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Unusual presentation of more common disease/injury

Salicylate intolerance: a masquerader of multiple adverse drug reactions

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Abstract

A female in her early 50s presented with a long-standing history of episodic urticaria and angioedema. She also reported urticarial reactions after ingestion of aspirin, prednisone and multiple antibiotics. These medications were all taken during upper respiratory tract infections. An elimination diet followed by a series of open challenges to food chemicals demonstrated an urticarial eruption following the ingestion of mints, which contain high levels of salicylates. A double-blinded placebo-controlled challenge to salicylate confirmed her sensitivity and explained her reaction to aspirin. The patient informed her treating physician of her copious ingestion of mints during upper respiratory tract infections. Drug hypersensitivity to antibiotics and prednisone was excluded on the basis of negative radioallergosorbent tests (RASTs) and/or absent skin-test responses and/or tolerance to oral challenges. This patient had a salicylate intolerance that caused her episodic urticaria and angioedema, and also masqueraded as a drug allergy due to the concurrent ingestion of mints.

BACKGROUND

This case highlights the importance of the systematic evaluation of a patient in order to elucidate the causative agent and also to exclude confounding factors. Similar approaches in other patients may also prevent the unnecessary restriction of medications. A methodical evaluation begins with a thorough history that may have elicited the concurrent copious ingestion of mints on each of the occasions that a drug was deemed responsible for the patient's symptoms.

CASE PRESENTATION

A 51-year-old female presented with a 15-year history of episodic urticaria and angioedema that resulted in numerous presentations to the emergency department. She reported that in her late

30s she developed adverse reactions to aspirin, penicillin, cephalexin, erythromycin and prednisone characterised by urticaria and angioedema. Her reaction to aspirin also involved throat constriction. These medications were all prescribed on various occasions for the treatment of upper respiratory tract infections. More recently, she developed urticaria and angioedema accompanied by throat constriction following ingestion of ibuprofen taken for the relief of arthralgia. There were no readily identifiable food precipitants for her episodes at her initial assessment by an allergist. There was no history of atopic disease. She was taking no regular medication or complementary therapy. She was a heavy smoker with an 80-pack year history. She was a housewife and mother of six children.

INVESTIGATIONS

Laboratory investigations revealed a normal full blood count and thyroid stimulating hormone level. Antithyroid peroxidase and antinuclear antibodies were not detected and serology for hepatitis B and hepatitis C was normal. The patient was also evaluated for IgE-mediated and non-IgE-mediated food sensitivity. Skin-prick testing to foods, recorded by the patient as having been ingested prior to her urticarial eruptions, were negative. She was then placed on a diet devoid of food chemicals such as salicylates, monosodium glutamate, nitrites, sulphites, amines and benzoate, and subsequently challenged to foods containing these chemicals ([table 1](#)). The patient developed an urticarial reaction following the ingestion of mints, a sweet that contains a high level of salicylates. A double-blinded placebo controlled challenge to sodium salicylate resulted in an identical reaction and explained her reaction to aspirin. She disclosed retrospectively that she always ingested copious amounts of mints during an upper respiratory tract infection. The patient was then investigated for drug hypersensitivity to antibiotics and prednisone in a stepwise fashion. Her radioallergosorbent tests (RASTs) to penicillin, amoxicillin and ampicillin were negative. No responses were detected following skin-prick and intradermal testing to benzylpenicillin, ampicillin, cephalothin and cephalexin. No adverse reaction was observed following incremental oral challenges to amoxicillin, cephalexin, roxithromycin and prednisone. A salicylate-restricted diet resulted in abrogation of her urticarial episodes confirming its causative role. Hence, her salicylate sensitivity was masquerading as adverse reactions to a number of drugs.

DIFFERENTIAL DIAGNOSIS

Chronic idiopathic urticaria and angioedema. Multiple antibiotic and drug sensitivity.

TREATMENT

An anaphylaxis action plan was formulated until the patient's investigations were completed. She was advised to take a non-sedating antihistamine for any cutaneous reaction and administer her adrenaline autoinjector for a severe reaction characterised by cardiorespiratory symptoms. Following her diagnosis of salicylate intolerance, the patient was placed on a salicylate-restricted diet. The use of aspirin and non-steroidal anti-inflammatory drugs was prohibited and a MedicAlert bracelet was fashioned, stipulating sensitivity to these medications. She was permitted to take penicillins, cephalosporins, macrolides and prednisone.

OUTCOME AND FOLLOW-UP

The patient has had no episodes of urticaria, angioedema or anaphylaxis after 18 months of a salicylate-restricted diet. She has had courses of penicillin without any adverse reaction.

DISCUSSION

This is the first case that we are aware of a confirmed food intolerance masquerading as multiple drug allergies. The patient's diagnosis could only be confirmed after double-blinded placebo-controlled food challenges to food chemicals and RAST, skin-test and oral challenges to various drugs were performed. Although, urticaria and anaphylaxis are the main clinical manifestations of an IgE-mediated β lactam allergy,¹ further evaluation and confirmation with in vitro and/or in vivo testing is prudent in to avoid unnecessary restriction of these antibiotics.² Various other factors or cofactors such as viral infections (eg, Epstein–Barr virus, cytomegalovirus, HIV), preexisting disease (eg, autoimmune diseases), host factors (eg, genetic variation, differences in drug metabolism) may be primarily responsible and these factors do not necessarily preclude future use of the culprit drug.^{3,4} Furthermore, in many patients, the history of drug allergy is ill-defined or poorly recalled.

Aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) can induce or exacerbate cutaneous eruptions in 20% of patients with chronic urticaria.⁵ This form of urticaria, known as aspirin-induced urticaria is related to inhibition of COX-1 and is typified by cross-reactivity with NSAIDs.⁶ Urticarial and angioedema typically occur 1–4 h following ingestion of aspirin and in severe cases can cause glottic and lingual oedema resulting in throat constriction.⁷ In a small number of cases, urticaria and angioedema are mediated by anti-aspirin IgE antibodies and there is an absence of cross-reactivity with other NSAIDs.⁸ COX-1 is necessary for the synthesis of prostaglandin E₂, which in turn inhibits 5-lipoxygenase, an enzyme responsible for leukotriene production that mediates mast cell degranulation and release of histamine and cytokines. COX-1 inhibition by aspirin therefore results in excessive lipoxygenase activity and release of mast cell mediators.⁹ Salicylates are found in plant-derived foods in quantities that vary in different fruits, vegetables, herbs and spices, teas, plant-based confectionaries and honeys.¹⁰ Many studies have reported that up to 75% of individuals with aspirin-induced urticaria respond to dietary restriction of salicylates.^{11–13} Desensitisation therapy involving the incremental administration of aspirin until a therapeutic dose is reached has proved successful in treating COX-1-mediated asthma and urticaria,¹⁴ as well as IgE-mediated urticaria and anaphylaxis. It is not proven effective in ameliorating aspirin-exacerbated chronic urticaria and hence was therefore not a feasible option for our patient.¹⁴ The prognosis of the aspirin-induced urticaria is unknown but rechallenge to salicylates at 12 months following the implementation of a restricted diet demonstrates persistent reactivity.¹⁵

This case highlights that food intolerance may need to be considered as a confounding factor in a patient with a history of adverse reactions to multiple drugs, especially if they also experience similar reactions in the absence of an obvious precipitant.

LEARNING POINTS

- Adverse reactions to medication warrants careful evaluation, which may include skin testing and incremental oral challenges to avoid unnecessary drug restriction.

- A careful dietary history including ingestion of food chemicals such as salicylates may aid in the identification of the triggers involved in episodic urticaria and angioedema.
- IgE-mediated reactions to foods are confirmed with skin-prick testing whereas double-blinded placebo-controlled food challenges are required to ascertain non-IgE-mediated intolerances to food chemicals.
- Sensitivity to aspirin, which can manifest as urticaria and angioedema, can be observed following the ingestion of salicylate-containing foods.
- Dietary restriction of salicylates may reduce or ameliorate cutaneous eruptions in aspirin-induced urticaria but aspirin desensitisation is an ineffective strategy.

Footnotes

Competing interests: none.

Patient consent: Patient/guardian consent was obtained for publication.

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Figures and Tables

Table 1

The order of dietary challenges performed and the reaction observed

Food ingested	Chemical tested	Reaction observed
Lemonade	Sodium benzoate	None
Citric acid	Metabisulphite 80 mg, nitrites	None
Dark chocolate	β phenylethylamine	None
Tuna	Sodium/potassium natural amine	None
Banana	Sodium/potassium natural amine	None
Capsules	Monosodium glutamate 2.5 g	None
Ham	Nitrite	None
Mint	Salicylate	Urticaria and angioedema
Capsule	Calcium carbonate 200 mg	None
Capsule	Sodium salicylate 300 mg	Urticaria and angioedema

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