Food-induced skin rashes beyond allergy: diagnostic challenges in histamine intolerance and mastocytosis

NIEALERGICZNE WYSYPKI SKÓRNE PO SPOŻYCIU POKARMÓW: WYZWANIA DIAGNOSTYCZNE W NIETOLERANCJI HISTAMINY I MASTOCYTOZIE

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Streszczenie

Obecnie częstość występowania zgłaszanych przez pacjentów alergii pokarmowych rośnie. Objawy skórne związane z przyjmowaniem pokarmów, takie jak świąd i wysypka, są często interpretowane jako przejaw alergii pokarmowej. Jednak inne schorzenia, takie jak nietolerancja histaminy, nietolerancja laktozy, atopowe zapalenie skóry, przewlekła pokrzywka czy mastocytoza, również mogą być przyczyną wymienionych wyżej objawów klinicznych. W niniejszej publikacji przedstawiono wyjątkowy przypadek kliniczny, w którym współwystępowanie nietolerancji histaminy i mastocytozy skórnej skutkowało wystąpieniem objawów skórnych wywołanych przez pokarmy.

Słowa kluczowe: alergia, alergia pokarmowa, jagoda, doustna próba prowokacji

Summary

Currently, the prevalence of self-reported food allergies is increasing. Food-related skin symptoms such as pruritus and rash are often attributed to food allergy. However, other conditions such as histamine intolerance, lactose intolerance, atopic dermatitis, chronic urticaria, or mastocytosis may also present with similar symptoms. This report presents a rare clinical case involving the coexistence of histamine intolerance and cutaneous mastocytosis, which resulted in food-triggered skin manifestations.

Key words: allergy, food allergy, blueberry, oral food challenge

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Introduction

The most common question that patients ask clinicians is: “What did I eat that provoked the symptoms?“ or “Which products should I avoid in the future?“. Currently, up to 20% of adults have reported experiencing adverse reactions to food. However, the prevalence of food allergy is estimated only up to 10% [1]. Skin symptoms are the most common manifestation of food allergies [2]. They include urticaria, pruritis, flushing and angioedema. Those signs usually resolve within minutes and up to two hours after their onset Ocular involvement (eye redness, lacrimation, itching), respiratory involvement (rhinorrhea, nasal congestion, coughing, wheezing), gastrointestinal symptoms (nausea, vomiting, abdominal pain, diarrhea), neurological and cardiovascular involvement (severe presentation) can rarely be seen in patients with food allergies. When it comes to food-related symptoms, the first thing that comes to mind is a true food allergy (IgE-mediated). However, adverse food reactions can be divided into immune-mediated and non-immune-mediated (or food intolerances) [3]. Food intolerances are non-allergic adverse reactions to food that can manifest with similar cutaneous, gastrointestinal, respiratory, or cardiovascular symptoms as food allergies. It is important to mention that both food allergies and food intolerances can range from mild discomfort to life-threatening reactions (e.g., anaphylaxis) [4]. In non-immune-mediated reactions, there is a delay in symptom onset, negative allergen-specific IgE (sIgE) serology (unlike in true food allergy), and the most common clinical presentations are chronic urticaria or angioedema [5]. True food allergy is diagnosed based on the patient's clinical history, allergen-specific IgE (sIgE) serology, or skin prick testing (SPT), as well as a supervised oral food challenge if the risk of reaction is moderate [1]. When food-related symptoms are present but allergy tests are negative, it is important to consider non–immune-mediated adverse food reactions and other conditions that cause histamine release (e.g., mastocytosis, mast cell activation syndrome) [6]. Histamine is a biogenic amine [2-(4-imidazolyl)-ethylamine] that binds to the specific H1, H2, H3 and H4 receptors and activate different signaling pathways [7]. Histamine mediates vasodilation, inflammatory responses, gastric acid secretion, bronchospasm, and both secretion and congestion in the respiratory system [8]. However, histamine receptors can be activated by histamine released from mast cells or basophils (endogenous), as well as by ingested histamine (exogenous). It is important to understand the underlying pathomechanisms and to differentiate histamine intolerance from other conditions associated with endogenous histamine release, such as chronic urticaria, mastocytosis, allergic and non-allergic asthma, rhinitis, and anaphylaxis [6].

The purpose of this paper is to describe a rare case of histamine intolerance occurring alongside with cutaneous mastocytosis in a patient who presented with food-induced maculopapular eruptions and urticaria.

Case description

In December 2024, a 59-year-old woman visited an allergist due to a one-year history of recurrent maculopapular rashes around her eyes, nose, and forehead.The rashes persist for 2 to 4 weeks. She also experienced flushing, itching skin and sneezing. Symptoms of urticaria appeared within minutes after consuming coffee, beer, and white wine. It was noted that the patient had previously seen both an ophthalmologist and a dermatologist, but the treatments prescribed had been ineffective. Additionally, the patient has Hashimoto's thyroiditis and is currently being treated with L-thyroxine.

During the objective examination, pink maculopapular lesions were observed around her nose and lower eyelids, along with erythema around her nasal alae.

To determine the underlying causes, laboratory tests were ordered, including tryptase concentration, diamine oxidase activity (DAO), molecular component diagnostics via the ALEX2 test, and skin patch testing to clarify the potential for contact dermatitis. A skin biopsy was recommended for the patient, however, she declined as the lesions were located on her face. The patient was advised to avoid factors that could induce heat, to follow a low-histamine diet, and to use emollients and a cream with SPF twice daily. For immediate relief, dexamethasone ointment (Oftan Dexa-Chlora) was prescribed for application around the eyes for up to three days. For maintenance therapy, tacrolimus ointment was recommended. Antihistamines were suggested for the relief of itching.

During the second consultation, the patient additionally reported facial skin redness and a burning sensation in the throat after consuming alcoholic beverages (wine, champagne), ginger, and spicy sauces. Based on the given information, the patient’s non-adherence to the low-histamine diet could be considered as a self-performed histamine challenge test at home. During objective examination, no positive dynamics were noted. Pink maculopapular lesions persisted around the nose and lower eyelids, along with erythema of the nasal alae.

Table 1. Laboratory and instrumental test values.

***In vitro* tests**	**Results of *in vitro* tests**	**Refference values**
TSH	0,64 mIU/L	0,38 – 5,33 mIU/L
anti-TPO	36,68 IU/ml	< 9 IU/ml
Tryptase	9.32 µg/L	<8.4 µg/L
DAO activity	2,6 U/ml	>10 U/ml
sIgE	<0.3 kUA/L	<0.3 kUA/L
***In vivo* tests**	**Results of *in vivo* tests**	**Refference values**
skin patch tests (S-1000, C-1000)	negative	negative

The patient was advised to continue the previously prescribed treatment, with the addition of topical Fucidin cream to treat secondary infection. Dietary recommendations included avoiding spicy foods and heat-inducing factors, as well as limiting physical activity.

The diagnosis of cutaneous mastocytosis was established based on recurrent clinical manifestations and elevated serum tryptase levels. Histamine

intolerance was diagnosed based on the clinical presentation i.e. the occurrence of maculopapular rash after eating foods rich in histamine, a self-performed histamine challenge test at home, and a deficiency of the DAO enzyme.

The patient was advised to avoid foods and medications known as histamine liberators, to take one Daosin (DAO enzyme) tablet before a large meal, to use emollients and tacrolimus ointment to reduce inflammation, and to take antihistamines as needed.

Case and diagnostic limitations

We acknowledge that a skin biopsy was not performed. The patient refused the procedure, as the main lesions were located on her face. The gold standard for diagnosing histamine intolerance is a histamine challenge test. In our case, the patient performed the test at home, violating the recommendations of a low-histamine diet. Repeated home challenges with histamine-rich foods, during which identical clinical symptoms were observed, were considered equivalent to a physician-supervised provocation test.

Discussion

Histamine intolerance (HIT) is a non-immune hypersensitivity reaction that results from an imbalance between the amount of histamine accumulated in the body and the body's ability to break it down, typically due to decreased activity of the diamine oxidase (DAO) enzyme also called a „barier enzyme“ [7, 9]. DAO, together with histamine-N-methyltransferase, plays a crucial role in the histamine degradation [9]. The foods with high histamine level include fish and seafood, chocolate, fermented products (e.g. cheese, pickles), certain vegetables and fruits (e.g., tomatoes, spinach, citrus fruits, strawberies, kiwi) and alcoholic beverages. Alcohol not only contains histamine but also inhibits DAO activity, thereby increasing histamine levels in the body [10]. According to the literature, the diagnosis of HIT typically requires the presence of at least two symptoms occurring within four hours after a meal, with improvement or resolution following a low-histamine diet [10]. One of the most studied diagnostic approaches for HIT is measuring DAO activity in serum. However, DAO levels can vary throughout the day or month in the same patient [6]. In our case, the patient performed an oral provocation test with histamine-rich food after long dietary regime. Therefore, the diagnosis was made based on the clinical history, DAO test results, and the self-performed provocation test. The ALEX2 test was performed to exclude IgE-mediated food allergy, which showed negative results. In the literature, the skin prick test is described as one of the diagnostic options for HIT. However, this test does not allow for differentiation between HIT and food allergy [11, 6]. The gold standard for HIT treatment is considered to be a low-histamine diet combined with DAO supplementation and short-term use of H1 or H2 antihistamines [6]. Clinical studies have shown that after 4 weeks of elimination diet both gastrointestinal and cutaneous symtoms improved [9]. Reaserch shows that supplementation with DAO enzyme cofactors such as copper, zync, vitamin C, and vitamin B6 should be used as adjunctive therapy [12]. Our patient was advised to follow a low-histamine diet, to suplement with DAO enzyme before large meals, to avoid medications that decreas DAO activity (e.g. ibuprofen, acetylsalicylic acid) and to take antihistamines if pruritus persist.

Mastocytosis may be a contributing risk factor for histamine accumulation, as patients with this condition are predisposed to DAO deficiency [7]. The symptoms of histamine intolerance are often nonspecific and vary between individuals. According to the literature, the most common manifestations are gastrointestinal symptoms such as nausea, vomiting, bloating, fullness after eating, diarrhea, constipation abdominal cramps, and gastroesophageal reflux [10, 9]. Moreover patients with the histamine intolerance could also experience respiratory symptoms (nasal congestion, rhinitis, rhinorrhea), cardiovascular symptoms (tachycardia, hypotonia), skin symptoms (sudden flushing, itching on the face and the body, pruritus) and neurological symptoms (dizziness, migraine, fatigue, insomnia) [6, 7, 10]. However, our patient had skin symptoms such as recurrent maculopapular rashes around the eyes, nose, and forehead, skin flushing, itching, and respiratory symtoms such as sneezing. The patient did not experience any gastrointestinal symptoms. It is important to mention that medications such as verapamil, chloroquine, cimetidine, and clavulanic acid can reduce DAO activity by up to 90%. In addition to genetic predisposition, acquired factors may also contribute to reduced DAO activity [11]. Our patient had no history of using the medications mentioned above.

Mastocytosis is a disorder characterized by increased proliferation and activation of atypical mast cells [13]. The clinical features observed in mastocytosis are due to the increased presence of mast cells in tissues and the amount of mediators they release [14]. During degranulation, mast cells release numerous mediators, including histamine, heparin, serotonin, tryptase, chymase, chondroitin sulfate, carboxypeptidase, prostaglandin D2, TNF-α, and interleukin-4 [13]. From a clinical perspective, histamine is the most significant mediator. Mastocytosis is classified into cutaneous mastocytosis (CM) and systemic mastocytosis (SM). The most frequent cutaneous manifestation of mastocytosis is urticaria pigmentosa or maculopapular CM, which is typically associated with warmth, flushing and pruritus of the skin. However, in CM other cutaneous forms such as mastocytoma, diffuse cutaneous mastocytosis may also appear. Symptoms can be triggered by spicy foods, hot beverages, changes in climatic temperature, alcohol or medications [13, 14]. Our patient had urticaria symptoms, facial redness and a burning sensation in the throat after drinking coffee, alcoholic beverages, consuming ginger and hot sauce. Systemic mastocytosis should be considered in patients presenting with recurrent anaphylaxis or frequent, severe abdominal pain [14]. The patient did not experience gastrointestinal symptoms such as nausea, vomiting, or severe abdominal pain, and did not complain of musculoskeletal pain, which are common in SM [13, 14, 15]. Anaphylaxis is a life-threatening complication of SM and can be triggered by foods, medications, exercise, or Hymenoptera stings. The prevalence of anaphylaxis in patients affected by mastocytosis is almost 50%. Medications are common anaphylaxis triggers in SM patients [16]. However, our patient tolerates medications well and has never experienced anaphylaxis. In order to diagnose CM, the patient needs to meet the diagnostic criteria, such as clinical symptoms of urticaria pigmentosa or maculopapular CM, diffuse cutaneous mastocytosis, or solitary mastocytoma, as well as histologically confirmed mast cell infiltrates on skin biopsy [14, 15]. It is important to note that mast cells may also be increased in the skin biopsy in other conditions,

such as chronic urticaria, scleroderma, or at sites of extended antigenic contact [14]. A persistently elevated baseline serum tryptase level > 20 µg/L is one of the minor diagnostic criteria for SM. Serum tryptase concentration is not considered when diagnosing CM. Our patient had a slightly elevated serum tryptase level of 9.32 µg/L (normal range <8.4 µg/L) and experienced a rapid onset of urticarial lesions after drinking coffee or alcoholic beverages, or after consuming spicy foods. The diagnosis of CM was made based on recurrent symptoms and elevated serum tryptase level. Performing a skin biopsy would have been appropriate. However, the patient declined. According to the literature, CM treatment is focused on trigger avoidance such as spicy foods, hot beverages, temperature changes, alcohol, and certain medications as well as symptom control. Mediator-related symptoms, such as pruritus and flushing, are treated with H1-receptor antagonists. Topical corticosteroids are an effective option for treating cutaneous mast cell lesions [14, 15]. Our patient was advised to avoid spicy foods and heat-inducing factors, limit physical activity, and take antihistamines if pruritus persists.

Both HIT and mastocytosis are complex and heterogeneous conditions that can present with similar cutaneous, gastrointestinal, neurological, and cardiovascular symptoms. In our patient, HIT and mastocytosis manifested predominantly with cutaneous symptoms triggered by food. In such cases, it is important to differentiate HIT and mastocytosis from true food allergy and to prescribe appropriate treatment.

Table 2. A comparison of the symptoms of histamine intolerance and mastocytosis observed in the patient and described in the literature

Symptoms of histamine intolerance observed in the patient	Symptoms of histamine intolerance described in the literature	References
Cutaneous: maculopapular rashes around the eyes, nose, and forehead, skin flushing, itching **Respiratory: sneezing** **Gastrointestinal: No** **Cardiovascular: No** **Neurological: No**	**Cutaneous:** pruritus, sudden flushing, itching, rash on the face and on the body ***Respiratory:** nasal congestion, rhinitis, rhinorrhea **Gastrointestinal:** abdominal pain, diarrhea, constipation, nausea, vomiting, bloating, fulness after eating ***Cardiovascular:** tachycardia, hypotonia ***Neurological:** dizzines, migraine, fatigue, insomnia	[6, 7, 9, 10, 12]
Symptoms of mastocytosis observed in the patient	**Symptoms of mastocytosis described in the literature**	**References**
Cutaneous: urticaria, face redness **Respiratory/gastrointesitnal: only burning sensation in the throat** **Anaphylaxis: No** **Cardiovascular: no** **Musculoskeletal: no** **Neuropsychiatric: no**	**Cutaneous:** Flushing, pruritus, blistering, hives; urticaria, Darier's sign ****Gastrointestinal:** diarrhea, nausea, vommiting, abdominal pain, heartburn **** Anaphylaxis** ****Cardiovascular:** syncope, palpitations ****Musculoskeletal:** bone pain, back pain, osteoporosis ****Neuropsychiatric:** anxiety, irritability, depression, mood swings	[13, 14, 15]

* less frequent symptoms of histamine intolerance [12]; **systemic mastocytosis (SM) symptoms

Conclusions

This report describes a rare case of histamine intolerance coexisting with cutaneous mastocytosis. In the context of adverse food reactions, it is important to distinguish between immune-mediated and non-immune-mediated mechanisms. When testing for IgE-mediated food allergy is negative, other conditions such as histamine intolerance or mastocytosis should be suspected. Assessing diamine oxidase activity and serum tryptase concentration can assist in differentiating between histamine-related conditions.

References

1. Onyimba F, Crowe SE, Johnson S, Leung J. Food Allergies and Intolerances: A Clinical Approach to the Diagnosis and Management of Adverse Reactions to Food. Clin Gastroenterol Hepatol. 2021 Nov;19(11):2230-2240.e1.
2. Mendonca CE, Andreae DA. Food Allergy. Med Clin North Am. 2024 Jul;108(4):655–70.
3. Hon E, Gupta SK. Gastrointestinal Food Allergies and Intolerances. Gastroenterol Clin North Am. 2021 Mar;50(1):41–57.
4. Hage G, Sacre Y, Haddad J, Hajj M, Sayegh LN, Fakhoury-Sayegh N. Food Hypersensitivity: Distinguishing Allergy from Intolerance, Main Characteristics, and Symptoms—A Narrative Review. Nutrients. 2025 Apr 16;17(8):1359.
5. Gargano D, Appanna R, Santonicola A, De Bartolomeis F, Stellato C, Cianferoni A, et al. Food Allergy and Intolerance: A Narrative Review on Nutritional Concerns. Nutrients. 2021 May 13;13(5):1638.
6. Reese I, Ballmer-Weber B, Beyer K, Dölle-Bierke S, Kleine-Tebbe J, Klimek L, et al. Guideline on management of suspected adverse reactions to ingested histamine. Allergol Sel. 2021 Oct 5;5:305–14.
7. Zhao Y, Zhang X, Jin H, Chen L, Ji J, Zhang Z. Histamine Intolerance—A Kind of Pseudoallergic Reaction. Biomolecules. 2022 Mar 15;12(3):454.
8. Hrubisko M, Danis R, Huorka M, Wawruch M. Histamine Intolerance—The More We Know the Less We Know. A Review. Nutrients. 2021 Jun 29;13(7):2228.
9. Shulpekova YO, Nechaev VM, Popova IR, Deeva TA, Kopylov AT, Malsagova KA, et al. Food Intolerance: The Role of Histamine. Nutrients. 2021 Sep 15;13(9):3207.
10. Smolinska S, Winiarska E, Globinska A, Jutel M. Histamine: A Mediator of Intestinal Disorders—A Review. Metabolites. 2022 Sep 23;12(10):895.
11. Wagner A, Buczyłko K, Zielińska-Bliźniewska H, Wagner W. Impaired resolution of wheals in the skin prick test and low diamine oxidase blood level in allergic patients. Adv Dermatol Allergol Dermatol Alergol. 2019 Oct;36(5):538–43.
12. Jochum C. Histamine Intolerance: Symptoms, Diagnosis, and Beyond. Nutrients. 2024 Apr 19;16(8):1219.
13. Jackson CW, Pratt CM, Rupprecht CP, Pattanaik D, Krishnaswamy G. Mastocytosis and Mast Cell Activation Disorders: Clearing the Air. Int J Mol Sci. 2021 Oct 19;22(20):11270.
14. Carter MC, Metcalfe DD, Komarow HD. Mastocytosis. Immunol Allergy Clin North Am. 2014 Feb;34(1):10.1016/j.iac.2013.09.001.
15. Pardanani A. Systemic mastocytosis in adults: 2023 update on diagnosis, risk stratification and management. Am J Hematol. 2023;98(7):1097–116.
16. Kaakati RN, Khokhar D, Akin C. Demographics, Types of Patient-Reported Allergic Diseases, and Anaphylaxis in Mastocytosis: A Single-Center US Experience. J Allergy Clin Immunol Pract. 2025 Feb;13(2):398–406.