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1. Introduction

Urticaria, also known as hives, is a common pruritic skin disease which is characterized by erythematous and edematous papules and plaques. These lesions have a transient nature which means a single-lesion heals within 24 h but new lesions may occur recurrently. The disease may be idiopathic or inducible and it is called chronic when intermittent attacks last for more than 6 weeks [1].

The lifetime prevalence of urticaria is 10–20%, while this rate is approximately 2% in its chronic form [1, 2]. Urticaria can occur at any age but the chronic urticaria form is more common in adults. The disease can affect both genders but female predominance is evident [2].

Cutaneous mast cells and mediators that are released as a result of mast cell degranulation are located at the center of urticaria pathogenesis [3]. Triggering factors may cause mast cell degranulation via different mechanisms such as direct activation or IgE-mediated allergic activation. The common outcomes are the release of mediators such as histamine and their clinical effects. Beside pruritus, these vasoactive mediators are responsible for vasodilation and subsequent erythema and edema [3, 4]. Activation of mast cells in superficial dermis causes urticarial papules and plaques while angioedema occurs as a result of mast cell involvement in deeper tissues [5].

There are many triggering factors for urticaria but determining a specific cause is not always possible. This quest is more complicated in some cases, especially in chronic ones. In addition to classification as acute or chronic, the disease may also be defined with etiologic factors, such as physically induced, autoimmune, or idiopathic urticarial [6]. Drugs, viral, bacterial or parasitic infections, insect bites, foods, physical factors, autoimmune diseases, and emotional stress are leading causes in etiology [6, 7].

It is known that infections may cause urticaria but the mechanism is unclear [8]. It is also difficult to determine if the trigger was an infection or a drug used for the treatment of infection. Nonsteroidal anti-inflammatory drugs and antibiotics, especially beta lactams, constitute a significant proportion of drug etiology. These drugs mainly cause urticarial reaction via
IgE-mediated immunologic pathways [9]. In addition, some drugs such as vancomycin, narcotic analgesics, barbiturates, neuromuscular blockers, and radiocontrast agents may cause urticarial eruption via direct mast cell degranulation [9, 10]. Nonsteroidal anti-inflammatory drugs may also trigger urticaria by interfering with arachidonic acid metabolism via cyclooxygenase 1 enzyme inhibition. This blockage leads to increased synthesis of cysteinyl leukotrienes. This form of urticarial reaction is called pseudoallergy [10].

Physically induced urticarias are thought to occur as a result of increased mast cell sensitivity to environmental stimuli. Physical factors that may trigger urticaria include ultraviolet light, pressure, vibration, exercise, water contact, cold or heat exposures, and increased body temperature [11].

Systemic diseases can also be the underlying cause of urticaria. Therefore, the presence of any accompanying systemic symptoms is significant. Autoimmune and rheumatologic diseases constitute the majority of this group [12]. Systemic diseases include cutaneous vasculitis, systemic lupus erythematosus, celiac disease, diabetes mellitus, Sjögren’s syndrome, rheumatoid arthritis, autoimmune thyroid disease, and mastocytosis [1, 12]. Malignancies may also trigger urticaria and the disease tends to be persistent in this case [13].

Elementary lesion of urticarial eruption is papule or plaque with erythema and edema. Circumscribed, pink-to-red lesions elevated from the skin vary in size and shape. These plaques which may tend to merge with central pallor can affect any region of the body [14]. Pruritus is the main annoying symptom which mostly interferes with daily activities of the patients [15]. Although a single urticarial lesion is transient, repetitive character of the eruption is a significant problem. Lesions persisting beyond 24 h with residual petechia or hyperpigmentation, especially if accompanied by systemic symptoms such as fever and arthralgia, may suggest urticarial vasculitis in differential diagnosis and warrant skin biopsy [16].

Angioedema may accompany urticaria if the mast cells in the deeper dermis and subcutaneous tissue were involved in reactions. When this occurs, the lips and eyelids are the regions mainly affected [1]. Urticaria may also be a component of severe systemic allergic reactions, anaphylaxis, and so patients should always be examined for accompanying signs and symptoms such as flushing, swollen lips and tongue, difficulty in breathing, hoarse voice, hypotension, dizziness, hypotonia, syncope, nausea, vomiting, abdominal pain, and incontinence [17].

Diagnosis of urticaria is mostly based on anamnesis and physical examination. Due to the transient nature of the rash, there may be no lesions during a doctor visit. In this case, the clinical history of intensely pruritic lesions that heal within a few hours may be the only clue for urticaria diagnosis. In uncertain cases, asking patients to take a photo when they have a rash is a helpful method. It may be advisable to mark a single lesion and note the time it appeared and disappeared to determine the duration. Observation of characteristic erythematous and edematous papules and plaques supports the diagnosis. Association with angioedema and/or anaphylaxis should always be kept in mind and questioned [1, 2].

Skin biopsy is not indicated for the diagnosis of urticaria unless there is suspicion of urticarial vasculitis or mastocytosis. If vasculitis is suspected, an additional skin sample should be taken.
for immunofluorescence examination. Histopathological findings of urticaria include interstitial edema and perivascular mixed cellular infiltrate. T lymphocytes are predominant cells in this infiltrate but eosinophils, neutrophils, and basophils may also exist in a lesser extent [18]. Leukocytoclasis and fibrinoid necrosis of vessel walls are signs in favor of vasculitis [16].

Once the diagnosis is confirmed, it becomes important to find out triggering factors, if possible. Detailed anamnesis is important to determine any triggering medication, infection, or physical stimuli such as scratching, sunlight, pressure, heat or cold contact, exercise, and water. Challenge tests may be performed for the diagnosis of physical urticaria but caution should be exercised during the procedure because serious systemic allergic reactions can develop.

Autologous serum skin tests may be used to differentiate autoimmune urticaria, but patients should cease antihistamines at least 3 days prior to the procedure. In this subtype of urticaria, intradermal injection of patient’s own serum results in an urticarial reaction within 30 min [19].

It is not indicated to use laboratory tests for patients with acute urticaria unless they have signs and symptoms suggesting an underlying systemic disease [1]. In chronic cases, initial laboratory examinations may include complete blood count, fasting blood glucose, erythrocyte sedimentation rate, C-reactive protein, kidney and liver function tests, urinalysis, and total serum Immunoglobulin-E levels. Additional tests such as antinuclear antibody, rheumatoid factor, complement C3 and C4 levels, thyroid hormones and autoantibodies, serology of Hepatitis viruses, *Helicobacter pylori* antigen, and fecal parasite examination can be performed if an infectious disease or an autoimmune disease is suspected [1, 12].

After diagnosis, determining the severity of the disease becomes important to evaluate the treatment response objectively. There are some scoring systems used for this purpose, one of which is the urticaria activity score (UAS). It is a widely used scoring system questioning the intensity of pruritus and the number of wheals in a day. Higher scores mean a more severe disease [20].

2. Conclusion

Generally, the disease is self-limited and it shows regression in a few weeks for most cases. Some patients may have persistent symptoms for months or years and the disease is considered chronic beyond 6 weeks.

If possible, the prevention of trigger is the first step of treatment. Treatment aim is to control symptoms with minimal side effects. H1 antihistamines are the drugs most commonly used for this purpose. Second-generation H1 antihistamines, such as cetirizine and loratadine, are used as first-line treatment options. These newer, non-sedative antihistamines are more preferred than first-generation ones such as hydroxyzine and diphenhydramine. First-generation antihistamines may have also the disadvantage of anticholinergic side effects in addition to their sedative effects. In unresponsive cases, dose increment up to fourfold of standard therapeutic doses is recommended by the latest guidelines [1, 21]. Increasing the dose of a particular antihistamine is thought to be superior to the combined use of multiple antihistamines at standard doses [21]. H2 antihistamines may be used in combination with H1 antihistamines.
Short-term systemic glucocorticoid therapy may be administered in addition to antihistamines for acute urticarial attacks, particularly when accompanied by angioedema [1]. Long-term usage of systemic glucocorticoids is not recommended because of potential side effects.

Antileukotrienes, such as montelukast and zafirlukast, are generally added to antihistamines as second-line treatment options in chronic cases refractory to high-dose antihistamines. Immunosuppressive agents, especially cyclosporine, are efficient to treat chronic urticaria but potential side effects must always be kept in mind. Dapsone, hydroxychloroquine, sulfasalazine, and mycophenolate are other less recommended drugs for the treatment of urticarial [1, 21]. Omalizumab, which is a safer alternative to those mentioned above, has recently come to the forefront in the treatment of chronic urticaria. It is an anti-IgE monoclonal antibody which has a good efficacy and safety profile [22, 23]. It also has the ease of use with monthly subcutaneous injections.

Since chronic urticaria treatment may become complicated, treatment switch, or combination is not surprising for most cases.

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