

Prevention of Mast Cell Activation Disorder-Associated Clinical Sequelae of Excessive Prostaglandin D₂ Production

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Established Facts

- Spontaneous or continuous release of 1 or more mast cell-derived mediators occurs in mast cell activation disorder, a condition in which lesions of mastocytosis are not present in the bone marrow.
- Prostaglandin D₂ is produced only by mast cells and not by basophils.

Novel Insights

- Symptoms from mast cell degranulation may be accompanied exclusively by excessive release of prostaglandin D₂, but not histamine, in some patients with mast cell activation disorder.
- Aspirin therapy is successful at preventing symptoms in these patients, whereas treatment with only antihistamines is generally ineffective.

Key Words

Mast cell activation • Mastocytosis • Prostaglandin D₂

Abstract

Background: Patients with systemic mastocytosis have increased numbers of mast cells in the bone marrow and other organs, such as the liver, spleen, gastrointestinal tract and skin. Symptoms result from the local and remote effects of mediator release from mast cells and from the local effects of increased mast cell numbers in various organs. Patients with mast cell activation experience many of the same clinical symptoms as do patients with systemic mastocytosis from chronic or spontaneous release of mast cell mediators.

We report 4 patients with mast cell activation symptoms from selective release of prostaglandin (PG) D₂, but not histamine, and their improvement with aspirin therapy. **Methods:** Bone marrow biopsy specimens obtained from 4 patients with symptoms suggestive of mastocytosis were examined by tryptase immunostaining. Baseline levels of serum tryptase and urinary 11 β -PGF_{2 α} and N-methylhistamine were obtained. In 2 of the 4 patients, urinary 11 β -PGF_{2 α} and N-methylhistamine samples were also measured during acute symptoms. **Results:** Baseline increase in urinary excretion of the PGD₂ metabolite 11 β -PGF_{2 α} was found in 2 patients. In the remaining 2 patients, baseline levels of urinary 11 β -PGF_{2 α} and N-methylhistamine were normal, but during acute symptoms, the excretion of 11 β -PGF_{2 α} increased mark-

edly. Treatment with aspirin resulted in normalization of 11β -PGF_{2α} excretion in the 2 patients with elevated baseline levels and in prevention of symptoms in all 4 patients. **Conclusions:** These results suggest that mast cell activation may be manifested by a selective excessive release of PGD₂. These patients respond to administration of aspirin but not to antihistamines.

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Introduction

Mast cell activation, the spontaneous release of mast cell-derived mediators in the absence of excessive mast cell proliferation, results in chronic or episodic clinical symptoms that may be indistinguishable from those of systemic mastocytosis (SM). This constellation of symptoms, including flushing, palpitations, light-headedness, syncope, dyspnea, chest pain, nausea, vomiting, diarrhea, pruritus, paresthesias, chronic fatigue and central nervous system dysfunction, has been termed 'mast cell activation disorder' (MCAD) [1]. In addition to SM, conditions that mimic MCAD include exercise-induced anaphylaxis, postprandial exercise-induced anaphylaxis, idiopathic anaphylaxis and anaphylactoid attacks.

Exercise-induced anaphylaxis [2], a syndrome characterized by cutaneous pruritus, generalized urticaria, collapse, gastrointestinal tract symptoms and upper respiratory distress, has been differentiated from MCAD chiefly by the absence of urticaria and wheezing in MCAD [1]. Morphologic examination of cutaneous mast cells in exercise-induced anaphylaxis patients has shown evidence for degranulation [3]. Elevations in plasma histamine levels have been reported in patients with exercise-related hypotension but not in patients with only cutaneous or subcutaneous manifestations. Complement levels have been normal in all cases reported [4].

Postprandial exercise-induced anaphylaxis [5] has been attributed to a shift of blood flow to the splanchnic and skeletal muscle vasculature. Both normal [5] and elevated [6] levels of histamine have been reported following postprandial exercise-induced anaphylaxis. These patients differ from those with idiopathic anaphylaxis, in whom exercise is not a causal factor, and from patients with exercise-induced asthma, in whom asthma is the sole symptom [5].

Idiopathic anaphylaxis, a syndrome with symptoms of upper airway obstruction, bronchospasm, hypotension, collapse, gastrointestinal tract symptoms and flushing [7], has no identifiable triggers [8]. Prophylactic treat-

ment with prednisone and H₁ antihistamines has been reported to improve the clinical outcome in patients with frequent episodes of idiopathic anaphylaxis [9].

The paucity of reported cases of mast cell degranulation prompted this retrospective review of the clinical histories and laboratory findings from 4 patients with symptoms associated with excessive prostaglandin (PG) D₂ release, normal N-methylhistamine excretion and no bone marrow evidence of SM. These PG-producing patients likely represent a disorder of mast cell activation. This study was approved by the Mayo Clinic Institutional Review Board.

Case Reports

Patient 1

A 39-year-old woman was referred for 2 attacks of generalized pruritus, hives, flushing, vomiting, irregular breathing, hypotension, presyncope and a sensation of throat swelling. During 1 of these episodes, she had additional symptoms of abdominal cramps and diarrhea. Triggers for her symptoms were not identified. Following her first episode, she started with desloratadine 5 mg/day and was given an EpiPen for future use; however, her symptoms occurred so rapidly on the second occasion that she had no opportunity to use the EpiPen. Known clinical sensitivities included strawberries (pruritus, dermatitis), cat (rhinoconjunctivitis) and metals (contact sensitivity). There was no history of weight loss, spinal or rib pain, bone fractures, alcohol intolerance or aspirin idiosyncrasy. Past medical history was remarkable for a 1-year history of night sweats and a recent diagnosis of adult-onset diabetes mellitus, for which she was given glipizide twice daily. Physical examination at our clinic was unremarkable. There were no skin lesions of urticaria pigmentosa. Normal laboratory studies included skin tests to foods and specific IgE serology to molds, dust mites, orange and strawberry. The patient continued with desloratadine 5 mg/day. Mast cell mediator quantitation on blood and urine samples that were obtained following her next attack revealed increases in both the serum tryptase level and the 11β -PGF_{2α} excretion but normal excretion of N-methylhistamine (table 1). Bone marrow biopsy was negative for changes of mastocytosis. The patient was dismissed home on a program of desloratadine 5 mg/day and, additionally, aspirin 325 mg/day. Thereafter, her urinary excretion of 11β -PGF_{2α} was normal, and she has remained free of symptoms.

Patient 2

When first evaluated 5 years previously, this patient reported a constellation of symptoms, including food (soybeans, peanuts and shellfish), exertion and antibiotic-induced urticaria and angioedema. The previous year he had experienced an episode of encephalitis as well as several episodes of bronchitis. Gastrointestinal biopsies and the peripheral eosinophil count were normal. Treatment had included cetirizine, ranitidine, rabeprazole sodium, montelukast and 'as needed' use of an EpiPen for his attacks. Physical examination at the time of his evaluation at our clinic was unremarkable. Laboratory evaluation for immunodeficiency

Table 1. Laboratory test results

	Serum tryptase ng/ml (<11.5)	Calcitonin ng/l (0–7.9)	Urinary 11 β -PGF _{2α} ng/24 h ($\leq$ 1,000)	Urinary N-methylhistamine μ g/g Cr (30–200)
Patient 1				
Baseline	2.48	8.3	899	107
During symptoms	30.6	8.4	4,770	74
With aspirin 325 mg/day			294	76
Patient 2				
Baseline	6.63	<3	2,907	140
With aspirin 243–325 mg b.i.d. ¹	15.1	<5	128	80
Patient 3				
Baseline	5.21	8.7	78	91
During symptoms	15.5	<3	3,397	203
With aspirin 325 mg b.i.d.	3.93	<3	620	97
Patient 4				
Baseline	4.39	<3	1,706	149
With aspirin 325 mg b.i.d.	9.92		1,393	135
With aspirin 975 mg b.i.d.			452	120
	Hemoglobin g/l (135–177)	Eosinophils $\times 10^9/l$ (0.05–0.5)	Leukocytes $\times 10^9/l$ (3.5–10.5)	Lymphocytes $\times 10^9/l$ (0.9–2.9)
Patient 1				
Baseline	131	0.34	10.9	4.1
During symptoms				
With aspirin 325 mg/day				
Patient 2				
Baseline	124	0.18	5.1	1.68
With aspirin 243–325 mg b.i.d. ¹				
Patient 3				
Baseline	129	0.06	4.8	1.1
During symptoms				
With aspirin 325 mg b.i.d.				
Patient 4				
Baseline	144	0.1	5.4	1.67
With aspirin 325 mg b.i.d.				
With aspirin 975 mg b.i.d.				
Figures in parentheses indicate reference ranges. Cr = Creatinine.				
¹ Values are representative.				

was normal; however, the excretion of 11 β -PGF_{2 α} was markedly increased (table 1). Specific IgE serology tests were positive to numerous foods, with the strongest reactions to barley, wheat, peanut and string bean and milder reactions to fish and shellfish, all of which he continued to avoid.

The patient began with aspirin 162 mg twice daily and had a dramatic improvement in the number and severity of attacks. He was able to resume vigorous exercise and sports activities. The urinary 11 β -PGF_{2 α} excretion decreased to the normal range. Thereafter, he did well for several years on a program of aspirin 81 mg 3 or 4 tablets twice daily, doxepin 30–50 mg at bedtime, rabeprazole sodium 10 mg/day, ranitidine 150 mg twice daily, loratadine 10 mg/day and montelukast 10 mg/day. The serum trypt-

ase level was first found to be mildly elevated 20 months after his initial presentation and thereafter ranged from 12.4 to 19.3 ng/ml (normal <11.5 ng/ml). He subsequently developed iron-deficiency anemia and was found to have gastritis and 3 fundal ulcers containing eosinophils. Ferrous sulfate 325 mg twice daily was begun, and ranitidine was increased to 300 mg twice daily. Forty-four months after his initial presentation, he developed eosinophilia ($2.144 \times 10^9/l$). Evaluation for secondary causes of eosinophilia was normal, and a bone marrow biopsy was negative for leukemia, lymphoma and mastocytosis. CHIC2 deletion analysis was negative. Treatment was begun with prednisone 40 mg/day, with an excellent eosinopenic response, and further tapering was successful. He remained free of his initial symptoms.

Patient 3

A 51-year-old man was seen for attacks of gastrointestinal tract cramps, diarrhea, pruritus, flushing and angioedema. On 3 occasions, he had experienced hypotension and loss of consciousness, and on 1 occasion, he had experienced hypertension. There was never any associated dyspnea or swelling of the tongue or throat. Between attacks he felt well. He had no history of food allergy. A trial of cetirizine 10 mg/day after his second attack did not prevent his attacks. Medications included aspirin 325 mg/day and valsartan for cardiovascular disease. Physical examination at our clinic was within normal limits. Baseline urinary levels of 11β -PGF_{2α} and N-methylhistamine were normal (table 1). Bone marrow biopsy was negative for lesions of mastocytosis. Radioallergosorbent tests to common inhalants, pollens and molds were negative. He began with famotidine with no change in his symptoms. Subsequently, a urine sample obtained during one of his spells showed a marked elevation in the urinary level of 11β -PGF_{2α} at a time when the urinary N-methylhistamine was only marginally increased (table 1). The patient's dose of aspirin was increased to 325 mg twice daily while famotidine 10 mg/day and cetirizine 10 mg/day were continued. A follow-up measurement of the urinary level of 11β -PGF_{2α} excretion was normal (table 1), and he had only 1 mild attack during the next 24 months.

Patient 4

A nonatopic 30-year-old man was referred for an 18-month history of attacks consisting of abdominal cramps and diarrhea, periorbital swelling, a sensation of throat swelling, generalized pruritus and flushing. Treatment consisted of immediate intramuscular epinephrine and oral diphenhydramine with subsequent emergency department therapy consisting of additional diphenhydramine, ranitidine and corticosteroids administered intravenously and orally. He was taking stable doses of escitalopram oxalate and bupropion for depression and obsessive compulsive disorder, respectively. Drug intolerances included aspirin and ibuprofen, which had induced periorbital swelling. Skin tests elsewhere had been negative for inhalant allergies. Physical examination was remarkable only for exogenous obesity. Bone marrow aspirate and biopsy revealed no morphologic or immunophenotypic features of mast cell disease. Although the N-methylhistamine excretion was normal, his baseline excretion of 11β -PGF_{2α} was elevated. Because of his prior history of aspirin intolerance, his aspirin dose was cautiously increased, beginning with 0.1 mg and increasing in a stepwise fashion until a dose of 325 mg had been administered. The dose of aspirin was thereafter adjusted upward until the excretion of 11β -PGF_{2α} returned to normal. This was associated with cessation of his attacks despite subsequent discontinuation of all antihistamines.

Discussion

MCAD has been proposed as a clinical entity distinct from idiopathic anaphylaxis [1]. The general term 'anaphylaxis' can be applied to the sudden onset of life-threatening symptoms due to the IgE-mediated release of mast cell and basophil mediators. The triggering factor can be identified in certain patients. One epidemiologic study in

which 154 episodes of anaphylaxis were examined retrospectively identified a suspected allergen in nearly 70% of the episodes, most often a food, medication or insect sting [10]. Anaphylactoid reactions, such as the response to radiocontrast medium, which mimic the symptoms of anaphylaxis, can result from mast cell and/or basophil degranulation caused by non-IgE-mediated stimulation [11]. In the case of radiocontrast medium, a variety of biologic effects, in addition to complement activation, have been documented in vivo and in vitro that may contribute to symptoms of the anaphylactoid response. Examples of these effects include serotonin release from platelets and platelet aggregation [12], disseminated intravascular coagulation [13, 14], increased airway resistance [15, 16] and inactivation of enzyme systems [17, 18].

Serum tryptase values have been elevated in samples taken between 1 and 4 h after the precipitating event in 6 of 6 patients seen for anaphylaxis to various triggers [19]. Prolonged elevation of tryptase levels has been reported in a case of protracted anaphylaxis [20]. Simultaneous measurements of other mast cell-derived mediators and parallel analysis of bone marrow biopsies for the presence of SM were not done in these studies. Biphasic systemic anaphylaxis, in which symptoms recur 1 to several hours after the initial onset, has been reported [21]. Delayed symptoms did not occur in any of our patients.

Idiopathic anaphylaxis, as implied by the term, has no identifiable precipitant. In a cohort of 175 patients with idiopathic anaphylaxis reported in 1990, the most common symptoms were urticaria or angioedema (100%), upper airway obstruction (62%), bronchospasm (31%), syncope (24%), hypotension (25%), gastrointestinal tract symptoms (17%) and flushing (16%) [22]. Idiopathic anaphylaxis may also occur in a pediatric population, with symptoms and severity similar to that in adults [23], and recurrent anaphylaxis has been a presenting feature in some cases of pediatric mastocytosis [24].

On the basis of our experience with these cases, release of PGD₂ can occur independently of histamine as reflected in the disparate urinary levels of their metabolites. It is possible that excessive release of PGD₂ could be a sign of early mastocytosis before characteristic lesions appear in the bone marrow. No morphologic evidence of SM was present in any patient marrow examined, and testing for CD2 and CD25 markers was negative.

For patients with acute allergic reactions, the finding of normal tryptase values along with elevated plasma histamine levels suggests that basophils may contribute to the reactions [25]. However, in our cases, the elevated uri-

nary excretion of 11β -PGF_{2 α} , a metabolite of PGD₂, can be ascribed solely to mast cell degranulation because PGD₂ is not produced by basophils [26]. Baseline tryptase levels were normal in all of our patients and increased markedly in 2 patients concomitantly at times of dramatic increases in PGD₂ release. Infusion of PGD₂ at rates of 16–128 ng/kg/min into normal volunteers causes intense facial flushing and nasal congestion [27]. Histamine appears to be much more potent than PGD₂ or the PGD₂ metabolite $9\alpha,11\beta$ -PGF₂ in the elicitation of wheal-and-flare responses in normal skin [28, 29], where the effect of PGD₂ and its metabolite is primarily the enhancement of vasodilation but not vasopermeability.

PGD₂ has been detected in several clinical conditions associated with mast cell degranulation or increased mast cell numbers, and measurement of the excretion of PGD₂ metabolites has been suggested as a method to monitor mast cell activation [30]. Inhaled PGD₂ is a more potent bronchoconstrictor than histamine in both atopic non-asthmatic subjects and in normal subjects [28]. Patients with localized cold [31] or heat [32] urticaria release PGD₂ into the venous effluent draining the challenge site. SM patients experiencing flushing, hypotension, tachycardia, dizziness, syncope, dyspnea, headache, diarrhea, nausea and vomiting have been found to produce in-

creased amounts of both histamine and PGD₂ [33], and massive increases in both plasma and urinary $9\alpha,11\beta$ -PGF₂ levels have been documented during mast cell activation in SM [34]. Similar to our patients, addition of aspirin to therapeutic programs afforded a favorable clinical response when antihistamines alone had failed to completely control symptoms [33]. Aspirin has also been useful as a prophylactic agent for other reported patients with shock syndrome associated with PGD₂ overproduction in SM [35]. The mediator profiles of the patients reported here suggest that in certain circumstances, mast cells may selectively release PGD₂ but not histamine and that this release is associated with symptoms that subsequently can be controlled by addition of aspirin to a program of antihistamines and other agents that have proven ineffective.

In summary, the clinical histories and laboratory findings in 4 patients with symptoms from the selective release of PGD₂ are presented. In none of the patients was evidence for marked histamine release found, and treatment with antihistamines was ineffective at preventing symptoms. There was no morphologic evidence for SM in bone marrow biopsies. Patients' symptoms responded well to long-term therapy with aspirin at doses between 325 mg/day and 975 mg twice daily.

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