

Acute severe urticaria and angioedema leading to myocardial infarction

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CHIEF COMPLAINT

A 56-year-old white man was transferred to Johns Hopkins Coronary Care Unit from a community hospital where he was admitted for substernal chest pain radiating to the left side of the neck, shoulder, and arm.

HISTORY OF PRESENT ILLNESS

One week before this admission, he was treated in the emergency department for angioedema of the hands and generalized urticaria. This lasted for about three days and was treated with oral diphenhydramine. No specific triggering factor was found.

Approximately eight hours prior to the onset of the current episode of chest pain, he began to experience itching and swelling of face and hands. Despite taking 50 mg diphenhydramine orally, the itching worsened and he developed generalized urticaria. The swelling of his face and eyes progressed until the eyes were almost shut. He was treated with intravenous corticosteroid (125 mg methylprednisolone), H₂ blocker (20 mg famotidine), and intramuscular H₁ blocker (50 mg diphenhydramine) in the emergency department. He returned home from the hospital with the urticaria and the swelling still present. Two and one-half hours later, he felt substernal chest pain and returned to the emergency department.

Medications

He had been taking lovastatin, 20 mg qd, and ranitidine, 150 mg bid, for 3 years; enteric coated aspirin, qd for 2 years; etodolac, 300 mg tid for 3 months; vitamin C and E tablets qd for 2 months; garlic and cod liver oil tablets for 3 weeks; beta carotene and selenium tablets off and on for several weeks.

Allergy Profile, Past Medical History

There was no history of urticaria, angioedema, asthma, rhinitis, or eczema during childhood. About 2 years ago, he had undergone percutaneous transluminal angioplasty of left anterior descending coronary artery.

Social History and Review of Systems

He had smoked cigarettes for 40 years, but he had discontinued 2 years ago. He has been drinking alcohol regularly. The review of systems was unremarkable.

Physical Examination

The patient was a healthy appearing caucasian man with blood pressure 120/80 mm Hg, pulse 60 beats per minute, respiratory rate 16 breaths per minute, and oral temperature 98.6 °F. The skin was normal without hives or angioedema (at the time of our examination). The head, eyes, and ears were normal. He had no cervical lymphadenopathy. The lungs, heart, abdomen, and neurologic examinations were normal.

Laboratory and Diagnostic Studies

His electrocardiogram was consistent with acute myocardial infarction (Fig 1). The cardiac isoenzymes were elevated. The complete blood count and

chemistry panel were within normal limits. The chest radiograph was also normal.

CLINICAL COURSE

He received thrombolytic therapy in the emergency department. On the following day, cardiac catheterization revealed 99% proximal right coronary artery stenoses. Subsequently, he was transferred to the Johns Hopkins Hospital. Percutaneous transluminal coronary angioplasty of the right coronary artery was accomplished successfully.

QUESTION

The temporal sequence of events is shown in Table 1. The principal question raised by this clinical case is: whether acute urticaria and angioedema caused or led to the events precipitating myocardial infarction.

PREVIOUS CASE REPORTS

On review of literature, there have been few related case reports.

A letter to the editor by Hirsh described a patient admitted to a coronary care unit with myocardial infarction occurring minutes after a bee sting.¹

Bristow et al reported a 51-year-old man who developed urticaria and experienced chest pain with electrocardiographic changes consistent with myocardial ischemia (ST segment depression in EKG leads II, III, AVF). Approximately one hour later, he became bradycardic, hypotensive with ST segment elevation in EKG leads II, III and AVF. Three months later, intravenous infusion of ergonovine during coronary angiography resulted in chest pain, hypotension, bradycardia,

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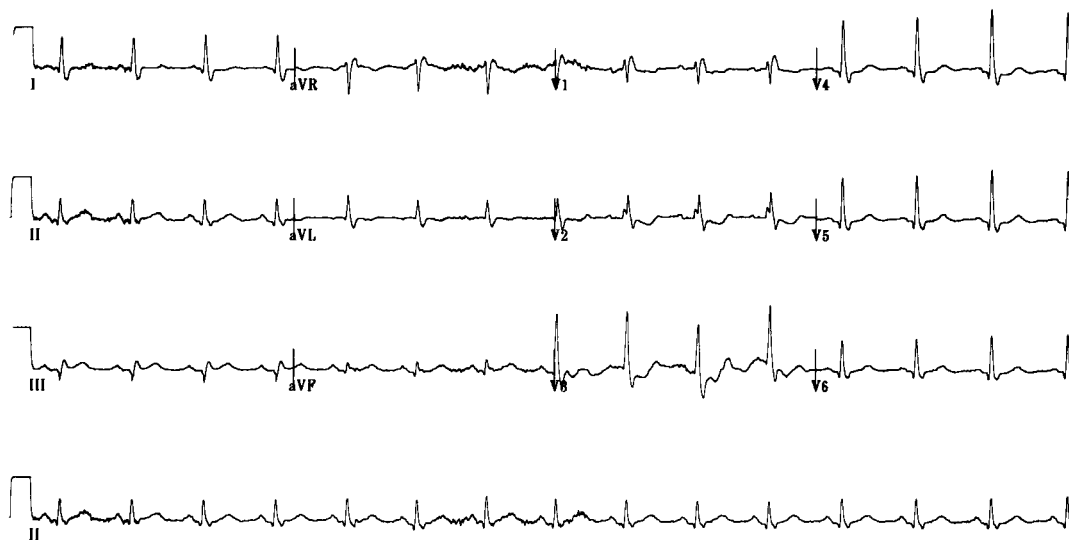


Figure 1. 12-lead surface electrocardiogram. ST segment elevation in leads II, III, aVF; depression in leads V₂, V₃ and right bundle branch block.

and identical EKG changes (ST segment elevation in leads II, III, and AVF). Total occlusion of right coronary artery during this episode was reversed with intravenous infusion of nitroglycerin. The authors concluded that his urticaria-associated episode of chest pain, hypotension, and bradycardia was the result of right coronary artery spasm, myocardial ischemia, and compromised left ventricular function.² This was probably triggered by vasoactive mediators released from

mast cells and basophils at the time of the urticarial eruption.

Hypersensitivity angiitis was associated with myocardial infarction in two reported cases. Saunders and Ford reported a 56-year-old man who developed a skin rash secondary to quinidine. About six days after stopping quinidine, he died with chest pain, hypotension, and shock. At autopsy, there was no atherosclerosis. The pathologic findings indicated that he had developed hypersensitivity myo-

carditis and angiitis of the vasa vasorum of the marginal branch of the left circumflex coronary artery at the time of the skin eruption. The proteolytic enzymes disrupted the vessel wall. Subsequent hemorrhage into the arterial wall formed a dissecting hematoma that ultimately caused total obstruction and initially asymptomatic infarction. In addition, acute arterial spasm was possibly induced by vasoactive peptides released locally by mast cells. The hematoma extended through the ventricular wall causing chest pain and subsequent death from tamponade.³

Barrett published a report of a 42-year-old woman who died within one hour of increasingly severe chest pain. Autopsy revealed complete luminal obstruction of the left coronary artery. The histologic sections showed hemorrhage into the wall of this artery with lateral compressive occlusion consistent with dissecting aneurysm. There was inflammatory infiltrate composed predominantly of eosinophils. Arteritis was not found in any other organ sections. There was no evidence of cystic medionecrosis in the coronary vessels and aorta. The author concluded that an isolated dissecting coronary artery aneurysm produced sudden death in this patient who had a long history of

Table 1. Temporal Sequence of Events

Time Period, hours	Event
0	Onset of urticaria + angioedema involving face and hands; took oral diphenhydramine.
1/2-1	Intensification of angioedema (eyelids almost completely shut); urticaria spread onto the entire body surface.
2-3	Treatment at a local hospital emergency department (ED): IV diphenhydramine, steroids, H ₂ -blocker.
7	Discharged from ED on tapering oral prednisone course.
8-12	Onset of substernal chest pain; persistent presence of urticaria and angioedema.
14	Ambulance summoned: chest pain + B.P. 220/140 In ED: acute myocardial infarction diagnosed and thrombolytic therapy administered.
12-24	Cardiac catheterization: 99% proximal right coronary artery stenosis 50% non-flow limiting stenosis of left anterior descending and circumflex coronary arteries. Percutaneous transluminal angioplasty of right coronary accomplished successfully.

allergy. The aneurysm was probably the result of hypersensitivity angitis.⁴

Forman et al described a 38-year-old man who underwent cardiac catheterization for recurrent episodes of chest pain. The coronary angiogram revealed a mild lesion (<25% narrowing) of the proximal left anterior descending coronary artery. During the procedure, he experienced chest pain with ST segment elevation in lead I. Reinjection of contrast medium into left coronary artery revealed 95% luminal narrowing in the area that previously showed slight narrowing. Several months later, he was hospitalized for anterior myocardial infarction. After about 2 months, he suffered sudden cardiac death following severe chest pain. At autopsy, the histologic sections of the left anterior descending coronary artery showed increased numbers of mast cells at the site of the previously demonstrated spasm. The number of mast cells was greater than that found in any of the control arteries from five age-matched and sex-matched subjects with coronary artery disease and sudden death and in five control subjects who died of trauma in accidents. There was no increase in mast cells in coronaries that had been free of vasoconstriction.⁵ This study suggested that atherosclerotic coronaries have increased mast cells although this is based on one case. The mast cell degranulation and vasoactive substances such as histamine derived from mast cells may play an important role in the pathogenesis of coronary spasm.

DISCUSSION

Kalsner and Richards studied coronary arteries of ten patients whose cause of death was attributed to coronary heart disease.⁶ The control group consisted of 18 patients who died from noncardiac events. The portions of coronary arteries were removed within ten hours of death. Supernatants of minced and homogenized tissue were analyzed for histamine. The concentration of histamine in coronary arteries of cardiac patients was nearly double that of the control group. The atherosclerotic segments of arteries showed significant

elevation of histamine concentrations. Ring preparations of arteries from cardiac patients responded with markedly greater contractions to histamine than did those from noncardiac patients. The authors concluded that stores of histamine are substantially increased in coronary tissue of cardiac patients suggesting a role of allergic reactions in coronary artery disease.⁶

Ginsburg et al studied 12 patients with non-exertional chest pain who were given intravenous histamine to investigate its role in coronary artery spasm. Histamine provoked coronary artery spasm in four patients. In six patients, neither histamine nor ergonovine provoked coronary spasm and subsequent workup revealed noncardiac etiologies for their chest pain. Of two ergonovine positive patients, coronary spasm was not provoked by histamine in one and was equivocally positive in another. This study indicated that histamine is capable of inducing coronary artery spasm.⁷

Recently, Ito et al studied the role of cardiac mast cells in myocardial ischemia in pigs. The left anterior descending coronary blood flow and myocardial regional function (segment shortening) was measured in 13 pigs. Intracoronary administration of complement C5a resulted in reduction in coronary blood flow and depression in regional myocardial contractile function in the left anterior descending coronary region. This was accompanied by increases in coronary venous thromboxane B2 and histamine. Lodoxamide tromethamine, a mast cell inhibitor, attenuated the C5a-induced fall in coronary blood flow and contractile function. Lodoxamide also reduced the C5a-induced increase in coronary venous thromboxane B2 and histamine. The H₁ and H₂ histamine receptor blockade had no similar effect. The conclusion from this study was that complement C5a-induced myocardial dysfunction was associated with cardiac mast cell degranulation and mediator release.⁸ Although histamine did not appear to play a role, the data indicated that C5a induced the release of cardiac mast cell vasoactive

eicosanoids, including thromboxane A2.

The mast cells are the major primary effector cell in immediate hypersensitivity reactions including urticaria and angioedema. Activation of mast cells can occur immunologically by cross-linking of Fc receptors for IgE or by less specific stimuli such as histamine releasing factors, physical stimuli (temperature or osmolarity changes), and opiate drugs. The activated mast cells release a number of mediators that cause both an immediate phase response and a more persistent state of inflammation referred to as a late phase response.⁹

Although mast cell mediators such as leukotriene C4 (LTC4) and platelet activating factors are more potent than histamine on a molar basis, histamine is more important than the other two because of its greater concentration in tissues following mast cell degranulation.

The direct vasoactive and smooth muscle spasmogenic effect of these mediators is capable of causing local vasospasm. In addition, endothelial cell swelling and interstitial edema from inflammation may cause further narrowing and a state of nearly total occlusion of the blood vessels. Mast cells are scattered throughout most solid organs and connective tissues. They have a predilection for proximity to nerves and small blood vessels.

During hypersensitivity reactions degranulation of cardiac mast cells has the potential of causing coronary vasospasm and subsequently a narrowing from inflammatory infiltrate. In our case, acute myocardial infarction was diagnosed a few hours after the onset of a severe episode of urticaria and angioedema while the patient was still symptomatic (urticaria and angioedema) despite treatment. The inciting factor to urticaria/angioedema was not identified; nevertheless, the key factor possibly was mast cell degranulation and release of vasoactive mediators including histamine. Cardiac mast cell degranulation may have occurred initially and the inflammatory infiltrate accentuated the coronary occlusion

from pre-existing atherosclerosis which then progressed to complete occlusion causing myocardial infarction. Whether he had silent ischemia between the onset of hives and the diagnosis of acute myocardial infarction is difficult to document. Early cardiac symptoms could have been masked by feeling generally unwell, having severe itching, and swelling of the face. In view of his history of coronary artery disease, it may be that his current coronary event after urticaria and angioedema was coincidental; however, consistent with several reported cases, urticaria/angioedema may have played a role. If it did not cause myocardial infarction by itself, it could have added to underlying coronary atherosclerotic disease. The patient did not experience hypotension during the entire episode, thus, excluding the possibility that decreased cardiac output from low blood pressure may have caused myocardial ischemia.

It is reasonable that in a subset of patients with urticaria or angioedema,

cardiac mast cell degranulation is triggered during the acute hypersensitivity reaction and could result in myocardial ischemia and/or infarction in those who have pre-existing coronary artery arteriosclerosis. The role of cardiac mast cell degranulation in coronary artery disease deserves further investigation.

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