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PSEUDOALLERGIC URTICARIA IN A POST-MENOPAUSAL WOMAN: A CASE REPORT

Dermatology

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ABSTRACT

Hormonal imbalance is an important factor but often underrecognized in the pathogenesis of urticaria, particularly in postmenopausal women. We report a case of a 47-year-old postmenopausal woman who presented with recurrent erythematous wheals and pruritus over the trunk for one month, along with tingling sensations in both upper limbs. The episodes were intermittent, occurring approximately every two weeks, with no identifiable external triggers or prior history of allergy. Laboratory investigations revealed elevated thyroid-stimulating hormone levels, diagnosed as Hypothyroidism, along with vitamin B12 deficiency. Hormonal profile showed elevated follicle-stimulating hormone and luteinizing hormone levels with reduced estradiol, confirming postmenopausal status. The patient was initially treated with Bilastine, resulting in complete resolution of urticarial lesions within one week. However, neurological symptoms persisted and improved after initiation of levothyroxine of 12.5 mcg and vitamin B complex supplementation. This case suggests that hormonal imbalance and thyroid dysfunction may contribute to urticaria through non–immunoglobulin E-mediated mechanisms. It highlights the importance of considering endocrine evaluation in patients with recurrent urticaria, especially in postmenopausal women.

KEYWORDS

INTRODUCTION

Urticaria, a skin reaction also known as hives and nettle rash. It causes red colored bumps which is said to be weal, itching. It is active by the release of histamine from mast cells. Based on the duration urticaria is divided into a) Acute, b) Chronic.

Acute urticaria usually associated with allergens, infections, Chronic spontaneous urticaria and chronic inducible urticaria such as dermatographic, cold, heat, pressure, solar, cholinergic urticaria comes under chronic urticaria which is linked to autoimmunity, and contact urticaria which can be immunological and non-immunological stimulated by food, plants, sting. This is characterized by nettle sting reaction; the best example is latex allergy. Comparatively chronic urticaria and contact urticaria eventually develops into life-threatening anaphylaxis in sensitive patients.

Chronic spontaneous urticaria (CSU) is primarily a mast cell–dependent disease, in which activation and degranulation of mast cells lead to the release of histamine and other inflammatory mediators. This process results in the characteristic clinical features of urticaria, including wheals (hives), angioedema, and pruritus (itching). In addition to mast cells, other cellular components such as basophils, eosinophils, and various inflammatory cells also contribute to disease pathogenesis.

The underlying mechanisms of CSU involve multiple interconnected pathways, including autoimmunity, inflammation, activation of the coagulation cascade, and stimulation of mast cell surface receptors, all of which contribute to chronic inflammation. CSU is widely considered an autoimmune disorder, supported by the presence of specific autoantibodies and its association with other autoimmune diseases.

Two major autoimmune mechanisms have been identified in CSU. The first is Type I autoimmunity (auto allergic CSU), in which Immunoglobulin E (IgE) antibodies are directed against self-antigens. Common targets include thyroid peroxidase (TPO) and interleukin-24 (IL-24). These IgE autoantibodies bind to the high-affinity IgE receptor (Fc epsilon receptor I, FcεRI) on mast cells, leading to their activation and degranulation. The second mechanism is Type IIb autoimmunity, mediated by Immunoglobulin G (IgG) antibodies, and less commonly Immunoglobulin M (IgM) and Immunoglobulin A (IgA), directed against either IgE or the FcεRI receptor on mast cells. This results in strong and sustained mast cell activation. Type IIb autoimmune CSU is often associated with more severe disease and is frequently linked to thyroid disorders such as Hypothyroidism.

The association between CSU and thyroid disease is well established, with many patients exhibiting anti-thyroid peroxidase (anti-TPO) autoantibodies, further supporting the autoimmune basis of the condition. This link explains the frequent coexistence of CSU with hypothyroidism.

Mast cell activation in CSU occurs through multiple mechanisms. The classical pathway is IgE-mediated, where allergens bind to IgE attached to FcεRI receptors, triggering degranulation. In addition, autoimmune activation occurs via IgG or IgE autoantibodies. There are also non–IgE-mediated pathways, particularly involving the Mas-related G protein-coupled receptor X2 (MRGPRX2), which is activated by neuropeptides and certain drugs, leading to pseudo allergic or neurogenic urticaria.

Several receptors play key roles in mast cell function, including FcεRI, c-Kit (a receptor important for mast cell growth and survival), MRGPRX2, and the complement component 5a (C5a) receptor, which mediates complement-induced activation. Various cytokines and mediators are involved in regulating mast cell activity, such as interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-6 (IL-6), interleukin-15 (IL-15), tumor necrosis factor-alpha (TNF-α), and chemokines like chemokine (C-C motif) ligand 2 (CCL-2). Among these, stem cell factor (SCF) is particularly important for mast cell differentiation, proliferation, and survival.

The complement system also plays a significant role in CSU pathogenesis. Activation of the complement cascade leads to the production of C5a, an anaphylatoxin that binds to its receptor on mast cells and amplifies degranulation, thereby worsening urticaria.

Characteristic cellular changes observed in CSU include basopenia (reduced basophil count), eosinopenia (reduced eosinophil count), and increased levels of circulating autoantibodies. At the intracellular level, mast cell activation involves key signaling proteins such as LYN kinase, spleen tyrosine kinase (SYK), and Bruton's tyrosine kinase (BTK), which act as central regulators of signaling pathways leading to mast cell activation and cytokine production.

An alternative activation pathway involves the MRGPRX2 receptor, which can be triggered by various agents including drugs (such as antibiotics and opioids), neuropeptides (e.g., substance P), and eosinophil-derived mediators. This pathway contributes to pseudo allergic urticaria, independent of IgE.

Importantly, many patients exhibit overlapping mechanisms, with both Type I and Type IIb autoimmune pathways present simultaneously, while a smaller proportion of patients may have non-autoimmune forms of CSU.

The skin is the primary target organ in CSU due to several factors, including the presence of C5a receptors, a high concentration of mast cells, and the expression of skin-specific autoantigens such as IL-24, which enhance localized immune responses.

Understanding the pathogenesis of CSU has important therapeutic implications. Anti-IgE therapy, such as monoclonal antibodies

targeting IgE, reduces mast cell activation by decreasing IgE levels and downregulating FcεRI receptor expression on mast cells and basophils. This ultimately leads to reduced histamine release and improvement of clinical symptoms.

Hormonal imbalance plays a significant role in the pathogenesis of urticaria, particularly in women. Estrogen and progesterone influence immune responses and mast cell activity. Estrogen has been shown to enhance mast cell degranulation and increase histamine release, thereby exacerbating urticaria symptoms. In contrast, progesterone may have immunomodulatory effects but can also trigger hypersensitivity reactions in certain individuals.

In postmenopausal women, declining estrogen levels lead to immune dysregulation, which may increase susceptibility to inflammatory and autoimmune conditions, including Urticaria. Additionally, hormonal fluctuations may alter cytokine profiles and mast cell responsiveness, contributing to disease onset or exacerbation.

The coexistence of Hypothyroidism further supports a hormonal and autoimmune interplay, as thyroid hormones are closely linked with immune regulation. This combined endocrine imbalance may predispose individuals to mast cell activation and chronic urticaria.

CASE PRESENTATION:

A 47 years old female post-menopausal women presented with chief complaints of recurrent erythematous wheals, and itching over the trunk region, and tingling sensation over right and left arms for 1 month. The symptoms are acute in onset, she frequently experienced similar episodes for every 2 weeks, she had attended menopause 8 months back, there is no past medical and medication history, during evaluation she was newly diagnosed with hypothyroidism and vitamin b12 deficiency. The patient was started with bilastine for 1 week, patient showed symptomatic relief, but tingling sensation was persisted, simultaneously she was started with hormonal replacement therapy with levothyroxine of 12.5 mcg once daily with vitamin b complex, following treatment patient showed complete recovery, including the resolution of neurological symptoms. Laboratory investigations conclude that abnormalities of hormonal and endocrine parameters including TSH- 126.5 µIU/mL, and LH- 47.7 mIU/mL, FSH- 111.60 mIU/mL, Estradiol(E2)- 5 pg/mL, based on the clinical presentation and laboratory findings the patient was diagnosed with hormonal induced urticaria.

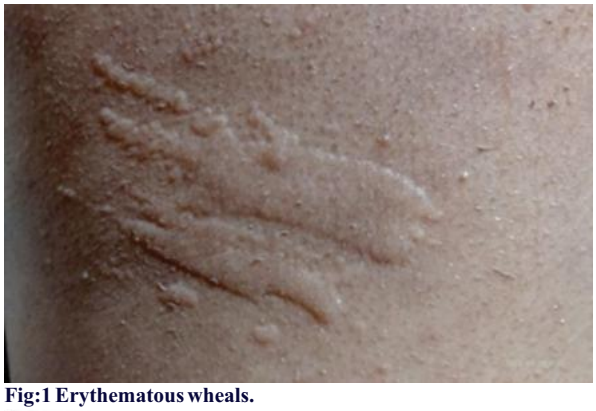

Fig:1 Erythematous wheals.

Test Name	Result	Biological Ref. Interval	Unit
Luteinizing Hormone (LH) & Follicle Simulating Hormone (FSH) Sample : Serum Method : ECLIA			
Luteinizing Hormone(LH)	47.47	Follicular Phase : 2.4 - 12.6 Ovulatory Phase : 14 - 96 Luteal Phase - 1.0 - 11.4 Post Menopausal Phase : 7.7 - 59.0	mIU/mL
Follicle-Stimulating Hormone(FSH)	111.60	Follicular Phase : 3.5 - 12.5 Ovulatory Phase : 4.7 - 21.5 Luteal Phase : 1.7 - 7.7 Postmenopausal : 25.8 - 134.8	mIU/mL
Estradiol (E2) Sample :Serum Method : ECLIA	5.00	Follicular Phase:12.5-166 Ovulatory Phase: 85.5-498 Luteal Phase:43.8-211 Postmenopausal:5.0-54.7 Pregnancy, 1st Trimester:215-4300	pg/mL

Fig: 2 Hormonal profile.

BIOCHEMISTRY DEPT

TEST NAME (METHOD)	RESULTS	BIOLOGICAL REFERENCE INTERVAL	UNITS
SERUM TSH (CLIA)	126.5	0.40 - 4.05	µiu/ml

Fig:3 Elevated thyroid stimulating hormone.

CONCLUSION:

Hormonal-induced urticaria differs from classical allergic urticaria in that it is not mediated by external allergens or antigen-specific Immunoglobulin E (IgE). Instead, it represents a form of pseudo allergic reaction, in which mast cell activation occurs through non–IgE-mediated pathways.

In true allergic urticaria, exposure to an external allergen leads to cross-linking of IgE bound to high-affinity receptors (FcεRI) on mast cells, resulting in degranulation and histamine release. However, in hormonally induced urticaria, mast cell activation occurs independently of allergen exposure and IgE sensitization.

Hormonal fluctuations, particularly involving estrogen and progesterone, can directly influence mast cell stability and responsiveness. Estrogen has been shown to enhance mast cell degranulation and increase histamine release, while progesterone may alter immune modulation and, in some cases, trigger hypersensitivity-like reactions. These hormonal changes are especially prominent in postmenopausal women, where endocrine imbalance leads to altered immune regulation.

Additionally, mast cells can be activated through alternative receptors such as the Mas-related G protein-coupled receptor X2 (MRGPRX2), which is responsible for pseudo allergic or non-immunologic activation. This pathway can be triggered by endogenous factors, neuropeptides, or internal physiological changes rather than external allergens. As a result, histamine release and urticarial symptoms occur without prior sensitization.

In the present case, the absence of identifiable external triggers, the intermittent nature of symptoms, and the association with hormonal imbalance and Hypothyroidism support a pseudo allergic mechanism rather than a true IgE-mediated allergic reaction. The favorable response to antihistamine therapy further indicates that histamine release was involved, but not necessarily through classical allergic pathways.

Thus, hormonally induced urticaria in this patient is best explained by a pseudo allergic, non–IgE-mediated mechanism driven by endocrine imbalance rather than a true allergen-induced hypersensitivity reaction.

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