed or reported.

**Table 3 Characteristics of majority of reported mast cell clonal diseases presenting systemic reaction to hymenoptera sting**

Reference	No of patients	Diagnosis	Male/female	Median age years (range)	Tryptase <20 ng/ml [n (%)]	Without skin involvement [n (%)]
Müller <i>et al.</i> [26]	3	2 cutaneous mastocytosis <sup>a</sup> + 1 systemic mastocytosis	1/2	34 (32–50)	Nr	0 (0)
Kors <i>et al.</i> [27]	5	5 systemic mastocytosis	0/5	49 (29–71)	Nr	2 (40)
Fricker <i>et al.</i> [1]	10	7 cutaneous mastocytosis <sup>a</sup> + 3 systemic mastocytosis	4/6	39 (29–51)	5 (50)	0 (0)
Oude Elberink <i>et al.</i> [2]	2	2 systemic mastocytosis	0/2	43–44	Nr	0 (0)
Biederman <i>et al.</i> [28]	1	1 cutaneous mastocytosis <sup>a</sup>	1/0	40	0	0 (0)
Ludolph-Hauser <i>et al.</i> [10]	13	13 cutaneous mastocytosis <sup>a</sup>	5/8	42 (30–66)	7 (54)	0 (0)
Dubois [3]	17	17 systemic mastocytosis	Nr	Nr	Nr	9 (53)
Rueff <i>et al.</i> [4]	29	21 cutaneous mastocytosis + 8 systemic mastocytosis <sup>a</sup>	Nr	Nr	Nr	Nr
Sonneck <i>et al.</i> [24]	5	4 ISM 1 MMAS	4/0 0/1	40 (33–50) 39	1 (25) 1/1	5 (100)
Akin <i>et al.</i> [23]	1	1 MMAS	1	42	1/1	1 (100)
Gonzales de Olano <i>et al.</i> [7]	21	21 ISM	17/4	50 (29–74)	2 (9)	16 (76)
Potier <i>et al.</i> [31*]	6	1 cutaneous mastocytosis + 5 ISM <sup>b</sup>	5/1	41 (29–59)	1 (17)	1 (17)
Bonadonna <i>et al.</i> [9**]	30	21 ISM 9 MMAS	13/8 9/0	48 (19–76) 51 (32–69)	6 (29) 6 (67)	26 (89)
Dugas-Breit <i>et al.</i> [33*]	56	32 cutaneous mastocytosis + 24 systemic mastocytosis	Nr	Nr	Nr	Nr
Guenova <i>et al.</i> [32*]	4	1 cutaneous mastocytosis + 3 systemic mastocytosis	3/1	64 (57–71)	1 (25)	Nr
Total	204	78 cutaneous mastocytosis, 115 systemic mastocytosis, 11 MMAS	64/38	Nr	31/92 (34)	60/114 (53)

ISM, indolent systemic mastocytosis; MMAS, Monoclonal Mast Cell Activation Syndrome; Nr, not reported.

<sup>a</sup> Bone marrow evaluation not performed or in a portion of cases.

<sup>b</sup> Bone marrow histology without evaluation of CD25/CD2 mast cell expression.

mastocytosis/MMAS would not have been diagnosed without CD25/CD2 mast cell coexpression and c-Kit mutation analysis. Therefore we recommend to refer HVA patients with raised sBT without skin involvement to a tertiary research centre with experience in mast cell disorders.

Recurrent anaphylaxis due to food or drug hypersensitivity may also indicate an underlying CMD. While some studies reported a comparable prevalence of venom, food and drug-induced anaphylaxis in patients with CMD [7,8], a recent study [9\*\*] reported a much higher prevalence of HVA than of food or drug hypersensitivity. This suggests some specificity in the association between mast cell disorders and HVA, deserving more detailed investigation.

The main characteristics of CMD in patients with SAR to hymenoptera stings are reported in Table 3 [33\*]. Similar to all patients with HVA the majority of patients with CMD are men (ratio 1.66), with a median age from 34 to 50 years. The sBT was less than 20 µg/l in 34%, and systemic mastocytosis was the most frequent diagnosis (51%). To our knowledge, no case of HVA associated with ASM or SM-AHNMD has been reported so far. Interestingly 53% of cases had bone marrow involvement without skin lesions.

Pardanani *et al.* [34\*] recently described 36 cases of BMM among a series of 159 ISM. Moreover, recurrent

anaphylactoid reactions were reported in 86% of cases, significantly more often than in other forms of ISM ( $P < 0.001$ ). This suggests that BMM is a condition with strong association with anaphylaxis. The frequency of detection of c-Kit mutation in this series (92%) was consistent with that generally reported in ISM [19], suggesting that D816V mutation alone is not a good predictor of anaphylactic episodes in patients with mastocytosis.

### Diagnostic aspects

In patients with SAR to hymenoptera stings, venom-specific sensitization can be detected by skin or serological tests, which are also safe in mastocytosis. The most frequent type of sensitization in patients with CMD is to Vespidae. In a study of 30 patients with CMD, 16 were allergic to *Vespula* species, nine to *Polistes dominulus* and only one to *Apis*. In this series, four patients had negative tests [9\*\*]. Similar results were reported by other authors [5,7]. One possible explanation for the association with Vespidae could be that their venom contains more potent mast cell-activating peptides, although they deposit a 10 times smaller amount of venom than honey bees [35].

Venom-specific IgE sometimes cannot be detected in patients with mastocytosis or increased sBT. This has been attributed to increased absorption of circulating

**Table 4 Venom immunotherapy in patients with clonal mast cell disorders**

Reference	No. of patients	Diagnosis	No. of patients stop VIT due to side-effects	No. of patients protected/no. of patients exposed	Type of protocol
Müller <i>et al.</i> [26]	2	2 cutaneous mastocytosis	0	1/1 <sup>a</sup>	Not reported
Kors <i>et al.</i> [27]	3	3 ISM	2	Not reported	Semi-rush
Engler and Davis [41]	1	1 systemic mastocytosis	0	1/1	Rush
Fricker <i>et al.</i> [1]	10	3 systemic mastocytosis 7 cutaneous mastocytosis	0	1/1 4/5 <sup>b</sup>	Conventional/rush
Haerberli <i>et al.</i> [5]	10	only raised tryptase	1/10	6/10 <sup>c</sup>	Ultra Rush/rush/conventional
Dubois [3]	12	7 ISM 5 only raised tryptase <sup>d</sup>	6 2	1/7 3/5	Not reported
Bonadonna <i>et al.</i> [9**]	16	16 ISM	0	11/13 <sup>b</sup>	Rush modified
Gonzales de Olano <i>et al.</i> [7]	21	21 ISM	0	9/12 <sup>b</sup>	Conventional/cluster
Total	75	53 ISM 9 cutaneous mastocytosis 15 only raised tryptase	11/75 15%	37/55 67%	

ISM, indolent systemic mastocytosis.

<sup>a</sup>Protected during venom immunotherapy (VIT); systemic reaction after interruption of VIT.

<sup>b</sup>Systemic reaction but less severe than before VIT.

<sup>c</sup>No statistically significant difference with patients with normal level of tryptase.

<sup>d</sup>Raised tryptase basal level but evaluation of bone marrow negative for mastocytosis.

IgE by the large amount of mast cells [5,36] or also to direct mediator releasing activity of hymenoptera venom proteins or peptides [27]. Patients with anaphylaxis following hymenoptera stings but without venom specific serum IgE often have increased sBT levels and a diagnosis of CMD [9\*\*]. Some of the patients with negative standard tests, however, exhibit sensitization to venom in cellular tests. Therefore basophil histamine release or basophil activation tests are a suitable diagnostic option in skin test and sIgE-negative patients with mastocytosis [4]. The fact that some patients with mastocytosis develop anaphylaxis following insect stings, while others do not, and that many patients react only to stings of one species and tolerate stings by others, also supports the high significance of IgE-mediated mechanisms in patients with CMD [37\*].

One of the main diagnostic problems is the decision about which patients should undergo bone marrow examination, which is an invasive technique. The currently accepted criteria for performing a bone marrow biopsy in patients with HVA is a sBT more than 20 µg/l, or of signs and symptoms of systemic mastocytosis [18]. Nonetheless, as shown in Table 3, 34% patients with HVA and CMD have a sBT less than 20 µg/l [9\*\*,23,24,38]. It has been proposed, that the sBT cut-off should be lowered to 11.4 µg/l [39\*\*]. Additional criteria in favour of bone marrow biopsy may be negative allergy tests, frequent or severe systemic side-effects to VIT and VIT failure [4].

### Mastocytosis and venom immunotherapy

The treatment of choice in patients with HVA is VIT. Nonetheless, the use of VIT in patients with mastocytosis

remained a matter of discussion for years [40\*\*]. Some authors have suggested that anaphylactic reactions in patients with mastocytosis are more frequently non-IgE-mediated and therefore VIT would be of no benefit. In addition, several reports suggested an increased occurrence of side-effects during VIT in patients with mastocytosis [2,3,5], whereas recent studies, involving large numbers of patients, demonstrated that VIT is usually well tolerated and efficiently protects against further anaphylactic sting reactions (see Table 4) [1,3,5,7,9\*\*,26,27,41].

Although most patients with CMD tolerate VIT well, some may develop severe and recurrent SAR, making it difficult to reach the maintenance dose of 100 µg [42]. Interestingly sBT tends to decrease during VIT [33\*]. According to a recent study of the EAACI interest group on venom allergy the overall incidence of side-effects in patients with mastocytosis is increased in patients with vespid but not with bee venom allergy, when compared to unselected patients undergoing VIT (F. Ruëff, B. Przybilla, MB Biló *et al.*, manuscript in preparation). When adverse reactions occur, it is recommended to repeat the last dose without further increase and to use a premedication with H1-antihistamines [43]. Two recent reports [44,45] describe successful prophylactic treatment with omalizumab in patients with mastocytosis, who were unable before to reach maintenance because of severe side-effects.

In patients with mastocytosis and HVA it is recommended that all injections are performed under medical supervision and with emergency equipment immediately available [46]. Also during VIT, they should always carry

an emergency medication set including an epinephrine autoinjector.

Three to 5 years of VIT induces long-term protection in most HVA patients [14], but in patients with mastocytosis and venom induced anaphylaxis, three fatalities have occurred after VIT discontinuation [2,47]. Therefore, it is generally recommended to continue VIT for life in this situation.

While most patients with mastocytosis are protected by VIT, a minority may develop SAR after re-exposure. In this situation it is recommended to increase the maintenance dose to 200 µg or more as in patients with HVA but no CMD [38,42,48].

Some aspects of VIT treatment in patients with mastocytosis are still unclear: should you test and treat a patient with CMD without a history of SAR after stings? Should you treat a patient with CMD and a definite history of bee venom allergy but also weakly positive tests to *Vespa* venom with both venoms? Two reports [47,49] on fatal sting reactions in patients with mastocytosis and no history of previous SAR to stings address these questions, but cannot give definite answers. Should we treat a patient with CMD and definite history of SAR to stings, but negative diagnostic tests? If yes, with which venom? Fricker *et al.* [1] administered VIT to two patients with negative tests, and reported protection to a re-sting in one of them. While a diagnostic sting challenge would be unethical [13] in this situation one report indicates that cellular tests like the basophil activation test may be helpful in this situation [4].

## Conclusion

The occurrence of CMD in patients with HVA is well ascertained, but probably underestimated. Lowering of the diagnostic cut-off level of sBT from 20 to 11.4 µg/l for further analysis including bone marrow biopsy and sensitive tests to detect clonality of mast cell would improve the diagnostic accuracy and be important especially for patients with SAR and elevated sBT, who are at a high risk of very severe or even fatal reactions. VIT is effective in this situation and recommended for life. Moreover, the diagnosis of CMD allows one to prevent further complications of the disease. Still under discussion is what to do with sensitized CMD patients without previous SAR. The strong association of CMD and HVA suggests a specific pathogenetic link between them, which deserves further analysis.

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## 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

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 402–403).

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