

The spectrum of acquired and familial cold-induced urticaria/urticaria-like syndromes

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Cold urticaria syndromes are heterogeneous and can be classified into acquired and familial disorders (Box 1) [1,2]. Acquired cold urticaria (ACU) syndromes are characterized by the development of urticaria or angioedema after cold exposure. Although these syndromes are considered benign and self-limiting, several concerns should be addressed in patients with these disorders. Patients with ACU syndromes are susceptible to shock-like reactions during aquatic activities [1–3]. All patients with ACU syndromes should be informed fully of the risks associated with aquatic activities to prevent drowning. ACU syndromes sometimes are associated with serious underlying diseases, such as malignancies [4–6], systemic leukocytoclastic vasculitis [7], and infectious diseases [8–12]. These underlying diseases should be diagnosed and treated without delay to minimize their serious medical consequences. Most ACU disorders are diagnosed by cold contact stimulation tests in which an immediate wheal or angioedema is induced after application to the skin of a cold stimulus of 0°C to 4°C (eg, ice cube) [1,2]. Certain ACU disorders (eg, atypical ACU [2,13,14]) do not exhibit wheal formation after standard cold contact stimulation tests (0°C–4°C) are conducted, and consequently their diagnosis must depend on history and other diagnostic procedures.

There are two autosomal dominant familial cold syndromes: delayed cold urticaria [15] and familial cold urticaria, which has been renamed familial cold

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Box 1. Classification of acquired cold urticaria and familial cold urticaria*ACU with positive cold stimulation time test (CSTT)*

Primary ACU

Secondary ACU

Cryoglobulinemia

Infectious diseases

Leukocytoclastic vasculitis

Miscellaneous: insect stings, drugs, neoplasms

Atypical ACU: atypical responses to CSTT

Systemic ACU

Cold-dependent dermatographism

Cold-induced cholinergic urticaria

Delayed cold urticaria

Localized cold reflex

Familial types

Delayed cold urticaria

Familial cold auto-inflammatory syndrome

auto-inflammatory syndrome (FCAS) [16–18]. The latter disorder has been classified in the family of hereditary periodic fever syndromes, including familial Mediterranean fever, Muckle-Wells syndrome, hyper-IgD syndrome, tumor necrosis factor–associated syndrome, and chronic infantile neurologic cutaneous and articular syndrome (CINCA) [19]. An intense amount of research involving FCAS and other auto-inflammatory syndromes is providing a better understanding of innate immunity and related inflammatory responses.

Historical background

The first cases of ACU were reported in the 1860s with descriptions of swelling of the skin and shock-like symptoms after cold exposure [20]. Duke described “urticaria caused by the action of physical agents,” which included cold urticaria as a prototype of cold hypersensitivity [21]. These urticarial entities subsequently were referred to as physical allergies [22]. Cold urticaria received more attention in 1936 after Horton and Brown’s report, which noted the association of life-threatening, shock-like reactions during aquatic activities [3]. These observations were confirmed in a study that noted that 70% of patients

with ACU, who were referred to a specialty center, exhibited histories of systemic reactions (eg, generalized urticaria, angioedema, or shock-like symptoms) with aquatic activities [1,2].

Researchers have recognized the value of studying ACU syndromes, as they represent reproducible in vivo models of immediate hypersensitivity. Some of the earliest investigations of histamine release were observed in ACU disorders [23–25]. By using in vivo cold challenge techniques, several other mediators (eg, neutrophilic chemotactic activity [26], eosinophilic chemotactic factor [27], platelet-activating factor [28]) were detected in patients with primary ACU. These experiments may represent the first detection of these mediators in a human disease.

Diagnostic cold contact test for acquired cold urticaria

The CSTT is defined as the minimum time of cold contact stimulation required to induce an immediate coalescent wheal [1,2]. A cold (0°C–4°C) stimulus (eg, ice cube in a plastic bag) is applied to the subject's forearm for 5 minutes (Fig. 1). The skin is allowed to re-warm to normal skin temperature. If a coalescent wheal is elicited (Fig. 2), the test should be repeated with shorter times of cold stimulation at 1-minute decrements to establish the minimum



Fig. 1. CSTT performed with beakers filled with ice slurry.



Fig. 2. Confluent wheals appear after 2- and 4-minute applications of cold stimulus to separate skin sites. The minimum time of cold stimulus necessary to induce a confluent wheal (CSTT) was 2 minutes for this patient.

time for induction of a coalescent wheal. To avoid desensitization of the skin to cold, the cold stimulus is not applied to the same skin location. If the test is negative at 5 minutes, the cold stimulus should be applied at 1-minute increments for up to 10 minutes as described before to determine the minimum time for induction of a coalescent wheal. If the test is negative after a 10-minute ice challenge, the patient probably does not have typical ACU.

One other test that has been recommended to diagnose this condition is “hand immersion in 10°C water for 5 minutes” [29]. Hand immersion may induce angioedema (Fig. 3). Caution is advised with this test, as there are descriptions in the literature of patients who have experienced systemic reactions (eg, tachycardia, hypotension, and EKG evidence of t-wave inversions) after hand immersion in ice water for 5 to 6 minutes [3,30]. Use of the CSTT can provide the minimum time required to induce a coalescent wheal and avoids prolonged cold stimulation of an extremity, which could be associated with a systemic reaction.

The CSTT may be negative in atypical forms of cold urticaria. When it is positive in the typical ACU syndromes, it can provide important clinical information for the management of these patients. The CSTT provides a reproducible in vivo test that can be used to determine suppression of cold-induced urtication by medications. There is an inverse relationship between the CSTT and the level of patient sensitivity to cold. Patients with a short CSTT are predictably more sensitive to cold and have a greater likelihood to experience systemic reactions during aquatic activities [1,2].

Diagnostic classification of acquired cold urticaria syndromes

ACU syndromes are divided into two classes: (1) disorders that can be diagnosed by a positive CSTT and (2) disorders with atypical responses to a CSTT.



Fig. 3. Angioedema of the hand after immersion in cold water.

Acquired cold urticaria disorders with a positive cold stimulation time test

This class includes primary ACU (primary ACU) and secondary ACU (secondary ACU).

Primary acquired cold urticaria

Synonyms for primary ACU that commonly are used in medical literature include the following: essential ACU, primary cold urticaria, idiopathic cold urticaria, cold contact urticaria, and essential local cold contact urticaria [1,2].

Diagnosis. The diagnosis of primary ACU depends on (1) historical or physical evidence of acquired cold-induced wheals or angioedema; (2) negative evidence of underlying diseases that is demonstrated by a normal panel of laboratory tests (discussed later in this article), including complete blood cell (CBC) count, erythrocyte sedimentation rate (ESR), antinuclear antibody (ANA), infectious mononucleosis serology, syphilis serology, total complement, and cryoglobulin; and (3) positive immediate induction of urticaria or angioedema with a CSTT at 0°C to 4°C.

Clinical characteristics. Primary ACU is the most common of all ACU syndromes [31,32]. It occurs abruptly, and most studies indicate that it affects individuals of both sexes with equal incidence [1,2,33]. The mean ages of patients in several series ranged from 18 to 25 years [1,2,32]; however, the disorder can affect a wider age range of ages, from 3 months [34] to 74 years [32]. Symptoms may develop months or years before the patients first are evaluated, suggesting that the affected mean age is less than 18 to 25 years [1,32]. Primary ACU symptoms can be induced by exposure to cold environments, [1,2,31], aquatic activities [1,23], ingestion of cold foods and liquids [29], handling of cold objects [34] and other cold stimuli. Clinical manifestations are protean and may involve the following organ systems:

- Skin: nonpseudopodic wheals
- Oropharynx: swelling of the lips, tongue, pharynx
- Lower respiratory tract: hoarseness, wheezing
- Cardiovascular system: hypotension, tachycardia
- Gastrointestinal system: hyperacidity, ulcers, diarrhea
- Reproductive system: uterine contractions
- Central nervous system: headaches, disorientation

Patients can develop pruritic wheals or angioedema, which may be localized or generalized [1,2,32]. The skin lesions usually disappear after several hours. The wheals are typically nonpseudopodic and frequently conform to the shape of the cold stimulus (see Color Fig. 2) [1,2].

Spontaneous recovery of primary ACU has occurred within 1.5 to 2.0 years after onset of symptoms [32]; however, symptoms may persist for a few months [35] to 20 years [15] or longer [32]. The mean duration of symptoms for primary ACU ranges between 4.8 to 9.3 years [1,32]. There is no definitive method to predict the duration of cold urticaria symptoms. There seems to be a correlation between increasing CSTT measurements and improving tolerance to natural cold stimulation [1,2]. Based on these observations, it may be possible to use serial measurements of the CSTT as a means to predict the improvement of symptoms.

Factors determining cold-induced clinical reactions. The clinical patterns of primary ACU that evolve after natural cold exposure are defined as (1) type I, localized urticaria or angioedema; (2) type II, systemic reactions characterized by one or more episodes of generalized urticaria or angioedema without hypotensive symptoms; and (3) type III, severe systemic reactions with one or more episodes of generalized urticaria or angioedema associated with hypotension (eg, dizziness, fainting, disorientation, shock) [1,2]. In a study population of predominantly patients with primary ACU, the incidences of these clinical patterns were 30% for type I, 32% for type II, and 38% for type III [1]. The incidence of severe systemic reactions (type III) in other primary ACU populations ranged from 40% [32] to 42% [36].

Many factors could determine whether a patient may experience any one of the aforementioned clinical patterns. There is a predictable relationship between the time of cold challenge needed to induce a positive wheal response (CSTT) and the type of clinical reaction that patients may experience from natural cold exposure. One retrospective study of patients with primary ACU documented that cold-induced hypotensive reactions (type III) occurred more frequently in patients with a positive CSTT of 3 minutes or less (eg, 57%; 13 of 23 patients) compared with patients with a positive CSTT of more than 3 minutes (eg, 24%; 4 of 17 patients) [1,2]. There seems to be an inverse relationship between the time of cold challenge needed to induce a positive wheal response (eg, CSTT) and the propensity to experience cold-induced hypotensive reactions.

Severe reactions more typically are associated with aquatic activities. Several factors may explain why patients develop severe clinical patterns during aquatic activities, such as: (1) a larger body surface area may be exposed to cold temperature during swimming or related activities; (2) the low temperature of cold water may cause a more rapid decrease of skin temperature or core body temperature; and (3) aquatic activities may be associated with a longer duration of exposure to cold temperature. Any combination of these factors could be responsible for severe clinical reactions (types II and III) with aquatic activities.

Laboratory features and pathogenesis. The following laboratory tests are normal in primary ACU: CBC count, ESR, ANA, infectious mononucleosis serology, syphilis serology, rheumatoid factor, total complement, cold agglutinin, cold hemolysin, cryofibrinogen, and cryoglobulin [1,31]. No data implicate specific antigens that can induce or exacerbate primary ACU. Houser et al [37] and Hogendijk [38] described cases of primary ACU that were exacerbated after a bee-sting reaction. These case reports described an apparent relationship between a bee sting, onset of cold urticaria, and subsequent exacerbation of cold urticaria symptoms after a repeat sting by the same bee species. Assuming that the relationship is valid, one might reclassify this report and similar case reports as examples of secondary ACU (see discussion of secondary ACU later in article). Cases of secondary ACU have erupted after a multitude of antigenic events listed in secondary ACU, such as infectious mononucleosis and drug induction.

It is estimated that 20% to 30% of patients with primary ACU have serum factors that passively can transfer cold urticaria activity to normal recipient skin [39,40]. Sherman and Seebom [40] injected whole serum from a patient with primary ACU into the skin of a normal person. These investigators postulated that “the reactions of the serum were consistent with those of an antibody reacting at temperatures near 0°C with an antigen present in normal human skin.” Convincing evidence suggests that cold urticaria serum factors are identifiable with immunoglobulins. Houser et al [37] and investigators of two other studies [41,42] have demonstrated that cold urticaria serum factors in primary ACU are associated with IgE. Two independent studies have demonstrated that cold urticaria serum factors in primary ACU are associated with IgM [43,44].

The identification of cold urticaria serum factors with IgE has led several investigators to postulate an autoimmune mechanism involving interaction of IgE autoantibodies with a cold-dependent skin antigen [37,45,46]. Data from Kaplan's in vitro model of cold urticaria suggested that a cold-dependent skin component is involved in the pathogenesis of this disorder [45]. These experiments demonstrated that a cold-dependent skin component, such as an antigen, is essential for histamine release. Further support for this autoimmune theory depends on immunochemical identification of the putative cold-dependent skin antigen. Alternatively, other immune mechanisms have been proposed to explain primary ACU. Studies by Gruber and Kaplan [47] demonstrated the presence of autoantibodies to IgE in patients with primary ACU (referred to as idiopathic cold urticaria) and in patients with other forms of urticaria. IgG anti-IgE antibodies were detected in five of nine patients with cold urticaria, four of eight patients with urticarial vasculitis, and three of six patients with chronic urticaria. IgM anti-IgE antibodies were detected exclusively in patients with cold urticaria (ie, two of nine patients). The functional role of these autoantibodies was explored using peripheral leukocytes and passive transfer techniques. Histamine release was detected in a system composed of normal basophils that was exposed to a cold urticaria serum with high titer IgM anti-IgE autoantibodies. Reduction of histamine release was observed in this system after adsorption of the patient's serum with IgE and anti-IgM immunoadsorbents, suggesting that an IgM anti-IgE immunoglobulin was responsible for the serum's histamine-releasing activity. Based on this data, it is reasonable to speculate that previously reported IgM serum cold urticaria factors [43,44] may have represented IgM anti-IgE autoantibodies.

No unified theory has been proposed to explain the role of IgE [37,41,42] and IgM [43,44] cold urticaria serum factors and the function of IgM or IgG anti-IgE autoantibodies [47] in primary and secondary ACU. One possibility is that ACU may be caused by a common mechanism of autoantibody induction. After antigenic stimulation, such as infectious mononucleosis or a bee sting, the evolving antibody response by way of molecular mimicry could include anti-idiotypic antibodies of the IgG or IgM class with anti-IgE activity. Cold temperatures presumably encourage interaction of IgM or IgG anti-IgE autoantibodies with IgE attached to mast cells, which in turn activate mast cells and cause mediator release. Supporting this hypothesis is the observation that 30% to 40% of patients with chronic idiopathic urticaria (CIU) exhibit autoantibodies (ie, IgG autoantibodies) to IgE and IgE high affinity receptors on mast cells that can cause histamine release from mast cells [48,49]. Kaplan et al [47] suggested that the histamine-releasing capability of autoantibodies that is associated with CIU also may involve complement activation. In case reports of patients with secondary ACU and cryoglobulinemia (see discussion of secondary ACU later in this article), purified monoclonal IgG cryoglobulins passively transferred cold urticaria activity [50,51]. Some of these cases of secondary ACU may be caused by complement activation. In view of the discovery of IgG anti-IgE antibodies in CIU [48] and primary ACU [47], it is possible that these cold urticaria-inducing

IgG cryoglobulins may exhibit anti-IgE activity [50,51]. The existence of IgE serum factors that passively can transfer cold urticaria may not be compatible with a unified autoantibody theory to IgE, unless the IgE serum factors exhibit anti-IgE activity or represent IgE antibodies that have complexed with circulating IgG or IgM anti-IgE antibodies. Additional mechanisms may be operative in cold urticaria. The IgE antibodies may represent an autoimmune response to a cold-altered skin antigen, as proposed by Kaplan [45].

There is significant evidence that mast cells and basophils are the primary target cells involved in primary ACU reactions. Degranulation of mast cells after cold challenges has been demonstrated by light and electron microscopy [52]. Data from Kaplan's in vitro model of primary ACU demonstrated that histamine release only can be induced with skin tissue and not with leukocytes, suggesting that the primary target cells are skin mast cells and not blood basophils [45]. Gruber and Kaplan [47] demonstrated evidence that histamine was released by using basophils with serum containing IgM or IgG anti-IgE autoantibodies [31].

Detection of mast cell- and basophil-derived mediators in the blood of patients with primary ACU has provided further support for the involvement of these cell types in this disorder. Using in vivo cold challenge techniques, numerous studies consistently have demonstrated plasma increases in levels of vasoactive mediators, such as histamine [28,53,54], prostaglandin D₂ [54], and platelet-activating factor [28,54], and has shown release of mast cell-derived chemotactic substances (eg, neutrophilic chemotactic factor [26] and eosinophilic chemotactic factor [27,55]).

The involvement of inflammatory cells (eg, neutrophils, monocytes) in the histopathology of primary ACU remains unresolved. Eady et al [56] subjected five patients with primary ACU to repeated cold challenges and examined skin biopsy specimens taken before and after the challenges. These studies revealed histologic evidence of perivascular cellular infiltrates of neutrophils, eosinophils, erythrocytes, monocytes, and fibrin deposition. These data suggest that delayed inflammatory cell involvement can occur in primary ACU if the skin is subjected to prolonged cold stimulation. Sustained cold stimulation may amplify inflammatory cell involvement by way of a late-phase mechanism. From a practical point of view, the involvement of inflammatory mechanisms in the pathogenesis of primary ACU may not develop, because most patients cease cold exposure as soon as symptoms erupt.

Secondary acquired cold urticaria

Diagnosis. The diagnosis of secondary ACU depends on (1) historical or physical evidence of acquired cold-induced wheals or angioedema, (2) positive immediate induction of urticaria or angioedema with a CSTT (0°C–4°C), and (3) positive evidence of an underlying disease or factor that has been associated with the induction of secondary ACU [1,2]. As with primary ACU, clinicians and investigators should be aware that cold-sensitive patients with secondary ACU may experience systemic reactions during prolonged cold immersion testing of an extremity or body part.

Types of secondary acquired cold urticaria. Based on the number of case reports, secondary ACU occurs most frequently with primary [50] and secondary cryoglobulinemia (eg, secondary to chronic lymphocytic leukemia [4], lymphosarcoma [5], leukocytoclastic vasculitis [7], hepatitis C virus infection [57], and angioimmunoblastic lymphadenopathy [58]). The actual incidence of secondary ACU associated with cryoglobulinemia is low. Approximately 3% to 4% of all cryoglobulinemias are associated with cold urticaria [59]. Data obtained from case reports of secondary ACU with primary and secondary cryoglobulinemia revealed the following demographic information: (1) Women are affected more frequently (3:1 ratio of women to men); and (2) the mean age of affected individuals was 49 years (age range, 13–80 years). These data contrast with data for primary ACU, in which it was shown that primary ACU more frequently affects younger individuals of both sexes with equal incidence [1,2].

The second most common type of secondary ACU is associated with infectious diseases. Case reports in the medical literature have described secondary ACU with syphilis [12,60], rubeola, varicella [61] hepatitis [57,62], and respiratory viral infections [32,63]. The best documentation describes the abrupt onset of cold urticaria with infectious mononucleosis [8–11].

Several studies have reported the induction of ACU with drugs such as penicillin [64], oral contraceptives [65], angiotensin-converting-enzyme inhibitor [66], and griseofulvin [67]. Cold agglutinins [31,68], cryofibrinogens [69], and cold hemolysins [12,70] frequently are mentioned in literature reviews as factors that occasionally are associated with ACU; however, the association between these factors and secondary ACU has been poorly documented in the literature. More data are needed to establish valid associations before these tests are requested routinely as part of ACU evaluations.

Leukocytoclastic vasculitis with ACU has been documented in five case reports [7,71–74]. A few case reports have described a causal relationship between neoplasms and ACU [4–6].

Clinical characteristics. Secondary ACU disorders exhibit cold-induced manifestations that are identical to those observed in primary ACU [1,2]. Patients can develop localized or generalized urticaria or angioedema and more severe systemic reactions with shock-like symptoms [1,2]. Patients also exhibit cold-induced clinical manifestations that are characteristic of the type of underlying conditions associated with secondary ACU. Clinical manifestations of secondary ACU with cryoglobulinemia include purpura (especially involving lower extremities), Raynaud's phenomenon, polyarthritis, cutaneous ulceration, gangrene, and other less common symptoms [50,51,59,75–77]. Manifestations of secondary ACU with leukocytoclastic vasculitis include cold-exacerbated urticaria that persists longer than 24 hours, maculopapular eruptions, polyarthritis, and purpura [7,71–73]. This disorder may involve renal, neuromuscular, and gastrointestinal systems [7].

Laboratory features and pathogenesis of secondary acquired cold urticaria with cryoglobulinemia. The diagnosis of cryoglobulinemia is made by letting serum clot at 37°C and removing the serum before cooling. The serum is stored at 4°C for 72 hours, which results in formation of a precipitate that dissolves on re-warming to 37°C [31]. Serum first must be separated from clotted blood at 37°C to avoid removal of cryoglobulins with the clot.

Several investigators have demonstrated passive transfer of cold urticaria activity with purified monoclonal IgG cryoglobulins [50,76]. Data suggest that complement activation was operative in some cases of secondary ACU with cryoglobulinemia (monoclonal and mixed) [51]. Serum complement measurements in patients with secondary ACU and IgG cryoglobulinemia revealed decreased levels of total hemolytic complement activity (CH₅₀) and decreased classic and alternative complement components [5,50,51]. Laboratory data suggest that some cold urticaria IgG cryoglobulins may have been responsible for complement activation, release of C5a and C3a, and degranulation of mast cells [50]. Another hypothesis may explain the association of cryoglobulinemia with ACU. Cold urticaria cryoglobulins could represent IgG anti-IgE autoantibodies that react with IgE attached to mast cells. Cold temperature may favor the interaction of IgG anti-IgE autoantibodies to IgE attached to mast cells, causing mediator release. This hypothesis is supported by data that demonstrated the presence of IgG anti-IgE autoantibodies in two studies of ACU (ie, presumably primary ACU) [47,78]. Although IgE generally is believed to be a noncomplement-activating immunoglobulin, it has been suggested that complement activation associated with cold urticaria cryoglobulins may be caused by the IgG anti-IgE antibody in IgG–IgE immune complexes [47].

Laboratory features of secondary acquired cold urticaria with leukocytoclastic vasculitis. The laboratory features of leukocytoclastic vasculitis with ACU include (1) decreased total complement levels (CH₅₀), decreased classic components (C1q, C2, C4, C3), and occasional evidence of complement activation in immunofluorescent skin biopsies; (2) skin-biopsy evidence of leukocytoclastic vasculitis by light microscopy (ie, cellular infiltrates of polymorphonuclear leukocytes around and within the walls and lumina of small blood vessels with fibrin deposition, extravasation of red blood cells, and nuclear debris) [7,57, 71–73]; and (3) occasional demonstration of immune complexes [7,57].

Laboratory features of secondary acquired cold urticaria with infectious diseases. Patients with ACU secondary to syphilis exhibit a positive serology (eg, rapid plasma reagen [RPR]) [12,60]. A few case reports describe positive Donath-Landsteiner tests that suggest the presence of cold hemolysins [12,60]. One study on the serum of a patient with syphilis and cold urticaria demonstrated the presence of cold hemolysins and a serum factor capable of passively transferring cold urticaria [12].

Patients with secondary ACU caused by infectious mononucleosis exhibit a positive serology for mononucleosis (ie, mono spot test, increased Epstein-Barr virus antibody levels in convalescent serum compared with acute serum) [8–11].

Acquired cold urticaria disorders with an atypical response to cold stimulation time test

This diagnostic class of patients exhibit historical or physical evidence of acquired cold-induced urticaria and angioedema and atypical responses to a standard immediate cold contact test at 0°C to 4°C (eg, CSTT) [1,2].

Systemic atypical acquired cold urticaria

Synonyms [1,79–81] for systemic atypical ACU include systemic ACU, systemic cold urticaria, and generalized cold urticaria.

Diagnosis. Diagnostic parameters for systemic atypical ACU include the following: (1) historical or physical evidence of acquired cold-induced urticaria or angioedema, (2) normal laboratory profile, (3) negative immediate CSTT (0°C–4°C), and (4) positive induction of urticaria or angioedema after exposure to unique cold environmental conditions [1,2].

Clinical characteristics. Approximately 20% of all ACU syndromes are diagnosed as systemic atypical ACU [1,2]. Patients with this disorder can exhibit localized urticaria or angioedema or more severe cold-induced systemic symptoms with hypotension [1,2]. Generalized urticaria or angioedema can develop in regions of the body that are not exposed to cold [79,82]. Patients usually recognize that induction of their cold urticaria symptoms can be reproduced by exposure to unique cold environmental conditions, such as cold humid air [80].

Laboratory features. There are no distinguishing laboratory features for systemic atypical ACU other than the negative response to standard cold contact stimulation tests. Experiments by Illig et al [79] demonstrated that symptom induction is related to a decrease in mean body temperature during exposure to cold environmental conditions. In some patients, cold urticaria can be induced by exposure to a lesser cold stimulus (ie, 8°C–15°C) [83]. These observations suggest that patients with systemic atypical ACU require unique temperature conditions that must be reproduced to elicit a positive urticaria or angioedema response.

Cold-dependent dermatographism

Diagnosis. Diagnosis is defined by (1) historical or physical evidence of acquired cold-induced urticaria or angioedema, (2) negative immediate CSTT (0°C–4°C), and (3) induction of urticaria after stroking pre-cooled skin [82,84,85]. This disorder should be differentiated from case reports describing

the frequent combination of primary ACU and dermographism that occurs at normal skin temperature [32,85].

Clinical characteristics. Dermographic whealing can be demonstrated after stroking pre-cooled skin. The skin is stroked immediately during the cooling of skin, because dermographic wheals do not develop when the skin temperature returns to normal [82]. Clinical histories include localized cold-induced urticaria (type I) [82] or severe systemic reactions [84] to cold (type III) with vomiting, cramping, abdominal pain, diarrhea, generalized hives, and syncope.

Cold-induced cholinergic urticaria

Diagnosis. Diagnosis is made by (1) historical or physical evidence of acquired cold-induced wheals or angioedema, (2) negative immediate CSTT (0°C–4°C), (3) exercise in cold environments leading to generalized urticaria, and (4) a positive methacholine skin test [86]. This disorder should be differentiated from case reports that describe the combination of primary ACU and heat-induced cholinergic urticaria [87,88].

Clinical characteristics. Patients with this disorder develop punctate urticaria after exercising in cold environments. Exercise in warm environments does not induce urticaria, as observed with heat-induced cholinergic urticaria. Cold-induced cholinergic urticaria usually is generalized and can occur in clothed areas of the body.

Delayed cold urticaria

Diagnosis. Diagnosis is made by (1) historical or physical evidence of acquired urticaria developing 12 to 48 hours after natural cold exposure and (2) negative immediate CSTT (0°C–4°C). Urtication develops 12 to 48 hours after application of a cold contact stimulation test, however [89–91].

Clinical characteristics. Patients exhibit delayed urticaria (ie, 12–48 hours) after natural cold exposure [89–91]. The urticarial lesions typically are confined to cold-exposed skin and mucosal surfaces, such as the lips and oropharynx. None of the case reports described cold-induced shock reactions (type III).

Localized cold-reflex urticaria

Diagnosis. Diagnosis of this condition depends on (1) historical or physical evidence of acquired cold-induced urticaria, (2) negative immediate CSTT at the direct site of cold stimulation, and (3) positive immediate urticarial response at a skin location that is distant (ie, 5–8 cm) from the site of cold stimulation [14,92].

Clinical characteristics. Two patients have been described with this atypical form of ACU [14,92]. Both patients exhibited pinhead- or punctate-sized pruritic wheals after cold exposure. Neither patient had histories of shock-like reactions from cold exposure. Existence of this variant is supportive of Toth-Kasa's

contention that nerve pathway stimulation may be important in the pathogenesis of ACU [93].

Familial delayed cold urticaria

Diagnosis. Diagnosis depends on (1) historical or physical evidence of pruritic urticarial-like lesions developing as a delayed response (9–18 hours) after cold stimulation, (2) negative immediate CSTT but with urtication developing several hours after application of a cold contact stimulation test, and (3) autosomal dominant inheritance of delayed cold urticaria responses.

Clinical characteristics. Patients develop erythematous, pruritic, urticaria-like swellings of the skin approximately 9 to 18 hours after cold exposure. The delayed urticaria typically resolves into hyperpigmented skin lesions. Family studies suggested an autosomal dominant mode of inheritance for this disorder [94].

Familial cold auto-inflammatory syndrome

FCAS previously was referred in the medical literature as familial cold urticaria, cold hypersensitivity, familial cold polymorphous eruption, cold pathergy, and cold-specific vasomotor neuropathy. It traditionally has been included in the spectrum of cold urticaria, even though the rash associated with this inherited disease is not a true urticaria by physical appearance or histopathology. This disorder has been included in the family of auto-inflammatory diseases and more specifically in the hereditary periodic fever disorders, because the episodic cold-induced rash is associated with fever and other systemic inflammatory symptoms [19].

Historical background. In 1940, Kile and Rusk described a large North American family with members who developed urticaria-like eruptions after cold exposure [16]. The report demonstrated that this syndrome was distinct from classic ACU in that patients did not develop localized urticaria immediately after direct contact with cold water, but developed a rash hours after a generalized cold exposure. The family in the report described symptoms of fever, chills, and arthralgias associated with the rash. Since that time, approximately 20 families have been reported with this same clinical picture primarily in North America and Europe. These reports demonstrate the transmission of FCAS in an autosomal-dominant fashion (Fig. 4). Sporadic cases have been documented, as is common for autosomal dominant diseases. There is variability in the clinical picture of FCAS in that some family members have more severe symptoms, and a few families have members that have developed systemic amyloidosis.

Clinical characteristics and laboratory features. Up to 60% of patients with FCAS develop a cold-induced rash at birth, and 95% develop the rash in the first 6 months of life [12]. Other symptoms develop later in childhood and persist throughout life. Longevity is usually normal in patients with FCAS. Most

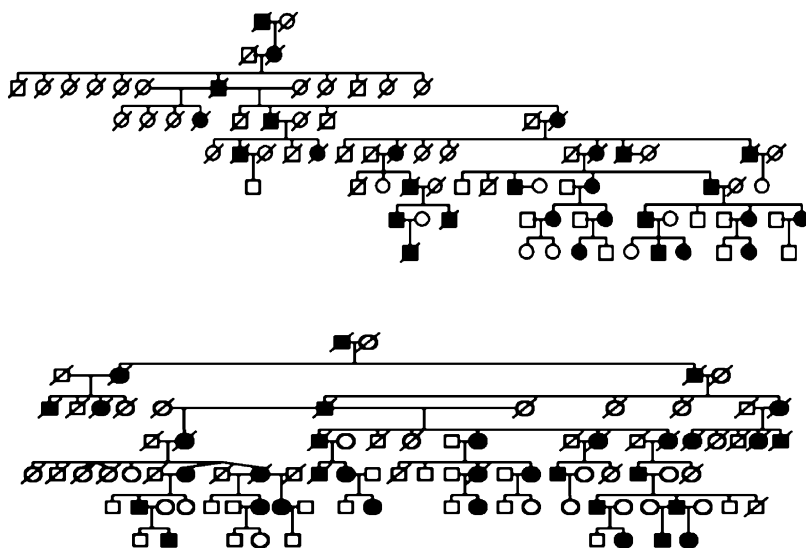


Fig. 4. Pedigrees of two families with FCAS demonstrating autosomal dominant (black circles and black squares) inheritance. ●, affected male; ○, unaffected male; ■, affected female; □, unaffected female; diagonal line, deceased.

patients experience some baseline daily symptoms in the absence of cold exposure; however, exposure to mild temperatures, such as air-conditioned rooms, is sufficient to elicit attacks. The development of the rash often is delayed (1–2 hours after exposure). Most attacks last less than 1 day, and some patients describe a diurnal pattern of attacks in the afternoon or evening that resolve by



Fig. 5. FCAS exanthem after cold exposure. The exanthem is characterized by erythematous maculopapular lesions.



Fig. 6. Close-up view of FCAS exanthem.

morning. The rash occasionally has urticarial features but more commonly is characterized by erythematous and edematous papules and plaques (Figs. 5, 6). The rash is rarely pruritic and often is described as tender. Additional symptoms include conjunctivitis, sweating, headache, drowsiness, thirst, and nausea [17]. Laboratory abnormalities include polymorphonuclear leukocytosis, occasionally ranging from 20,000 to 40,000 during acute episodes, and increased markers of inflammation, such as elevated sedimentation rates and levels of C-reactive protein [95,96]. Skin biopsies taken from patients with FCAS have shown dermal

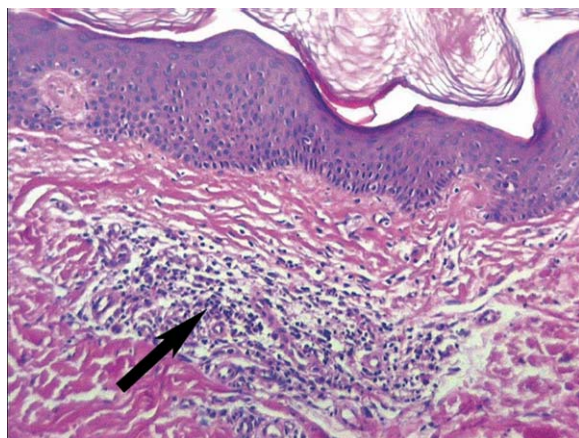


Fig. 7. Skin biopsy specimen of FCAS characterized by presence of marked perivascular polymorphonuclear infiltration in the dermis.

edema and a perivascular leukocytic infiltrate consisting primarily of neutrophils (Fig. 7) [96]. Increased vascularity has been described, although vasculitis is not reported commonly. There is no evidence of increased histamine release or mast cell degranulation in these patients, which occurs in primary cold urticaria.

Diagnosis. Several features of FCAS differentiate it from typical ACU, including the early age of onset, delayed response of 1 to 2 hours after cold exposure, and development of significant leukocytosis. Additional symptoms that may be experienced during an attack include fever and arthralgia. FCAS can be differentiated from typical ACU and familial delayed cold urticaria (discussed elsewhere in this article), because the CSTT is negative in FCAS. Based on experience with 80 patients, the diagnosis of FCAS can be made using the following diagnostic criteria [17,97]:

- Presence of one major criterion, namely recurring intermittent episodes of fever and rash that primarily follow natural or experimental generalized cold exposures and the presence of three or more of the following five minor criteria:
- Disease inheritance is of autosomal dominant pattern.
- Age of onset is less than 6 months of age.
- Duration of most attacks is less than 24 hours.
- Conjunctivitis is associated with attacks.
- Deafness, periorbital edema, lymphadenopathy, and serositis are not present.

Genetics and pathophysiology. The gene for FCAS was identified on a relatively narrow region of chromosome 1q44 [18]. Mutations were isolated to a single novel gene termed *CIAS1* (cold-induced auto-inflammatory syndrome) [98]. Investigators identified more than nine mutations in exon 3 of *CIAS1* in patients with FCAS [97,99,100]. Some patients with classic FCAS features do not possess mutations in *CIAS1*, suggesting the involvement of additional genes.

CIAS1 mutations have been identified in two other auto-inflammatory diseases that exhibit some similarities to FCAS [101,102]. Muckle Wells syndrome (MWS) is an autosomal dominant inherited condition that is characterized by recurrent attacks of rash, arthritis, and fever with no consistent trigger, such as cold exposure [99]. Approximately two of three patients with MWS also develop progressive sensorineural hearing loss, and one of three patients develops systemic amyloidosis resulting in renal disease (nephrosis) [103]. Another auto-inflammatory disorder with mutations of *CIAS1* is the CINCA syndrome (chronic infantile disease involving neurologic, cutaneous, and articular systems) [101]. It is characterized by chronic severe systemic inflammation with fever, arthritis, and rash. Patients also develop hearing loss, chronic aseptic meningitis, seizures, developmental delay, ocular abnormalities, characteristic dysmorphic features, and cartilaginous overgrowth of the distal femur and patella [104].

Overlap in clinical features may blur the margins between these auto-inflammatory diseases, making it difficult to differentiate between FCAS and MWS. Some patients with MWS report worsening of symptoms with cold exposure, and some families with FCAS develop amyloidosis. Some patients with CINCA have no obvious neurologic manifestations, and some patients with MWS have dysmorphic features that are consistent with CINCA. This overlap has prompted investigators to suggest that these three auto-inflammatory diseases are a spectrum of one disease, with FCAS as the mildest form and CINCA as the most severe form.

Despite the association of FCAS with cold, no role for cryoglobulins has been demonstrated in FCAS. Passive serum transfer studies were negative, arguing against a serum factor or circulating antibody. There is no evidence for histamine release, as is seen in primary and secondary ACU. Elevated serum levels of interleukin 6 (IL-6) have been found in the serum of four patients with FCAS, peaking approximately 4 hours after an experimental cold challenge (Hal Hoffman, MD, unpublished data, 2002, 2003). Levels of IL-1 RNA was elevated in the skin of four patients (Hal Hoffman, MD, unpublished data), and the serum level of granulocyte colony-stimulating factor has been reported to be elevated in one patient [105].

The identification of the gene responsible for FCAS has provided several clues to the pathogenic mechanisms involved in this disorder. *CIAS1* is expressed primarily in leukocytes (monocytes and granulocytes), which is consistent with the inflammatory nature of the disease. as granulocytes have a significant role in this disorder. *CIAS1* codes for a protein termed cryopyrin, which has structural features (domains) that are similar to some proteins involved in inflammation and apoptosis [98]. Several of these proteins have been linked to specific inflammatory diseases. The pyrin domain, located at the beginning of cryopyrin, first was identified in pyrin, a protein with unclear function that causes familial Mediterranean fever when it is mutated. This domain is similar to death domains (caspase activation and recruitment domains [CARDs]), which are part of several proteins that control apoptosis [106,107]. Structural features at the end of cryopyrin include a nucleotide-binding-site domain and multiple leucine-rich repeats. This combination is conserved in critical proteins in organisms as distantly related as plants (plant-resistance proteins) and insects (toll genes). Important human genes with this structure are toll-like receptors and nucleotide oligomerization domain (NOD) proteins, which are critical players in innate immunity [105]. The NOD2 protein has been implicated in susceptibility to Crohn's disease [108,109].

Some progress has been made in unraveling the pathways involved in cryopyrin function. Several groups of investigators have shown that cryopyrin interacts with another pyrin-containing protein called ASC (apoptosis-associated speck-like protein with a CARD), leading to activation of nuclear factor κ B (NF- κ B). NF- κ B is one of the transcription factors involved in regulating many inflammatory cytokines, including IL-6. It also has been shown that cryopyrin–ASC interactions lead to activation of caspase 1, an enzyme involved in IL-1

production [110,111]. These in vitro protein functions are consistent with the inflammatory pathways seen in vivo. Cryopyrin has a regulatory role in innate immune responses. It is unclear how alterations in cryopyrin cause the unregulated inflammation in response to cold.

Interrelationships between primary, secondary, and atypical acquired cold urticaria

Although the association of an underlying disease or factor distinguishes secondary ACU from primary ACU, there are important clinical and immunopathologic similarities between these diagnostic entities. Both exhibit (1) a positive immediate CSTT; (2) identical cold-induced manifestations such as urticaria, angioedema, and hypotensive episodes; (3) evidence that mast cells are the primary target cells [112] and that vasoactive mediators are involved in their pathophysiology [23,27]; (4) immunoglobulin serum factors that passively can transfer cold urticaria activity to skin [37,43–45,50]; and (5) involvement of anti-IgE autoantibodies [46,47,78] that may be identical to serum passive cold urticaria transfer factors, particularly for primary ACU. Another similarity between secondary ACU and primary ACU is derived from data suggesting that late-phase inflammatory mechanisms may be operative in some of these disorders. Evidence of involvement of inflammatory cell (eg, neutrophils, monocytes) has been described in primary ACU [56] after repeated cold challenge studies and in patients with secondary ACU caused by leukocytoclastic vasculitis [7,71,72]. Inflammatory cell involvement may indicate that late-phase reactions or vasculitis with immune complex mechanisms may be involved in the immunopathology of some of these disorders. Inflammatory mechanisms may evoke late-phase reactions in patients with cold urticaria who are subjected to prolonged environmental cold stimulation, such as during cardiac bypass surgery. All of the aforementioned similarities suggest that some cases of primary and secondary ACU could be viewed as related clinical disorders with common mechanisms of pathogenesis.

The natural history of atypical ACU needs to be studied more extensively. It is unclear if atypical ACU develops de novo or whether these disorders represent the end stage of other forms of ACU. Several cases of atypical ACU initially presented with clinical features of primary ACU. Some of these patients first exhibited a positive CSTT; after several years of follow-up, they converted to a negative CSTT [1]. Several patients remained symptomatic despite the negative CSTT. If these patients were evaluated for the first time without any previous knowledge of their primary ACU, they would have been diagnosed as systemic atypical ACU. The natural history of such cases raises the speculation that atypical ACU occasionally may represent an end stage of primary ACU. ACU syndromes probably are more interrelated than previously recognized, suggesting that long-term studies are needed to study the natural history of these heterogeneous disorders.

Management of acquired cold urticaria and familial cold urticaria syndromes

Acquired cold urticaria

A cardinal objective of ACU management is the prevention of shock reactions during aquatic and other cold-temperature exposures. A high percentage of shock-like reactions have been observed in patients with primary and secondary ACU who exhibited a positive CSTT of less than 3 minutes [1,2]. Patients with a negative CSTT (ie, atypical ACU) also have experienced systemic shock reactions during aquatic activities [1,2]. All patients with ACU (with or without a positive CSTT) should avoid aquatic activities until their symptoms have resolved spontaneously.

The pharmacologic management of ACU syndromes has been effective in suppressing symptoms. Cyproheptadine (Periactin) was the first H₁ antihistamine to be studied with a double-blind protocol [113]. Its efficacy in primary ACU was demonstrated by improved symptom scores and prolongation of CSTT measurements. Doxepin (Atapin, Sinequan), which is an antihistamine with H₁- and H₂-receptor antagonist activity, also suppresses cold urticaria reactions [28,114]. Other studies reported the benefits of treating primary ACU with combination H₁- and H₂-receptor antagonists, such as cyproheptadine with cimetidine [114], hydroxyzine with cimetidine, and terfenadine with cimetidine [115]. Other medications that have been beneficial include mizolastine (second-generation antihistamine) [116], cetirizine with zafirlukast [117], and montelukast alone (Singulair) [118]. The therapeutic efficacy of ketotifen in primary ACU has been well documented in several reports, including one double-blind study [119]. The therapeutic efficacy of the aforementioned medications has been demonstrated only in patients with primary and secondary ACU. There is a paucity of data supporting the therapeutic benefits of these medications in all forms of atypical ACU.

The doses of cyproheptadine and doxepin should be titrated to obtain optimal benefit with the least amount of side effects [1,2]. These medications may produce soporific side effects and can stimulate appetite and weight gain. Treatment with cyproheptadine should begin at 2 mg/d and then gradually increased to 2 to 4 mg three times a day, depending on spontaneous occurrences of cold urticaria and patient tolerance of side effects. Similarly, doxepin can be started at 10 mg/d and then gradually increased to 10 to 25 mg three times a day. Doxepin should not be used in conjunction with monoamine oxidase inhibitors or in patients with glaucoma or urinary retention. When treating with either medication, serial CSTT measurements should be used as objective indicators of cold urticaria suppression. A CSTT measurement of greater than 3 minutes should be a goal of pharmacologic therapy, because shock-like reactions occur more frequently in patients with primary and secondary ACU who have a CSTT of less than 3 minutes. By achieving this endpoint, patients may have a reduced risk for experiencing systemic shock-like reactions during cold expo-

sure [1,2]. If patients participate in aquatic activities, they should receive prophylactic therapy with one of these medications. They also should be advised to swim with a friend and instructed on the proper use of emergency adrenalin kits.

Several unrelated pharmacologic agents have been used in the treatment of cold urticaria syndromes. Several reports have described suppression of cold urticaria symptoms with large doses of penicillin [120,121]. Further studies are needed to confirm these observations and to elucidate the mechanism of penicillin action in these disorders. Corticosteroids have no suppressive therapeutic effect in primary or secondary ACU [122]. Use of corticosteroids in the therapy of cold urticaria syndromes seems to be inappropriate unless there is evidence of a late-phase inflammatory cell response or if the patient is exposed to prolonged cold stimulation, such as during cardiopulmonary bypass surgery [123,124].

When pharmacologic management is not effective, cold tolerance induction has been recommended [125]. One schedule suggests immersion of extremities and other body parts in 15°C water for 5-minute intervals every hour until the urticaria ceases [126]. This time-consuming procedure frequently leads to non-compliance. One follow-up study of 19 patients revealed that only two patients remained compliant 6 months after achieving tolerance to cold [36]. Cold tolerance can disappear rapidly if patients do not maintain a daily schedule of cold immersion, and a noncompliant patient unknowingly can become susceptible to cold-induced systemic reactions [127]. One theory suggests that tolerance is caused by exhaustion of mast cell mediators [127]. One study contradicted this theory, because electron microscopic studies revealed that intact mast cells in biopsy specimens of skin obtained from a patient with primary ACU were rendered tolerant to cold after repeated cold challenges [52].

Specialized situations may occur in the management of ACU syndromes. Underlying disorders that may be causing the cold urticaria symptoms, such as chronic lymphocytic leukemia with cryoglobulinemia, should be treated. The cold urticaria symptoms may improve, if chronic lymphocytic leukemia and cryoglobulinemia respond to chemotherapy. Another difficult management situation can present when patients with cold urticaria require surgery. Operating room temperatures should be increased to prevent cold induction of urticaria, angioedema, and hypotension. Intravenous fluids and blood transfusions should be pre-warmed to 37°C before administration to prevent induction of cold-induced symptoms [124]. One report described the successful management of a patient with primary ACU who underwent a hypothermic cardiopulmonary bypass procedure [123]. The patient was premedicated successfully with H₁ and H₂ antihistamines and intravenous corticosteroids. The rationale for using steroids was questioned in that report, because steroids did not prevent histamine release during the hypothermic bypass procedure. In that setting, however, the use of steroids may have inhibited mediator amplification associated with late-phase inflammatory reactions, because the patient undergoing bypass surgery was exposed to prolonged cold stimulation.

Familial cold auto-inflammatory syndrome

Up until recently, there were no definitive treatments for FCAS, so management consisted primarily of avoidance of cold. Corticosteroids have been effective if used in sufficiently high dosages (>30 mg/d of prednisone), but their long-term use is limited by side effects. Nonsteroidal anti-inflammatory drugs provide some relief from arthralgias but not other symptoms. Anabolic steroids and gold have been effective in a few cases [17]. The availability of new anticytokine therapies, specifically anakinra (the recombinant IL-1 receptor antagonist), has provided the promise of safe and effective therapies. Case reports concerning patients with MWS [128] have demonstrated significant effectiveness with anakinra in preventing symptoms and decreasing chronic systemic inflammation that can lead to amyloid-induced nephrosis. Four patients with FCAS have been treated effectively with the same medication (Hal Hoffman, MD, San Diego, CA, unpublished data, 2003). No controlled clinical trials or long term studies have been performed. A role for anakinra and other new therapies in FCAS has not been established definitively.

Summary

Investigations of cold urticaria syndromes have provided information that has added to the understanding of ACU, CIU, and innate immunity by way of investigations of FCAS. Continued exploitation of ACU should be encouraged, because this form of urticaria is reproducible and is an attractive model for investigation of urticaria [46]. Several mechanisms that are operative in ACU have been shown to be involved in the pathophysiology of CIU, such as the participation of a wide range of mediators and the potential role of circulating autoantibodies. FCAS is a reproducible disorder that is triggered by cold and is an excellent clinical model to study inflammation. The continued immunogenetic investigation of FCAS will provide elucidation of innate immune mechanisms that may have wide applications involving chronic inflammatory diseases, such as Crohn's disease, lupus erythematosus, and rheumatoid arthritis.

Studies of ACU have depended on serum passive transfer techniques that are no longer used because they are potentially unsafe. Kaplan's skin biopsy model of cold urticaria may be a promising alternative because it uses *in vitro* technology [45]. Applications of this *in vitro* model should be pursued to further characterize serum cold urticaria factors, autoantibodies, and the putative cold-dependent skin antigens that may be involved in the pathogenesis of these disorders. There is also a need to standardize cold test techniques. Cryoprobes developed by Curnow [16] and Toth-Kasa [129] may be useful in documenting temperature thresholds that can induce urtication. This technology may be useful in diagnosing patients with atypical ACU and reproducing cold urticaria for investigative purposes.

Long-term follow-up of all forms of cold urticaria would assist in understanding the natural history of these disorders. Acceptance of a diagnostic classification of cold urticaria disorders should be encouraged, so that data from future investigations can be collated more accurately and used for statistical analysis. The nomenclature and taxonomy proposed in this article can form the groundwork for a diagnostic classification of these heterogeneous disorders.

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