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Clonal Mast Cell Activation Syndrome with Anaphylaxis to Sulfites

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Established Facts

- Already known fact 1: occurrence of anaphylaxis in patients with systemic mastocytosis is a well-known complication.
- Already known fact 2: monoclonal mast cell activation syndrome (MCAS) has been associated with Hymenoptera-induced, drug-induced, food-induced or idiopathic anaphylaxis.

Novel Insights

- In addition to Hymenoptera-induced, drug-induced, food-induced or idiopathic anaphylaxis, sulfite-induced anaphylaxis may occur in patients with monoclonal MCAS or mastocytosis.

Key Words
Sulfites · Mast cell activation syndrome · Systemic mastocytosis · Anaphylaxis

Abstract
Sulfites are rarely suspected as causative agents of immediate-type hypersensitivity. We report on a 49-year-old male patient who developed recurrent severe hypotension after food ingestion. A diagnosis of monoclonal mast cell activation syndrome was established. In the double-blind, placebo-controlled food challenge, the patient reacted to potassium metabisulfite with anaphylaxis.

Introduction

Mastocytosis is a disorder characterized by abnormal accumulation of mast cells (MCs) in one or more organs. Occurrence of anaphylaxis in patients with systemic mastocytosis (SM) is a well-known complication [1]. Recently, the diagnosis in patients with mast-cell mediator-induced symptoms who only fulfill one or two minor SM criteria has been termed monoclonal mast cell activation syndrome (MCAS) [2, 3–5]. Sulfites are rarely suspected as causative agents of immediate-type hypersensitivity. We report on a 49-year-old male patient with severe hypotensive episodes in close temporal relationship to food

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ingestion. In the double-blind, placebo-controlled food challenge, the patient reacted to potassium metabisulfite with severe anaphylaxis.

Case Report

A 49-year-old male attended our mastocytosis outpatient clinic with a 4-year history of multiple recurrent episodes of severe hypotension and syncope following flushing, dizziness, tachycardia and palpitations. Reactions occurred within 30 min of the ingestion of food. On three different occasions, unconsciousness had developed after the ingestion of canned fish, onions, bread, orange juice or pasta with ketchup, bread and cheese or tuna, salad, olives and tomatoes taken together with red wine. The episodes required emergency department visits, where he received corticosteroids and antihistamines. The patient's medical history could not identify specific foods or elicitors other than being compatible with sulfite hypersensitivity. Seasonal allergic rhinitis was confirmed by sensitizations to grass pollen but not to relevant foods in skin tests or by identification of specific IgEs. Physical and dermatological examination showed no skin lesions typical for cutaneous mastocytosis. A skin biopsy of an unspecific hyperpigmented macula on the thigh showed a slight but not diagnostic increase in the number of MCs. Basal total serum tryptase level (Pharmacia UniCAP System; Phadia, Freiburg, Germany) was in the normal range (9.1–11.0 ng/ml) without a significant change over the observation period. A diagnosis of SM was suspected. Examination of the bone marrow and gastroendoscopic and colonoscopic biopsies revealed an increase of MCs but no compact MC infiltrates. The cytomorphology of MCs in bone marrow smears did not show any pathological changes. Urinary N-methylhistamine was 15.78 μg/mmol creatinine/m^2 body surface (<6.5 μg/mmol creatinine/m^2 body surface). In the bone marrow, but not in the skin, the presence of the Asp816Val KIT mutation, typical for mastocytosis, was demonstrated by laser capture microdissection of MCs followed by peptide nucleic acid-mediated PCR. The immunophenotypic study of the bone marrow biopsy revealed a low number of MCs (≤1%) and an expression of CD25 in KIT-positive bone marrow MCs. Osteoporosis was diagnosed by osteodensitometry. In the following allergological workup, placebo-controlled oral provocations were performed. Acetyl salicylic acid, histamine, ethanol, codein, paracetamol and other food additives were tolerated, but 15 min after oral administration of 300 mg potassium metabisulfite (equivalent to less than a maximum level of sulfites in wines), the patient developed flush, nausea and dizziness followed by tachycardia and a drop in blood pressure to an unmeasurable value. Immediate Trendelenburg positioning and therapy with antihistamines and corticosteroids stabilized the symptoms. Epinephrine was not given. Serum tryptase levels taken before and 2 h and 24 h after oral challenge with potassium metabisulfite increased 2 h after oral challenge from 9.06 to 37.5 ng/ml, but normalized 24 h after this reaction. The patient was instructed to follow a sulfite-free diet and a continuous daily treatment with cromoglicic acid 200 mg (1-1-1-1), fexofenadine 180 mg (1-0-1), dimetindene (2-2-2) and ranitidine hydrochloride 150 mg (1-1-1). Alendronate sodium was prescribed in a weekly schedule for treating the osteoporosis. The patient was prescribed an epinephrine autoinjector to be applied in the event of cardiovascular or respiratory reactions. No further episodes occurred for 2 years. For the following 3 years, the patient experienced occasional episodes, either triggered by inadvertent sulfite exposures or by other unknown cofactors.

Discussion

In patients with anaphylaxis and high tryptase levels, SM has to be excluded and an allergological workup is necessary. In our patient, the diagnosis of MCAS was made based on demonstration of CD 25-positive MCs carrying the Asp816Val mutation in c-kit, the gene for the main MC growth factor receptor kit and on the absence of further major (MC aggregates) or minor (abnormal morphology of MCs, tryptase value >20 ng/ml) SM criteria. MCAS has been reported to be associated with Hymenoptera-induced, drug-induced, food-induced or idiopathic anaphylaxis [6–8]. For our patient, a double-blind, placebo-controlled food challenge and his history demonstrated that potassium metabisulfite was an elicitor of anaphylaxis. Sulfites are preservatives E221–E227 used in wine, vinegar, dried fruits and vegetables, jam and marmalade, potato dishes and spices. Potassium metabisulfite sensitivity is exceedingly rare in the general population. Sulfites have been reported to precipitate attacks in 3–10% of subjects with bronchial asthma [9]. However, of 8 patients with SM and 25 with unexplained anaphylaxis, a sodium bisulfite challenge up to a dose of 200 mg was tolerated in all but 1 asthmatic patient in the unexplained-anaphylaxis group, who developed a drop in FEV_1. In this study, only 11 patients with unexplained anaphylaxis and none with mastocytosis had histories of anaphylactic episodes in a close temporal relationship to food ingestion [10]. Patients with mastocytosis, however, do not uncommonly self-report anaphylaxis after ingestion of alcohol or food, which could also be caused by the sulfites contained in these products [1]. In the majority of patients with immediate reactions to sulfites, IgE-mediated allergy has not been demonstrated. The release of histamine and other mediators as a consequence of MC degranulation through non-IgE-mediated mechanisms has been suggested, but these mechanisms remain unknown.

Anaphylaxis to sulfites, as first described in our patient, thus appears to be exceptional, but may be associated with MCAS. As we report the case of only 1 patient and as reprovocation is unethical, the possibility exists that the clinical reaction in the double-blind, placebo-controlled food challenge could be attributed to a coincidential spontaneous anaphylaxis. However, the history and improvement after a change of diet argue against this

possibility. It also may be argued that patients with a history that is compatible with MCAS or SM should be put on a sulfite-free diet without challenge, due to the risk involved. However, the diagnosis of sulfite hypersensitivity based on the history alone is not sufficient and as this is the first case described in this patient group, the hypersensitivity should be confirmed in future patients by means of challenge. In conclusion, this case illustrates that sulfites have to be excluded as an elicitor of anaphylaxis in patients with MCAS or mastocytosis, if the history is compatible.

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