

# Presentation of Untreated Systemic Mastocytosis as Recurrent, Pulseless-Electrical-Activity Cardiac Arrests Resistant to Cardiac Pacemaker

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## Established Facts

- Mast cells produce mediators, such as histamine, that can have adverse effects on cardiovascular function.
- Aspirin can be used to prevent prostaglandin D<sub>2</sub> production in patients with systemic mastocytosis who do not respond to treatment with a combination of H<sub>1</sub> and H<sub>2</sub> receptor antagonists.

## Novel Insights

- In the absence of typical skin lesions, undiagnosed/untreated systemic mastocytosis may be the cause of recurrent, pulseless-electrical-activity (PEA) cardiac arrests associated with extreme elevation of histamine (revealed by increased urinary *N*-methylhistamine excretion) and of serum tryptase.
- PEA cardiac arrests associated with systemic mastocytosis occurred despite pacemaker implantation, but were then able to be prevented by a combination of histamine H<sub>1</sub> and H<sub>2</sub> receptor blockers, aspirin, montelukast and oral sodium cromolyn.

## Key Words

Pacemaker · Pulseless-electrical-activity arrests · Systemic mastocytosis

## Abstract

Recurrent, pulseless-electrical-activity (PEA) cardiac arrests were the novel presentation of untreated systemic mastocytosis in an 85-year-old woman who lacked cutaneous findings of mastocytosis. Despite prior implantation of a dual-chamber cardiac pacemaker 3 weeks previously for similar spells, she experienced a PEA arrest accompanied by flushing, increased urinary *N*-methylhistamine excretion and se-

rum tryptase values on the day of presentation to our clinic. Bone marrow biopsy findings conducted to rule out breast cancer metastases showed 30% mast cell infiltration, aberrant expression of CD25 and a positive c-kit Asp816Val mutation. Treatment with a combination of H<sub>1</sub> and H<sub>2</sub> receptor blockers reduced flushing and eliminated hypotension. Maintenance medication included aspirin, cetirizine, ranitidine, montelukast, oral cromolyn sodium and an epinephrine autoinjector (as needed). At 6-month follow-up, the patient remained free of PEA arrests, flushing, or any clinical signs of mastocytosis or mast cell degranulation. PEA cardiac arrests may therefore be a presenting sign of untreated systemic mastocytosis.

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## Introduction

The human heart contains an abundance of mast cells, with the highest mean values observed in cases of mast cell neoplasia and giant cell myocarditis [1]. Mast cells are prolific producers of mediators (e.g. histamine), many of which can have a profound effect on the cardiovascular system, including the coronary arteries [2]. Activation of human heart mast cells by anti-immunoglobulin E (IgE), by antibody to the high-affinity IgE receptor, by the anaphylatoxin C5a or by therapeutic or diagnostic agents (e.g. general anesthetics and radiocontrast media) can cause the release of preformed mediators such as histamine, tryptase and chymase, as well as the *de novo* synthesis of leukotriene C<sub>4</sub> and prostaglandin (PG) D<sub>2</sub> [3]. The coronary arteries of patients who have died of coronary artery disease have been found to contain more histamine than those of patients who have died of noncoronary causes. In addition, high levels of serotonin have been identified [4] in the group with coronary artery disease.

H<sub>1</sub> (histamine<sub>1</sub>) receptors in the human heart mediate the contraction of coronary vascular smooth muscle without affecting ventricular or atrial tissue [5]. H<sub>2</sub> (histamine<sub>2</sub>) receptors mediate the relaxation of coronary artery vascular smooth muscle and a positive inotropic response of atrial and ventricular myocardium [5]. In this way, the H<sub>2</sub>-receptor antagonist cimetidine induces coronary artery spasm in patients with vasospastic angina [6].

Systemic mastocytosis (SM) is a clonal hematologic disorder in which abnormal mast cells proliferate diffusely in the body [7] and cause symptoms by local or remote effects of mast-cell-generated mediators [8]. Aspirin can be used to prevent PGD<sub>2</sub> production in patients with SM who do not respond to treatment with a combination of H<sub>1</sub> and H<sub>2</sub> receptor antagonists [9].

We describe the novel presentation of untreated SM as recurrent, pulseless-electrical-activity (PEA) cardiac arrests despite implantation of a dual-chamber cardiac pacemaker. The patient had no cutaneous evidence of mastocytosis. However, bone marrow biopsy findings showed 30% bone marrow infiltration by mast cells with aberrant expression of CD25, as well as the presence of the c-kit Asp816Val mutation. Serum tryptase and urinary *N*-methylhistamine were both markedly elevated contemporaneously with the PEA cardiac arrest. Treatment with a combination of H<sub>1</sub> and H<sub>2</sub> antihistamines, aspirin, montelukast sodium and oral disodium cromoglycate resulted in complete cessation of the patient's PEA cardiac arrests.

## Case Report

An 85-year-old woman arrived at our hospital emergency department by ambulance transfer from a local community hospital and suddenly became light-headed, short of breath and flushed from 'head to toe'; she was diaphoretic and hypotensive, without a palpable pulse. When she had first presented to the community hospital, she had had shortness of breath without associated chest pain; her troponin level was found to be normal, but her brain natriuretic peptide level was reported to have increased. Transfer to our hospital by ambulance was arranged, and she was stable during transfer.

Pulse oximetry values quickly declined to 50–60%. Cardiac monitoring showed a paced rhythm with one-to-one capture consistent with a PEA cardiac arrest. She was given fluids through 2 peripheral IVs, administered 50 µg of intravenous phenylephrine and underwent 2 min of cardiopulmonary resuscitation, after which she regained consciousness and spontaneous circulation without additional pharmacological intervention. Her systolic blood pressure ranged from 80 to 100 mm Hg. She was started on dopamine at 5 µg/kg/min and on bilevel positive airway pressure for respiratory acidosis. No shocks, epinephrine or atropine were given.

The patient had a history of 5–6 months of multiple similar syncopal events, with at least 4 previous PEA cardiac arrests. A prior workup for carcinoid syndrome had been negative. Evaluation for cardiac causes of syncope had also been negative; it included normal cardiac catheterization, coronary angiogram and echocardiogram. There was no significant valvular disease, and the ejection fraction and right-sided pressures were normal. A dual-chamber pacemaker had been implanted 3 weeks earlier for syncope.

Her medical history included gastroesophageal reflux treated with pantoprazole 40 mg/day, hypertension treated with atenolol 50 mg/day, stage 3 chronic kidney disease (with stable creatinine), breast cancer treated with anastrozole 1 mg/day and anemia. The only other concurrent medication was 81 mg/day of aspirin.

### *Hospital Course*

The patient was admitted to the critical care unit. The dopamine infusion was continued and an octreotide infusion was started. She was intubated for hypercapnic respiratory failure. There were no cutaneous signs of mastocytosis noted at this time or when she was initially evaluated in our emergency department. Her pacemaker was a Biotronik dual-chamber pacemaker (model Evia DR-T 359529). Initial interrogation showed normal pacemaker function. An electrocardiogram showed electronic atrial pacemaker and nonspecific ST-T wave abnormalities (fig. 1). The initial echocardiogram showed normal left-ventricular chamber size, a calculated ejection fraction of 64% and no regional-wall abnormalities. The right-ventricular size and systolic function were normal, and the right-ventricular systolic pressure was 46 mm Hg. Moderate circumferential pericardial effusion without evident tamponade physiology was noted; there was no evidence of chamber collapse. Mild to moderate tricuspid valve regurgitation was also noted. A chest computed tomography scan showed no evidence of aortic dissection or pulmonary emboli, but did reveal small bilateral pleural effusions and innumerable mixed lytic and sclerotic foci throughout the ribs and pelvis. A complete blood cell count revealed mild macrocytic anemia and eosinophilia. Findings from the studies that were conducted are summarized in table 1.

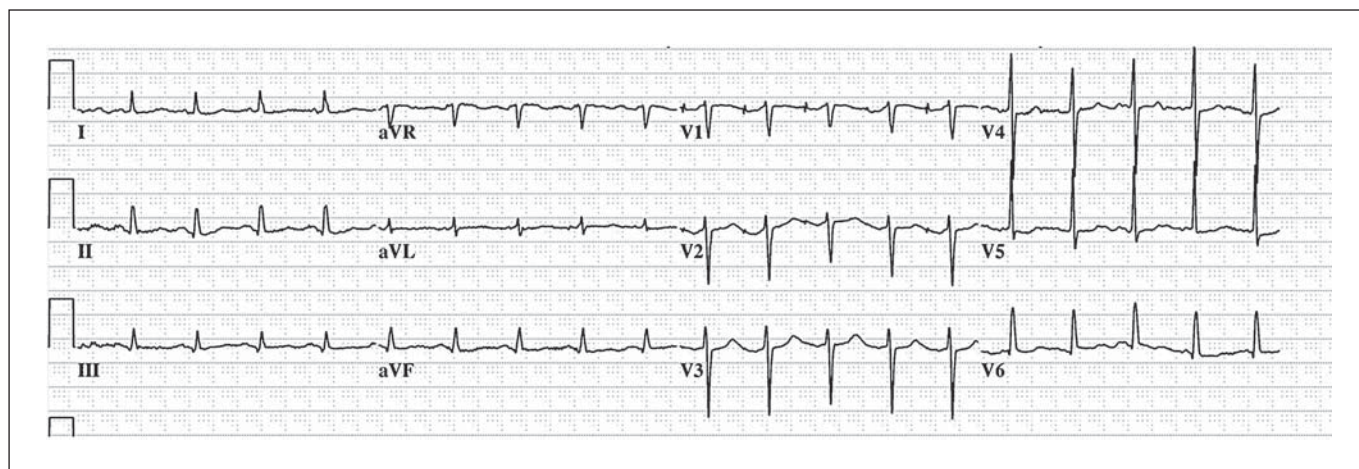


**Fig. 1.** Electrocardiographic tracing showing electronic atrial pacemaker and nonspecific ST-T wave changes.

**Table 1.** Diagnostic test results in an 85-year-old woman with SM-associated, recurrent, PEA cardiac arrests resistant to a cardiac pacemaker

| Test                                                                 | Result | Reference range |
|----------------------------------------------------------------------|--------|-----------------|
| Serum tryptase, ng/ml                                                | 335    | <11.5           |
| Fe/TIBC, %                                                           | 16     | 14–50           |
| Hemoglobin, g/dl                                                     | 9.1    | 12–15.5         |
| Vasoactive intestinal peptide, pg/ml                                 | 40     | <75             |
| Total protein, g/dl                                                  | 5      | 6.3–7.9         |
| Total eosinophil count, $\times 10^9/l$                              | 4.3    | 0–0.5           |
| C-reactive protein, mg/l                                             | 13.8   | <8.0            |
| Prothrombin time, s                                                  | 15.9   | 9.5–13.8        |
| Urinary <i>N</i> -methylhistamine (24 h), $\mu\text{g/g creatinine}$ | 2,309  | 30–200          |
| Urinary 11 $\beta$ PGF $_2\alpha$ , ng/24 h                          | 943    | <1,000          |
| Urinary 5-HIAA, mg/24 h                                              | 1.8    | <8              |

Fe/TIBC = Iron/total iron-binding capacity percentage; 5-HIAA = 5-hydroxyindoleacetic acid; PEA = pulseless-electrical-activity.

A bone marrow biopsy, performed to rule out metastatic breast cancer, showed hypercellular marrow with mast cell infiltrates comprising 30% of bone marrow cellularity. A test for the c-kit Asp816Val mutation was positive, and immunohistochemical stains showed the mast cells to be CD25 positive. There were no findings of metastatic breast cancer in either this bone marrow sample or in a separate computed tomography-guided biopsy of a left iliac bone lytic lesion, which again showed only mast cell infiltration. The serum tryptase level obtained within 1 day of her PEA arrest was 335 ng/ml (reference range <11.5 ng/ml). In addition, a 24-hour urine collection for *N*-methylhistamine that was obtained

2–3 days after her attack was also markedly increased at 2,309  $\mu\text{g/g creatinine}$  (reference range 30–200  $\mu\text{g/g}$ ).

The patient was extubated, pressors and octreotide were discontinued and a combination of  $H_1$  and  $H_2$  receptor blockers was started. She had additional episodes of flushing that were mild and were not accompanied by hypotension. She continued to do well; at hospital discharge 8 days after admission, she was maintained on a program of aspirin 162 mg twice daily, cetirizine 20 mg/day, ranitidine 150 mg twice daily, montelukast 10 mg/day, oral cromolyn sodium 200 mg 4 times daily and an epinephrine autoinjector (to use as needed). During the subsequent 6 months, she remained free of PEA arrests, flushing or any clinical signs of mastocytosis or mast cell degranulation. A serum tryptase level obtained 8 months after her attack remained elevated at 321 ng/ml.

## Discussion

Potentially treatable causes of PEA include hypovolemia due to massive bleeding and obstruction of circulation due to massive pulmonary embolism, cardiac tamponade or tension pneumothorax [10]. None of these causes appeared to be valid considerations for our patient. Also unlikely are other commonly mentioned reasons, including drug overdose, hyperkalemia, hypoglycemia or severe hypothermia [10]. PEA has been one of the most commonly discovered heart rhythms among inpatients requiring cardiopulmonary resuscitation, affecting from 29% (2,031/6,972) [11] to 42% (891/2,121) [12]. In-hospital PEA cardiac arrests generally have a poor prognosis, with 12.1% of patients surviving 24 h and only 4.8% surviving until hospital discharge in 1 series [12]. Significant predictors of survival after requiring in-hospital re-

suscitation include: (1) age, with progressively poorer survival with increasing age [11, 12]; (2) mode of arrest, with cardiac arrest less favorable than respiratory arrest; (3) primary arrhythmia, with PEA the least favorable when compared to ventricular tachycardia, ventricular fibrillation or asystole; (4) duration of resuscitation, with a duration of <15 min connoting a nearly 4-fold-better survival, and (5) time of day, with the least favorable time being between 1 a.m. and 7 a.m. [11, 12].

This elderly patient, who had survived several PEA cardiac arrests, received only a brief period of resuscitation (2 min) after arresting at a 'favorable' time of day. After the discovery of SM, treatment was redirected to inhibit mast cell mediator synthesis and end-organ effects. This approach resulted in resolution of the attacks, which had not been prevented by the implanted, fully functioning pacemaker, and served to confirm the importance of mast cell mediators in her recurrent symptoms. Importantly, the patient had no cutaneous findings of mastocytosis, which was discovered by bone marrow biopsy and supported by findings of elevated mast cell mediators in the serum and urine, prolonged prothrombin time and eosinophilia. She became pulseless in the context of ongoing symptoms of mast cell degranulation, which was confirmed by measurements of serum tryptase (within 1 day of her arrest) and urinary *N*-methylhistamine (2–3 days after her arrest) that were approximately 29 times and 11.5 times the upper limits of normal, respectively. In all likelihood, these mediator levels were even more elevated at the time of her initial presentation.

Our patient was taking a stable dose of  $\beta$ -blocker medication for chronic hypertension.  $\beta$ -Blockers may produce bradycardia in patients with anaphylaxis [13]; however, at the time of her attack, the patient had a fully functioning pacemaker, thereby obviating this potential side effect. In a separate review of 179 out-of-hospital cardiac arrest rhythms, the odds ratio for  $\beta$ -blocker use among PEA versus ventricular fibrillation patients was approximately 5.0, with approximately half of those who presented with PEA taking a  $\beta$ -blocker [14]. The specific reason for this association is not known.

Several clinical features of this patient's presentation resemble those of an anaphylactic episode. However, subsequent studies were more compatible with a diagnosis of SM. For example, anaphylaxis has been associated mainly with myocardial ischemia, conduction defects (atrial and ventricular arrhythmias) and T-wave abnormalities – none of which was evident during the course of illness of our patient [15]. PEA has been reported in cases of anaphylactic shock in which the position of the shocked

patient is acutely changed from lying down to sitting or standing, resulting in reduced venous return, empty vena cava and, subsequently, no blood flow through the right side of the heart or to the left side of the heart from the lungs [16]. In each of these reported cases, the inciting trigger for anaphylaxis was also known (i.e. antibiotics, insect stings or food [nuts]) [16]. In contrast, no trigger was ever identified in our patient, and she was not placed in an upright position at any time (cardiopulmonary resuscitation was administered immediately).

Anaphylactic reactions (e.g. to insect stings) can be a presenting manifestation of SM [17]. After an anaphylactic episode, the tryptase level can remain elevated for several hours before returning to normal. A recheck of serum tryptase is therefore recommended at least 24 h after complete resolution of all signs and symptoms to rule out a persistently high tryptase value consistent with SM [7]. Our patient had an acutely elevated tryptase level that did not decrease after recovery. This finding substantiates our belief that the elevation was chronic and not due to anaphylaxis. In addition, our patient was not exposed to any of the common triggers of anaphylaxis including (new) medications, foods or insect stings; she did not have hives or angioedema (common in anaphylaxis) and she recovered consciousness and spontaneous circulation without receiving epinephrine.

The effects of histamine on multiple organs include gastric acid secretion, smooth muscle contraction, mucus secretion, endothelial permeability, stimulation of nociceptive nerve fibers, tachycardia or arrhythmia and vasodilation. Vasodilation affects the skin, central nervous system and cardiovascular system (resulting in cardiac arrhythmia, hypotension and anaphylaxis) [18], which would explain the diffuse flushing in this patient; however, she remained hypotensive despite a functioning pacemaker. Her ongoing use of aspirin may explain the normal level of urinary 11 $\beta$ -PGF $_2\alpha$  excretion (table 1) [19]. Her initial and sustained response to mast cell mediator blockade suggests that PEA cardiac arrests may be a presenting sign of untreated SM.

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