Chronic Autoimmune Urticaria

Wardhana, E.A. Datau

Department of Internal Medicine, Siloam International Hospitals. Siloam Hospitals Group’s CEO Office, Siloam Hospital Lippo Village 5th floor. Jl. Siloam no. 6, Karawaci, Indonesia. Correspondence mail: wadiswas@yahoo.com.

ABSTRACT

Chronic urticaria is common and patients may present with transient eruption of itchy, erythematous, edematous swellings of the dermis, which lasts more than six weeks. One type of chronic idiopathic urticaria, and part of it, is the chronic autoimmune urticaria. The chronic autoimmune urticaria is caused by high affinity of IgE receptors (anti-FcεRI) and less frequently by anti-IgE autoantibodies, also the role of complement activation, that leads to mast and basophil activation. Despite many recent advances in the understanding of chronic autoimmune urticaria, this condition remains a major challenge in the terms of its etiology, investigations, and management.

Key words: chronic, autoimmune, urticaria.

INTRODUCTION

Urticaria is defined as intense, itching welts caused by allergic reactions to internal and external agents. The word of urticaria is derived from the latin word urtica, which means “nettle”, which are tooth-leaved plants covered with hairs capable of secreting a stinging fluid that immediately affects the skin on contact.1,2 Urticarial lessions resulting from localized edema of upper dermis are called wheals. By definition, acute urticaria resolves than six weeks, whereas the chronic urticaria (CU) lasts six weeks or more with continuous disease activity, but when occurring intermitently over a period of more than six weeks can be defined as episodic (Figure 1).1,3

Urticaria affects 15-25% of the population at least once in their life time. The chronic urticaria is more common in adults, affecting mainly middle-aged women, and is rare in children.
and adolescents. The CU, based on the cause, is divided into the CU caused by identifiable cause in 5-10% of the cases (the chronic physical urticaria including symptomatic dermatographism, delayed pressure urticaria, cold urticaria, aquagenic urticaria, solar urticaria, cholinergic urticaria, vibratory urticaria vasculitis; and the other is the chronic vasculitis urticaria), the chronic idiopathic urticaria in 50% of cases (up to 30% of chronic idiopathic urticarians have an autoimmune basis), and the chronic autoimmune urticaria (CAU) in more than 30% of cases.1,3

PATHOGENESIS

Genetic background is thought to be a relevant factor in autoimmune diseases, including CAU. A study in large population of CU patients showed a marked increase in prevalence of the disease among the first degree relatives and showing a family history of autologous serum skin test (ASST), which suggests the presence of circulating autoantibodies, and the association with autoimmune thyroiditis has long been recognized, and anti-thyroglobulin or anti-thyroid peroxidase antibodies can be detected in 25-30% of these patients.4 No obvious explanation for this association has been proposed. The recent observation that the DRB1*04-DQB1*0301 haplotype is significantly increased in these patients with Hashimoto’s thyroiditis, which may indicate a common genetic background. An association with Grave’s disease is less common.2,4 Nevertheless, there is some evidence of genetic predisposition, since particular major histocompatibility complex (MHC) alleles may contribute to the autoimmunity because they are inefficient at displaying self antigens, leading to defective negative selection of T cells, or because peptide antigens presented by these MHC alleles may fail to stimulate regulatory T cells. There is increased prevalence of MHC class I-Bw4 and MHC class II-DRB1*04 (DR4) and its associated allele, DQ*0302 (DQ8) genotype found in patients with in vivo and in vitro histamine-releasing activity.4,5

The mechanisms involved in the regulation and activation of immune cells in CAU have not been well investigated. Studies of the pathogenesis of CU indicate that a subpopulation of patients have a cutaneous autoimmune disease associated with antibody to the IgE receptor.6 Whereas atopic allergy is a well-defined T helper 2 cell (Th2)-type immunologic response, autoimmune disease are variable, although many are associated with Th1 lymphocytes, but the data presented from skin biopsies of CU had a Th0 (virgin or naïve Th) phenotype because there were significant increases in interferon-gamma (IFN-γ), interleukin 4 (IL-4), and interleukin 5 (IL-5) mRNA+ cells. Alternatively, it is also possible that there is a mixture of Th1/Th2 cell types. Allergen induced late-phase reaction (LPR) resembling the immune responsiveness of CU histologically, produce IL-4 and IL-5, but not IFN-γ.6,7 The Th0 arrive at each surveillance stopover in a secondary lymphoid organ via the bloodstream. In the case of lymph nodes and Peyer’s patches, the high endothelial venules (HEVs), which are specialized blood vessels, serve as the nidus of attraction for the T cells to enter the tissue. The extravasation of the Th0 through HEVs relies on the intercellular adhesion molecules (ICAMs) that engage the integrin lymphocyte function-associated antigen-1 (LFA-1).7

The Th0 lymphocytes may be found in the skin tissue of CU, since in the autoimmune diseases there is thymic T cells hyporesponsiveness or unresponsiveness (anergy) to the antigens expressed in the thymic environment during the early immune cells’ positive and negative selection and in induction of self-tolerance.8 The Th0 lymphocytes need at least two signals for their proliferation and differentiation into effector cells: signal 1 is always antigen, and signal 2 is provided by costimulators that are expressed on antigen-presenting cells (APCs). The best-defined costimulator for T cells are two related proteins called B7-1 (CD80) and B7-2 (CD86). These B7 proteins, which usually come from microbes, are recognized by a receptor called CD28, which is expressed on virtually all T cells, Signals from CD28 on T cells binding on APCs work together with signals generated by binding of T cell receptor (TCR) and coreceptor to peptide-MHC complexes on the same APCs.5,8

The CD28-mediated signaling is essential for initiating the response of Th0 lymphocytes. The T lymphocytes with receptors for the self antigens are able to recognize the antigens and thus receive prolonged signals from their antigen receptors, but the T cells do not receive strong costimulation because there is no accompanying innate immune response.5 Under this condition, the TCR may
lose their ability to transmit activating signals (aberrant signals). 9

The TCR α and β chain from the ligand-binding subunit which recognized antigenic peptides bound to MHC complex molecules. The signaling process is provided by γ, δ, and ε polypeptides of the CD3 complex as well as the ζ chain heterodimer and involves two principal signaling pathways.10 The first pathway depends on the stimulation of protein-tyrosine kinase (PTK) activity and involves at least three PTKs, Fyn, Lck, and ζ-chain associated protein kinase, which appear to form a cooperative kinase network. The second pathway, which depends upon the activity of PTKs, involves the induction of inositol phospholipid turnover which leads to protein kinase C (PKC) activation.10,11

The signaling on TCR activates serine/threonine kinase belonging to the mitogen-activated protein kinase (MAP kinase) or extracellular signal-regulated kinase (ERK) family. This molecular information is transmitted as signal from activated PTKs through serine/threonine kinases in the cytoplasm to reach transcription factors in the nucleus. The activation of TCR will translocate human son-of-sevenless (hSOS) into the inner surface of the plasm membrane and produce guanine nucleotide exchange factors (GNEF), which exchange the guanosine diphosphate (GDP) for guanosine triphosphate (GTP), to activate the proto-oncogen (p21Ras). The p21Ras plays an upstream role in signal transmitting by activating the MAP kinase.10,12 The aberrant expression and function of p21Ras pathway may be not only present in T lymphocytes during early phase of T-cell maturation, but also in the B lymphocytes response to antigenic stimuli that may disrupt B cells regulatory mechanisms, resulting ultimately in autoantibody production and autoimmune diseases (Figure 2).9

Although most patients with CU appear to have an idiopathic disorder, in a consistent proportion of cases an autoimmune (CAU) has been suggested, since they have circulating immunoglobulin G (IgG) directed against the alpha (α) subunit of the high affinity immunoglobulin E (IgE) receptor (anti-FcεRIα) and the less frequent is IgG anti-IgE antibodies (Figure 3).13 The IgG subclass analysis of the pathogenic IgG, resulted a preponderance of IgG1 and IgG3 anti-α. This to be consistent with complement dependence of the reaction, because IgG1 and IgG3 fix the classical complement pathway.14,15

The aberrant regulation of the p21Ras pathway in lymphocytes of patients with CIU: possible mechanisms leading to autoimmune disease. Genetically determined aberrant p21Ras signaling interferes with thymic T-cell selection (1), leading to a release of self-aggressive T cells (2). Alternatively, exposure to an unknown environmental trigger (3) results in an aberrant signaling in B and T cells (4) and disrupts immune balance. T cell–assisted (5) production of anti-FcεRI autoantibodies (auto Abs) by B cells (6) and a direct interaction of autoimmune T cells with mast cells (7) lead to autoimmune chronic urticaria.9

The activation of the classical complement pathway appears to be requisite. To initiate cell activation, the Fc portion of 2 IgG molecules in proximity must be able to bind to 2 of the 6 globular heads of C1q. To achieve this, only one fragment antibody (Fab) of each of 2 adjacent IgG molecules needs to bind to adjacent α-subunits. In this process the C5a is likely the cell activator and it is known to be a more effective cutaneous basophils and mast cells activator than is C3a (Figure 4).13,16 The complement activation and the release of C5a results not only in augmented mast
cells and basophils, but it is also a chemotactic for neutrophils, eosinophils, and monocytes, which is one of the factors that would distinguish this lesion from a typical allergen-induced cutaneous late-phase reaction.\textsuperscript{17}

![Figure 4. Diagrammatic representation of mast cell activation by cross-linking the IgE receptor, followed by complement activation and release of C5a. 13]

The autoantibodies in CAU are able to induce histamine release from mast cells and basophils via a direct cross-linking of adjacent IgE receptors or IgE itself. The activated mast cells and basophils will express the CD63, a member of the transmembrane-4 superfamily, which is a mast cell and basophils activation marker as a result of the fusion between intracytoplasmic granules and the plasma membrane. Another marker on activated mast cells and basophils, which is more specific, is CD203c (ectonucleotid pyrophosphatase/phosphodiesterase) is an ectoenzyme expressed only on resting and activated basophils, mast cells in response to cross-linking of the FcεRIα receptors and their CD34+ progenitor cells in peripheral blood.\textsuperscript{18} Histamine is certainly the main mediator involved in CAU, de novo (newly synthesises) of leukotriene C4 (LTC4) also induced. The LTC4 is about 1,000 times more potent than histamine in causing wheal and flare reaction. There is little evidence that platelet-activating factor, cytokines, and chemokines released by activated mast cells, are involved in the pathogenesis of urticarial lesions.\textsuperscript{4}

There is association of CAU with several other autoimmune disease. The CAU may have association with Hashimoto’s thyroiditis (less association with Graves disease) in 5-10\% of CAU, since there is anti-thyroperoxidase antibodies (anti-TPO antibody) segregate with the presence of antibodies to the IgE receptor (or to IgE).\textsuperscript{19} The low serum vitamin B12 has an association with CAU since there are antigastic parietal cell antibodies and chronic antral gastritis.\textsuperscript{20} The celiac disease may also be related to CAU since they share the same major histocompatibility complex (MHC) alleles (alotype DQ2-DQ8).\textsuperscript{21} Infection by several microbes, such as Helicobacter pylori, streptococcus, staphylococcus, yersenia, hepatitis A and B virus, and larvae of Anasakis simplex (cephalopods parasite commonly found in fish) may also induce CAU through the molecular mimicry mechanism between their antigens and host proteins.\textsuperscript{22,23}

**CLINICAL PRESENTATION**

The cardinal clinical presentation of urticaria that distinguish it from any other types of inflammatory eruption are the repeated occurrence of short-lived cutaneous wheals accompanied by redness and itching. The wheals are lesions ranging from a few millimeters to several centimeters in diameter, although if they run together and become confluent much larger plaques may occur. Urticarial wheals are generally paler than the bright red of the surrounding skin because of the compressing effect of dermal edema on the normally blood-engorged postcapillary venules. The surrounding skin may sometimes be conspicuously pale rather than red, giving the impression of a white halo.\textsuperscript{24,25} The wheals may be round or irregular with pseudopodia. The quality of itching may be pricking or burning and usually worse in the evening or nighttime. It is relieved by rubbing the skin rather than scratching.\textsuperscript{24}

**DIAGNOSIS**

A detailed history is of utmost importance, especially related to the duration of complaints. History should differentiate between types of lesions.\textsuperscript{26} It includes the history of recurrent transient hives or swelling, several associated diseases and family history of angioedema, diet, used drugs, infections such as upper respiratory tract infection, physical exertion, psychologic stress, alcoholism, cold, or solar exposure resulted in urticaria (aggravating factors). The urticarial lesions that last less than 1 hour is
usually a physical urticaria, with delayed pressure urticaria as an exception, as it has the peak of symptom between 3-6 hours and will disappear in 24 hours. The contact urticaria usually lasts in just a moment but it has a late phase reaction that lasts for several hours. In the typical urticarial vasculitis, the lesions may last more than 24 hours and still remain until 1 week. Several kinds of drugs may increase the risk of exacerbation and should avoid the using of this drugs: opiate, curare, radiologic contrast, several antibiotics such as penicillin, COX-2 inhibitor, aspirin, non-steroid anti-inflammatory drugs (NSAID), salicylate, and benzoate or tartazine contained in foods. The ACE-inhibitor and angiotensin II receptor inhibitor are drugs that usually cause angioedema.24-26

The additional examinations may help to make the diagnosis of CAU (Figure 5).25 The C1 esterase inhibitor level may help in diagnosing angioedema. Most investigators concur that laboratory test such as complete blood count (CBC), chemistry panel, complement level, and skin test in vivo and radio-allergosorbent test (RAST) for specific IgE which only give type I hypersensitivity, are non-contributory. The autoimmune markers such as anti-nuclear antibody (ANA), anti-TPO antibody, and other autoimmune markers such as rheumatoid factor are worthy of consideration since there are consistent findings of increased frequency with other autoimmune diseases.26,27

A simple screening test of CAU is the autologous serum skin test (ASST), using the

![Figure 5. Approach to the patient with urticaria/angioedema.25](image-url)
patient own serum injected intradermally, which resemble an IgE-mediated late phase reaction. This test is a useful tool for picking up patients with circulating wheal-producing factor (anti-FcεRI), with about 70% in sensitivity and 80% in specificity, but this test should be considered a crude screening test and should not be used as a specific test for the detection of circulating autoantibodies. The ASST positivity has been also reported to correlate with the duration attack and disease severity, but it also may give the false positive result due to the presence of other wheal-inducing factors in the serum such as mast cells specific factor or vasoactive kinin-like products released during the course of coagulation.

At present the most useful in vitro method for the diagnosis of CAU antibodies is the demonstration of the release of histamine (or another reactant) from the target basophils or dermal mast cells. The gold standard for detecting clinically relevant to autoantibodies to FcεRI (using immunoassays methods such as Western blotting and enzyme-linked immunosorbent assay or ELIZA) is the functional in vitro donor basophil histamine release assay (serum histamine releasing activity/HRA).

The four millimeter Skin Punch Biopsy may help to make the diagnosis of CAU, to differentiate with other type of urticarial lesion, especially the urticarial vasculitis which skin biopsy may reveal vascular injury with or without fibrinoid deposits in or around the vessel wall, endothelial swelling, perivascular neutrophilic infiltrate, leukocytoclasis (fragmentation of neutrophils with nuclear dust), and extravasation of red blood cells. In CAU, there are edema of the dermis or subcutaneous tissue, mild dilatation of venules but no evidence of vascular damage. There is mild into moderate peri-vascular infiltrate and it consists of monocytes and lymphocytes. There are also accumulation and degranulation of eosinophils and neutrophils. The histological appearance of the skin in CIU resembles that a late phase reaction, although the infiltrate in patients with CAU is characterized by more prominent granulocytes infiltrate than that of non-autoimmune patients, the frequency of other infiltrating cells is similar in both groups, although there is a slight increase in serum tryptase and cytokines in CAU patients. This small differences are too insignificant to be used as a diagnostic tool.

The differential diagnosis of CAU includes dermatological conditions with an urticarial component, such as cutaneous mastocytosis, urticarial vasculitis, popular urticaria, and urticarial phase of bullous pemphigoid.

**THERAPY**

A clear explanation that CAU is not allergic is important to address since inevitable conviction many patients hold that diet is a cause. Important information to patients must include useful websites and written information about the disease. Treatment plan should include treatment of identifiable cause, avoidance of aggravating factors, advice and written information about the condition, and antihistamines trial. Topical lotions in form of calamine lotion, menthol with aqueous cream, and crotamiton lotion are useful soothing agents in the treatment.

In chronic urticaria, H1 antihistamines are the cornerstone of symptomatic treatment. There is evidence for their beneficial effects, particularly for the relief of itching, but also for reducing the number, size, and duration of urticarial lesion. Relief of the wheals and flares might be incomplete because the vascular effects of histamine are mediated through its action at H2-receptors and also mediated by vasoactive substances including proteases, eicosanoids such as leukotrienes and prostaglandine, and neuropeptides. For optimal effectiveness in CAU, H1-antihistamines should be given on a regular basis rather than as needed. The H2 antihistamine receptor also gives beneficial effects in the treatment of CAU. Several studies showed that the combination of H1 and H2 antihistamines were effective in the treatment.
of CAU, although the results were not quite satisfying but may help to solve dyspepsia that frequently related to severe urticaria. The mast cells membrane stabilizer such as nifedipine may give beneficial effect in CAU, especially in those with hypertension.\textsuperscript{25,26,34}

The first line therapy of CAU is H1 antihistamine. The efficacy of the antihistamines in application to urticaria is attributed to their H1 activity upon the afferent C nerve fibres of the skin which reduces itching, upon the axonic reflexes of the skin which reduces erythema, upon the endothelium of the postcapillary venules which reduces extravasation and therefore wheal formation.\textsuperscript{35} Most antihistamines appear to possess antiinflammatory actions, including the reduction of pre- and neoformed mediators, reductions in cytokine, chemokine, and adhesion molecule expression, through stabilization of the mast cells and basophils membranes and inhibition of the transmembrane flux of calcium and intracellular cAMP, and also inhibition of cytoplasmic transcription factors such as nuclear factor kappa-β (NF-κβ) which activates with H1 receptors activation and migrates towards the nucleus where it interacts with nuclear DNA stimulating the transcription of cytokines, chemokines, adhesion molecules, and the generation of nitric oxide (NO) (Figure 6).\textsuperscript{35,36}

There are 3 generations on antihistamines, the first generation antihistamines’ potential is limited by the sedation caused by their effects on histamine receptors in the brain. The second generation antihistamines give no effect on central nervous system because they block peripheral H1 receptors without penetrating the blood-brain barrier, but may bring cardiac toxicity (cardiac arrhythmias). The third generation antihistamines are the safer version of an equivalent drugs (Table 1).\textsuperscript{36,39} A few skin reactions to H1 antihistamines have been described in the literature, usually demonstrated by oral provocation tests. Some mechanisms have been suggested, including a type I IgE mediated reaction (because a suggestive clinical history and of positive intradermal test to diphenhydramine and cetirizine), photosensitivity with phenothiazines and terfenadine, and paradoxical nonspecific histamine release.\textsuperscript{40}

The second line therapies of CAU are including doxepin, leukotriene receptor antagonist, corticosterone, and several kinds of drugs used to reduce the dose and frequency of corticosteroid use, such as dapsone, chloroquine and hydroxychloroquine, and sulfasalazine.\textsuperscript{33,41} Doxepin is a tricyclic antidepressant, with the dose of 10-25 mg and may be increased to 50 mg taken at night, shows its superiority over diphenhydramine, but it has side effects such as drowsiness, dry mouth, metallic taste, constipation, urinary retention, blurred vision, palpitation, and tachycardia. Prednisone is a corticosteroid drug which is commonly used for long term disease suppression, with the dose of 60 mg daily as pulse dosing for 3-5 days. It is wise to do skin biopsy before using corticosteroids, to differentiate it from angioedema.\textsuperscript{26,33} Zafirlukast (10 mg daily taken at bedtime) and montelukast (20 mg twice daily) are leukotriene receptor antagonists, used in combination with H1 antihistamines.\textsuperscript{33,42} Dapsone inhibits neutrophil adhesion, chemotaxis, lipoxygenase activity, and the cells’ ability to generate reactive oxygen species (ROS). Chloroquine and hydroxychloroquine are thought to have immunosuppressive effects by inhibition of MHC class II antigen presentation and production of inflammatory cytokines such as tumour necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and IFN-γ, raising the pH of phagolysosome and may induce basophilic differentiation of HL-60 cells by increasing the intracellular pH. In

| Table 1. Dosages of representative H1-receptor antagonists\textsuperscript{modified from 37-39} |
| --- | --- | --- |
| **Generation** | **Drugs** | **Dose** |
| **First** | Chlorpheniramine | 4 mg 3-4x/day or 12 mg sustained release formulation 2x/day |
| | Diphenhydramine | 25-50 mg 3-4x/day or at bedtime |
| | Hydroxyzine | 25-50 mg 3x/day or at bedtime |
| **Second** | Doxepin | 25-50 mg 3x/day or at bedtime |
| | Cetirizine | 5-10 mg daily |
| | Loratadine | 10 mg daily |
| | Acrivastine | 8 mg 3x/day |
| | Ebastine | 10-20 mg daily |
| **Third** | Mizolastine | 10 mg daily |
| | Levocetirizine | 5 mg daily |
| | Fexofenadine | 60 mg 2x/day or 120 or 180 mg daily |
| | Desloratadine | 5 mg daily |
neutrophils and monocytes hydroxychloroquine reduced superoxide production and release, and significant decrease on neutrophil lysosomal enzyme activity, raising such effects extend to other leukocytes.41

The third line treatments include: methotrexate, cyclosporine, sulfasalazine, mycophenolate mofetil, omalizumab, autologous serum therapy, intravenous immunoglobulin, and plasmapheresis.33 Methotrexate is a derivate of folic acid that interferes with dihydrofolate reductase and the production of DNA in actively dividing cells. A study found that methotrexate is effective in patients with CAU in a dose of 2.5 mg orally twice a day on Saturday and Sunday every week. Cyclosporine, in doses vary from 3-5 mg/kg as a starting dose and reduced over 3 or 4 months, is a powerful inhibitor of both cell mediated and humoral responses, inhibits the release of histamin from basophils and TNF-α production by mast cells.33 Sulfasalazine, in a dose varies from 2-6 g/day, will produce metabolite as 5-aminosalicylic acid causing reduction of IgE-induced release of histamine in human basophils and mast cells.41 Omalizumab is a recombinant humanized antibody against IgE, acts as a neutralizing antibody by binding IgE at the same site as the high-affinity receptor, as the result IgE is prevented from sensitizing cells bearing high-affinity receptors.33,44 Autologous serum therapy (AST) may prevent relapse of symptoms for durations as long as 2 years. Intravenous immunoglobulin, in a dose of 0.4 g/kg for 5 days, may act as anti-idiotypic antibodies capable of suppressing IgE autoantibodies.33 Mycophenolate mofetil may be used in patients who do not respond to antihistamines and or corticosteroid, and require aggressive therapy to control the disease symptoms. Plasmapheresis is useful in eliminating the functional autoantibodies.33,45 The autologous serum therapy is another method of therapy in CAU. The patients’ serum was separated by centrifuging 5 ml of blood at 2,000 rpm for 10 minutes to separate the serum. Thereafter, every week for nine consecutive weeks, the 2 ml of serum was deep intramuscular injected in alternate buttock or upper arms (autologous serum injection/ASI). Almost 60% of the patients with positive ASST show a significant improvement in their signs and symptoms. If the symptoms are back again or relapses, the booster ASI may be given to which they have responded again. With this method, the patients may get complete asymptomatic for more than 2 years.46

PROGNOSIS

Half of the patients with urticaria alone are free from lesions in 1 year, but 20% have lesions for more than 20 years. Prognosis is good in most syndromes.25 Although angioedema has a different mechanism, in about 50% of the patients with CAU may also have angioedema at the same time, and it has a worse prognosis since there is a possibility that the recurrent episodes of the disease will last until 5 years.25,26

CONCLUSION

Chronic autoimmune urticaria is in patients who may present with transient eruption of itchy, erythematous, edematous swellings of the dermis, which lasts more than six weeks. They have circulating IgG directed against α-subunit of the high affinity IgE receptor or anti-FcεRIα and the less frequent is IgG anti-IgE antibodies. Detailed history is of utmost importance, especially related to the duration of complaint, and should differentiate between type of lesions. The gold standard for detecting clinically relevant to autoantibodies to FceRI is the functional in vitro donor basophil HRA. There are many choices of therapies of CAU, but antihistamines are the first line therapy. Prognosis is good in most syndromes.

REFERENCES

6. Ying S, Kikuchi Y, Meng q, Kay B, Kaplan AP. TH1/ TH2 cytokines and inflammatory cells in skin biopsy specimens from patients with chronic idiopathic


