

Mastocytosis presenting as cardiac emergency

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Abstract Mastocytosis is characterised by clonal proliferation of mast cells in the skin and in various internal organs, and by symptoms related to an acute release of mast cell-derived mediators. In 20–30 % of patients, mastocytosis occurs without the typical skin lesions of *urticaria pigmentosa* that are usually the first clinical sign of the disease. In these patients, anaphylaxis is often the presenting sign of the disease. We report three cases in which a cardiac emergency (cardiac arrest or ventricular fibrillation) was the first clinical manifestation of anaphylaxis associated with systemic mastocytosis. All patients were men, none of them had previous episodes of anaphylaxis or other mediator-related symptoms, and none had major pre-existing cardiovascular condition. An eliciting factor was identified in one case (a wasp sting), but one was found in the other two. Elevation of the serum tryptase suggested a mastocytosis, which was confirmed by bone marrow biopsy. This case series demonstrates that

cardiovascular emergencies may be presenting signs of mastocytosis, and that elevation of serum tryptase after an acute cardiac event, if confirmed under basal conditions, may be useful for diagnosing this disease.

Keywords Anaphylaxis · Heart · Mastocytosis · Mast cell tryptase · Ventricular fibrillation

Introduction

Systemic mastocytosis is a rare disease characterised by mast cell proliferation, and an acute or chronic release of vasoactive mediators such as histamine, prostaglandins, leukotrienes and platelet-activating factor. According to current WHO classification, mastocytosis is defined as cutaneous or systemic according to the site of the proliferation of mast cells, i.e. limited to skin or involving internal organs [1]. The clinical course of systemic mastocytosis ranges from indolent forms, with a normal life expectancy, and requiring only symptom-directed therapy, to highly aggressive forms that need cytoreductive treatments [2]. The skin lesions are the first clinical manifestation in the majority of patients, and include typical maculopapular lesions, also known as *urticaria pigmentosa* [3, 4]. Nevertheless, systemic mastocytosis can occur without skin lesions in 20–30 % of patients [5, 6]. In this case, the clinical picture of the disease is dominated by mediator-related symptoms such as flushing, urticaria and angioedema, diarrhoea, hypotension and recurrent anaphylaxis. In patients without skin lesions, presenting signs and symptoms of mastocytosis can be quite variable and, in some cases, uncommon. Here, we report three cases in which a cardiac emergency was the first clinical manifestation of systemic mastocytosis.

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Methods and results

Case 1

A 72-year-old man previously in good health, suddenly complained of epigastric pain after dinner, rapidly followed by nausea, vomiting and loss of consciousness. Upon arrival at the emergency department (ED), he was unconscious, with respiratory activity, but pulseless. Electrocardiogram (ECG) showed no electrical activity. An endotracheal tube was positioned, and endotracheal epinephrine (2 mg) was administered, restoring cardiac activity. The ECG on hospital admission showed mild ST segment elevation in inferior leads and signs of anterior subendocardic ischemia. Echocardiography, coronary angiography and serum troponins were normal. During hospitalisation, several episodes of face flushing, not triggered by specific stimuli, diarrhoea and severe abdominal distension were recorded; some of these episodes were associated with severe hypotension that required infusion of colloids. The patient had previously suffered from recurrent erythematous eczema diagnosed as atypical psoriasis. Laboratory tests showed hypokalemia (2.5 mEq/l), thrombocytopenia (98,000/mm³), mild hypereosinophilia (700/mm³) and anaemia (Hb 8.1 g/dl, RBC 2,850 × 10³/mm³). Because of diarrhoea and flushing, a neuroendocrine neoplasm was suspected, but serum/plasma levels of chromogranin A, 5-hydroxyindolacetic acid, vanillylmandelic acid and homovanillic acid resulted were normal. Abdominal CT scan, gastroscopy and colonoscopy were negative. Food and hymenoptera venom allergy was investigated by skin prick test and specific serum IgE assay with negative results.

A laboratory test for tryptase showed markedly elevated values (75 ng/ml, normal range: <11.4 ng/ml). A bone marrow biopsy showed extensive mast-cell infiltration with atypical inter- and paratrabeular aggregates of CD117⁺, CD25⁺, CD2⁺ cells identified as mast cells. PCR–RFLP revealed D816V mutation of c-kit. According to current WHO classification [1], a diagnosis of systemic mastocytosis was made, and treatment with montelukast (10 mg/day) and interferon α 2b (initially 3 million units three times a week, then 6 million units three times a week) was initiated, with marked improvement in abdominal symptoms. Episodes of flushing and symptomatic hypotension persisted although less severe. Four months after discharge the patient died suddenly with cardiorespiratory arrest.

Case 2

A 57-year-old man, without previous history of allergic or cardiovascular diseases, developed general malaise, flushing and loss of consciousness while he was at work. He was

given cardiopulmonary resuscitation by colleagues. He came to the hospital in coma (Glasgow coma scale: 3), with severe hypotension and diffuse erythema. The ECG showed diffuse ST segment depression. Serum troponin was elevated (0.7 ng/ml). Echocardiography showed normal contractile function. CT scan revealed diffuse osteosclerotic lesions in multiple bone segments.

The serum tryptase was highly elevated (200 ng/ml) a few hours after the episode, and was still slightly elevated (19 ng/ml) after 10 days. Bone marrow biopsy showed mast cell infiltrates with paratrabeular aggregates of CD117⁺, CD68⁺ cells, mainly with spindle morphology, and rare CD117⁺/CD2⁺ cells. PCR–RFLP did not show D816V mutation of c-kit. Specific IgE antibodies for food, hymenoptera venom and aeroallergens were not detectable.

Considering the critical neurological condition (vegetative state caused by anoxic encephalopathy), cyto-reductive therapy was not started. The patient died 40 days later after an episode of flushing and severe hypotension.

Case 3

A 49-year-old man, developed severe local pain, fatigue, numbness in the upper limbs and tightness in the throat within few minutes after a wasp sting on his left ear. Being close to the hospital he was rapidly admitted to the ED with dyspnea, cyanosis and loss of consciousness. The patient was on treatment with atenolol (50 mg b.i.d.) for mild hypertension and had mild obesity and chronic gastritis. On admission, the patient was unconscious and pale, a blood pressure was not detectable, and the heart rate was 100 bpm. He was given hydrocortisone (1 g i.v.), antihistamines (chlorphenamine 10 mg i.v.) and i.v. fluids. The ECG showed initially ST segment elevation and then polymorphic ventricular tachycardia followed by *torsades de pointes* (Fig. 1). He was immediately treated with cardiac defibrillation and i.v. Mg²⁺-sulphate with restoration of a sinus rhythm. The patient was monitored in the Intensive Care Unit for 5 days, and was discharged with no further episodes of dysrhythmias.

On subsequent allergy evaluation, the patient reported that he had previous wasp stings that caused only local reactions. Of note, however, 3 days before the reaction, he started an oral NSAID (diclofenac 75 mg b.i.d.) for low back pain. Skin prick tests and intradermal tests with bee and wasp venoms (*Apis mellifera*, *Vespula spp.*, *Polistes spp.*, *Vespa crabro*) were negative. Specific serum IgE against these venom antigens was undetectable. Serum tryptase level 3 months after the sting was 25 ng/ml. The patient was prescribed self-injectable epinephrine. After 6 months, allergy tests and the determination of tryptase level were repeated and confirmed the previous findings. Because of the persistently elevated tryptase levels, the

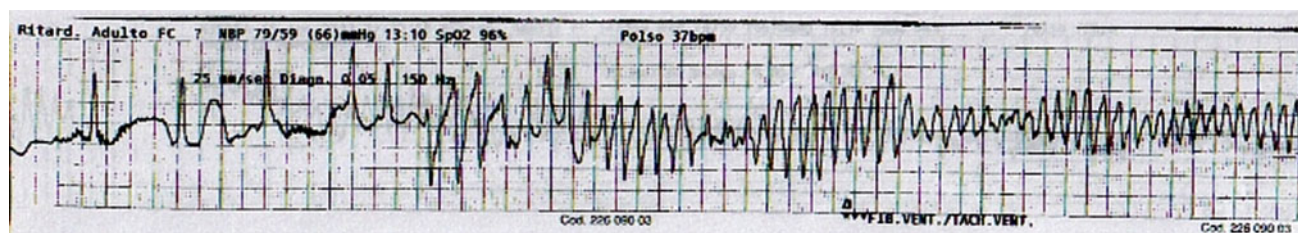


Fig. 1 ECG tracing (lead D-II) showing transition from sinus rhythm to ventricular fibrillation in patient 3, with systemic mastocytosis, after wasp sting

Table 1 Demographic and clinical characteristics of patients

Patient No.	Age	Gender	Cardiovascular manifestation	Trigger	Previous manifestations	Cofactors	Tryptase (ng/ml)	
							Acute	Basal
1	72	M	Cardiac arrest	Unknown	Skin eczema	Anaemia	ND	75
2	57	M	Cardiac arrest	Unknown	None	None	>200	19
3	49	M	Ventricular fibrillation	Wasp sting	None	Beta-blocker NSAID	ND	25

patient underwent bone marrow biopsy that showed multiple aggregates of CD117⁺, CD25⁺ and tryptase-positive mast cells, which confirmed the diagnosis of systemic mastocytosis. The patient is currently on follow-up and no further episodes of anaphylaxis have been reported.

Discussion

Presenting symptoms in patients with mastocytosis without skin involvement are heterogeneous and often mimic a variety of other allergic, metabolic and cardiovascular disorders. We describe three cases of mastocytosis whose first manifestation was an acute and unexpected cardiovascular event. Common features of these cases are (1) the occurrence of a major cardiovascular event as the first manifestation of the disease in patients without previous signs or symptoms of mastocytosis, and (2) the clinical picture dominated by severe dysrhythmias, such as cardiac arrest and ventricular fibrillation, rather than contractile or clearly ischemic heart dysfunction (Table 1). No patient in this series had a previous history of anaphylaxis or reported other significant mediator-related symptoms. None of them had skin lesions typical of mastocytosis. Except for patient 3, who had mild controlled hypertension, none of the patients had pre-existing cardiovascular conditions. The trigger was identified in one case (wasp sting in patient 3) but not found in the other two.

The release of mast cell-derived mediators in systemic mastocytosis can cause major cardiovascular and circulatory symptoms [7]. Mast cells are particularly abundant in the human heart where they are mainly located around coronary vessels [8]. The cardiac arrest and ventricular fibrillation

reported in our cases were likely related to the acute release of mediators such as histamine, platelet-activating factor, prostaglandins and leukotrienes. All these mediators are able to induce vasospasm of large coronary arteries, a global reduction of myocardial blood flow by influencing the vasomotor tone of small intramural coronary arteries, and may exert direct dysrhythmogenic effects [9].

We should consider the cardiac events in our patients as an indication of severe anaphylaxis due to the acute and massive release of cardioactive mediators. Anaphylaxis occurs in 20–40 % of adult patients with systemic mastocytosis, and is more frequent in patients without skin lesions [6, 10]. Eliciting factors can be hymenoptera stings, foods and drugs, but remain unknown in approximately one-third of cases. While cardiac arrest is considered part of the clinical picture of anaphylaxis, ventricular fibrillation is an uncommon presentation of the acute anaphylactic episode, particularly when no evidence of myocardial ischemia is detectable, as in patient 3.

It is interesting to note that anaphylaxis occurred in patient 3 after a wasp sting that, on previous occasions, had caused only local reactions. In this case at least two cofactors should be considered as potentially aggravating the clinical course of anaphylaxis, i.e. the long-term use of a beta-blocker and the oral treatment with a NSAID (diclofenac) in the prior 3 days before anaphylaxis. Patients taking antihypertensive agents including beta-blockers are considered at higher risk of severe anaphylaxis [11]. NSAIDs are also reported to increase severity of anaphylaxis, [12] and are well-known eliciting factors in patients with mastocytosis [13]. It is likely that diclofenac consumption in this patient contributed to increase the severity of reaction to the sting and to trigger anaphylaxis. Nevertheless, it is not currently known whether

NSAIDs may increase the rate of cardiac dysrhythmias during anaphylaxis.

Serum tryptase level greater than 20 ng/ml is one of the minor diagnostic criteria for systemic mastocytosis. However, increasing evidence suggests that this threshold should be lowered and even values just above the upper limit of normal (11.4 ng/ml) should be considered for the diagnosis of mast cell disorders [14, 15]. In patient 1, serum tryptase detection was not performed in the acute setting but this patient had a high basal level several days after cardiac arrest; in patient 2, the elevated tryptase a few hours after the cardiac arrest confirmed extensive mast cell degranulation, whereas in patient 3 tryptase basal value, measured 3 and 6 months after the event, was moderately elevated (25 ng/ml) as compared to a normal range. In all cases, however, increased tryptase values, either in the acute phase (patient 2) or as basal values after several days/months (patients 1 and 3), were suggestive for a mast-cell disorder and led to further diagnostic work-up that confirmed systemic mastocytosis. Our findings suggest that measurement of serum tryptase may be useful in cases of cardiac emergencies like unexplained cardiac arrest or severe dysrhythmias [16, 17].

This case series demonstrates that cardiovascular emergencies may be presenting signs of a rare disease like systemic mastocytosis. This disease should therefore be considered in the differential diagnosis of sudden cardiovascular events, especially in patients without a previous history of heart disease. Measurement of serum tryptase within 12–24 h after an acute cardiac event may be useful for suspecting systemic mastocytosis.

Conflict of interest None.

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