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How not to miss autoinflammatory diseases masquerading as urticaria

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Abstract

Urticarial skin reactions are one of the most frequent problems seen by allergists and clinical immunologists in daily practice. The most common reason for recurrent wheals is spontaneous urticaria. There are, however, several less common diseases that present with urticarial rash, such as urticarial vasculitis and autoinflammatory disorders. The latter include cryopyrin-associated periodic syndrome and Schnitzler's syndrome, both rare and disabling conditions mediated by increased interleukin-1 secretion. Apart from the urticarial rash, patients are suffering from a variety of systemic symptoms including recurrent fever attacks, arthralgia or arthritis and fatigue. Autoinflammatory diseases are often associated with a diagnostic delay of many years and do not respond to antihistamines and other treatments of urticaria. Also, the chronic inflammation may lead to long-term complications such as amyloidosis. It is therefore important not to miss these diseases when diagnosing and treating patients with chronic recurrent urticarial rash. Here, we present clinical clues and tips that can help to identify autoinflammatory disorders in patients presenting with chronic urticarial rash and discuss their clinical picture and management.

Abbreviations
AOSD, Adult-onset Still's disease; CAPS, Cryopyrin-associated periodic syndrome; CRP, C-reactive protein; CSU, Chronic spontaneous urticaria; ESR, Erythrocyte sedimentation rate; FCAS, Familial cold autoinflammatory syndrome; FMF, Familial Mediterranean fever; HIDS, Hyper-IgD and periodic fever syndrome; MAS, Macrophage activation syndrome; MKD, Mevalonate kinase deficiency; MWS, Muckle–Wells syndrome; NOMID, Neonatal onset multisystem inflammatory disease; PFAPA, Periodic fever, aphthous stomatitis, pharyngitis and adenitis; SAA, Serum amyloid A; SchS, Schnitzler's syndrome; SLE, Systemic lupus erythematosus; soJIA, Systemic-onset juvenile idiopathic arthritis; TNF, Tumour necrosis factor; TRAPS, TNF-receptor-associated periodic syndrome.

Urticarial rash: a diagnostic conundrum

Urticarial rashes are among the most frequent problems seen by allergists and clinical immunologists in daily practice. Patients present with multiple wheal-and-flare-type skin lesions that are usually itchy. Acute urticaria is characterized by transient recurrent wheals and/or angioedema for up to 6 weeks. It may be associated with acute upper respiratory tract viral infections or intolerance reactions to foods or drugs (1). In most cases, symptoms rapidly cease to occur after a couple of days or weeks, and the causes of acute urticaria are usually not a reason for ongoing concern.

Chronic urticaria is much less common than acute urticaria but still a frequent condition. In patients with recurrent

wheals, chronic spontaneous urticaria (CSU) is the most common underlying disease (Table 1). Chronic spontaneous urticaria, that is, recurrent spontaneous wheals, angioedema or both occurring on a regular basis for more than 6 weeks, has a point prevalence of 0.5–1% in the European population (2). It is often associated with intolerance reactions to food and drugs, chronic infections and autoreactivity (i.e. inflammatory skin reactions after intracutaneous injection of autologous serum) or functional autoantibodies (1). In addition, there are a number of inducible forms of chronic urticaria (e.g. dermographic, cold-induced, solar, cholinergic urticaria), which are elicited by physical or other stimuli such as water, UV light or an increase in body temperature. The underlying mechanisms of inducible chronic urticarias are largely unknown. As in spontaneous urticaria, the first-line symptomatic treatment of choice is the use of nonsedating antihistamines (3). Importantly there are several much less common diseases all of them autoinflammatory disorders, that mimick urticaria (4) (Table 1).

Autoinflammatory diseases

In contrast to autoimmune diseases, which are mediated by T and B cells and other key players of adaptive immunity, autoinflammatory diseases are disorders of the innate immune system. The best understood autoinflammatory diseases are the hereditary periodic fever syndromes, which include cryopyrin-associated periodic syndrome (CAPS), familial Mediterranean fever (FMF), hyper-IgD syndrome (HIDS) and TNF-receptor-associated periodic syndrome (TRAPS). They are characterized by episodic fever and chronic inflammation of the skin, joints and various other organs. Amyloid A amyloidosis as a result of the chronic inflammation is the most serious long-term complication of these diseases (5). Patients often suffer from a markedly impaired quality of life, and the number of missed school and working days is high (6, 7).

Autoinflammatory disorders are very rare entities, and limited disease awareness even among specialist physicians often results in a diagnostic delay of many years or even decades. Delay in diagnosis may lead to irreversible long-term complications, impaired quality of life and long-term, often poorly effective, immunosuppressive therapies including systemic glucocorticoids and others which carry their own serious side effects. Despite some recent important advances, the diagnosis and treatment of autoinflammatory syndromes remain challenging. Skin manifestations such as urticarial rash are among the earliest and most prominent symptoms in these disorders. In fact, urticarial eruptions are prototypic skin lesions of autoinflammatory conditions and can help to identify these diseases in their early stages (Table 2).

Cryopyrin-associated periodic syndrome

Urticarial rash, or in some cases maculo-papular rash, occurs in almost all patients with CAPS. Further symptoms include recurrent fever attacks, arthralgia or arthritis, eye inflammation, fatigue and headaches. Cryopyrin-associated periodic syndrome, also called cryopyrinopathies, used to be classified as three distinct entities and was previously referred to as familial cold autoinflammatory syndrome (FCAS), Muckle–Wells syndrome (MWS) or neonatal onset multisystem inflammatory disease (NOMID). It is now clear that CAPS covers a continuum of disease severity with considerable overlap in clinical symptoms and a lack of clear genotype/phenotype correlation (8) (Table 2). With about 1000 known patients worldwide, CAPS represents an orphan disease. It is caused by autosomal dominant mutations in the *NLRP3* gene that encodes cryopyrin, a key component of an intracellular multiprotein complex, named the NLRP3 inflammasome, which regulates the processing of interleukin-1β (IL-1β), a potent pro-inflammatory cytokine (9). The spontaneous secretion of IL-1β from macrophages (10) and skin mast cells of patients with CAPS (11) as well as the dramatic response to treatment with IL-1β neutralizing drugs (12–14) indicates that IL-1β plays a central role in the pathogenesis of CAPS. Cryopyrin-associated periodic syndrome is diagnosed on the basis of the clinical presentation, family history and laboratory work-up including mutation analysis. The treatment with IL-1β neutralizing drugs has been shown to be effective and well-tolerated in all three subgroups of CAPS (12–17).

Table 1 Underlying mechanisms and causes of chronic urticarial rash

Mast cell mediator–mediated	Interleukin-1-mediated*
Chronic spontaneous urticaria (CSU)	Cryopyrin-associated periodic syndrome (CAPS)
CSU due to autoreactivity	
CSU due to functional autoantibodies	Schnitzler's syndrome (SchS)
CSU due to infection	
CSU due to intolerance	Other autoinflammatory disorders:
CSU due to unidentified causes	
	NLRP12-associated cold-induced autoinflammatory syndrome (FCAS2)
Inducible urticarias	Systemic-onset juvenile idiopathic arthritis (soJIA)
	Adult-onset Still's disease (AOSD)
	Mevalonate kinase deficiency (MKD)
	TNF-receptor-associated periodic syndrome (TRAPS)

*Interleukin-1 may also be, at least in part, mast cell-derived.

Table 2 Autoinflammatory diseases that present with urticarial rash

	CAPS							MKD		
	FCAS	MWS	NOMID	Schnitzler's syndrome	NLRP12-associated FCAS	soJIA	AOSD	HIDS	Mevalonic aciduria	TRAPS
Skin manifestation	Urticarial rash	Urticarial rash	Maculo-papular exanthema >Urticarial rash	Urticarial rash	Urticarial rash	Fleeting salmon-coloured macular rash >urticarial rash	Fleeting salmon-coloured macular rash >urticarial rash	Morbilliform rash > urticarial rash		Migratory painful erythemas >urticarial rash
Gene/ Inheritance pattern	NLRP3/ Autosomal dominant	NLRP3/ Autosomal dominant	NLRP3/ Sporadic or autosomal dominant	Complex	NLRP12/ Autosomal dominant	Complex	Complex	MVK/Autosomal recessive		TNFRSF1A/ Autosomal dominant
Age of disease onset	First 6 months of life	Infancy to adolescence	Neonatal or early infancy	Ca. 50 years	Infancy to adolescence	<16 years	≥16 years	Infancy		Early childhood
Distinctive features	Symptoms mainly triggered by cold	Sensorineural hearing loss	Aseptic meningitis Arthropathy	Monoclonal gammopathy	Symptoms (exclusively) triggered by cold	Serum Ferritin/ Exclusion of other diseases	Serum Ferritin/ Exclusion of other diseases	Aphthous ulcers Lymphadenopathy Serum IgD ↑ MVK↓		Periorbital oedema Abdominal pain
Flare pattern	<24 h flares	24–48 h flares Continuous symptoms with flares	Continuous symptoms with flares	<24–48 h flares Continuous symptoms with flares	2–10 days flares	Strongly varying, monophasic, polyphasic and continuos courses possible	7–14 days flares	3–7 days flares		7–21 days flares
Amyloidosis risk	Low	25–33%	Low	Low	Not known		Low	Low		14–25% of patients
Complications		Sensorineural deafness in 40%	Chronic meningitis with CNS damage Severe infections	Lymphoproliferative disorder		MAS Devastating arthritis	MAS Devastating arthritis	Exacerbation after immunization	Cerebellar ataxia Mental retardation Haematological abnormalities	Fasciitis
Treatment	IL-1 blockade	IL-1 blockade	IL-1 blockade	IL-1 blockade IL-6 blockade	Glucocorticoids IL-1 blockade	Glucocorticoids IL-1 blockade IL-6 blockade	Glucocorticoids IL-1 blockade IL-6 blockade	Glucocorticoids TNF blockade IL-1 blockade		Glucocorticoids IL-1 blockade IL-6 blockade

CAPS, Cryopyrin-associated periodic syndrome; AOSD, Adult-onset Still's disease; soJIA, Systemic-onset juvenile idiopathic arthritis; HIDS, Hyper-IgD and periodic fever syndrome; MWS; Muckle–Wells syndrome; NOMID, Neonatal onset multisystem inflammatory disease; AOSD, Adult-onset Still's disease.

Schnitzler's syndrome

Schnitzler's syndrome (SchS) is characterized by recurrent urticarial skin lesions (Fig. 1) and a monoclonal gammopathy (IgM or IgG class) in combination with signs and symptoms of systemic inflammation (18). The frequency of urticarial rashes varies considerably among patients. Most patients report daily symptoms, but some experience urticarial rashes only a few times a year. Other symptoms in SchS include recurrent fever attacks, bone and muscle pain, arthralgia or arthritis, and lymphadenopathy (19) (Table 2). SchS is a very rare disease with <150 reported cases (20). The first symptoms usually start at the age of 50, and it seems to be an acquired disorder. Spontaneous remissions have only very rarely been reported (21, 22). About 15% of patients eventually develop a lymphoproliferative disorder, most often Waldenström's macroglobulinemia (20). The pathogenesis of SchS is unknown but widely assumed to be inflammasome- and IL-1β-mediated, similar to that of CAPS (23).

Owing to the limited awareness and rarity of the disease, many cases of SchS take years and even decades to be diagnosed. Consequently, patients usually receive multiple inadequate and useless therapies before being treated effectively. At present, there is no licensed standard therapy available for the treatment of SchS. Case series, however, report successful treatment of SchS with anti-IL-1 therapies resulting in complete or nearly complete remission of symptoms in almost all cases (24–28).

NLRP12-associated cold-induced autoinflammatory syndrome (FCAS2)

Recently, single cases of *NLRP3* mutation-negative, familial cold-induced rashes have been linked to mutations of the *NLRP12* gene (29, 30). The clinical phenotype of this rare autosomal dominant inherited disorder resembles a mild form of CAPS. Thus, symptoms in most patients are limited to cold-induced urticarial rashes, arthralgia and myalgia (30) (Table 2).

Adult-onset Still's disease

The main diagnostic criteria for Adult-onset Still's disease (AOSD) include recurrent fever attacks >39°C for a minimum of 1 week, pharyngitis, arthralgias, a neutrophilic leukocytosis as well as a salmon-coloured maculopapular exanthema, which typically appears with the onset of fever in the evenings and decreases in the mornings (31) (Table 2). In addition, urticarial rashes and persistent pruritic papules and plaques have been reported in AOSD (32). Laboratory findings indicative of AOSD include elevated serum ferritin levels with a reduced glycosylated ferritin fraction (33, 34). A diagnosis of AOSD requires exclusion of infectious diseases, malignancies and other rheumatologic diseases.

Systemic-onset juvenile idiopathic arthritis (soJIA, syn M. Still's disease)

Systemic-onset juvenile idiopathic arthritis is characterized by intermittent high-spiking fever, a maculopapular or urticarial exanthema (Fig. 2) and developing (poly-) arthritis in children <16 years of age (35). The clinical presentation of symptoms in soJIA is similar to that seen in AOSD, besides that the occurrence of arthritis is a mandatory criterion (Table 2). The absence of autoantibodies or human leucocyte antigen associations as well as the favourable response to IL-1 (36–38) or IL-6 blocking (39) agents in treatment-resistant courses supports the hypothesis that soJIA is rather a polygenic autoinflammatory disease than autoimmune disorder (35, 40).

Figure 1 Urticarial exanthema in a patient with Schnitzler's syndrome (SchS).

Figure 2 Fleeting salmon-coloured maculo-papular exanthema in a patient with systemic-onset juvenile idiopathic arthritis (soJIA).

Mevalonate kinase deficiency (MKD)/Hyper-IgD and periodic fever syndrome

Mevalonate kinase deficiency includes HIDS (one of the four classic monogenic autoinflammatory diseases) and the clinically more severe mevalonic aciduria. Both are caused by mutations in the gene coding for mevalonate kinase. Patients with HIDS present with recurrent fever, abdominal pain, diarrhoea, aphthous ulcers and morbilliform exanthema rather than urticarial lesions (Fig. 3). In addition, mevalonic aciduria is associated with cerebellar ataxia, mental retardation, haematologic abnormalities and early death (41) (Table 2). Typically, IgD levels are highly elevated in MKD patients.

TNF-receptor-associated periodic syndrome

TNF-receptor-associated periodic syndrome is another monogenic autoinflammatory disease and caused by mutations in the gene encoding the TNF-receptor superfamily 1A. Clinical symptoms include recurrent fever attacks, abdominal pain, arthralgia and annular wandering erythema with underlying myalgia or, less frequently, urticarial plaques (Fig. 4). Also, periorbital oedema is often present in patients with TRAPS (42) (Table 2).

Clinical signs and symptoms other than urticarial rash that may point to autoinflammatory disease

In CAPS, for example, urticarial rash is often the earliest and one of the most prominent symptoms. But autoinflammatory diseases and allergic or autoimmune disorders share many other clinical features. The list of clinical signs and symptoms frequently presented to allergists and clinical immunologists that could also be associated with autoinflammatory disease includes inflammation of the anterior eye or uveitis resulting in eye redness and pain, periorbital oedema, serositis, stomatitis (aphthae), pustules and ulcers, meningeal inflammation causing headache, abdominal pain and diarrhoea, arthralgia, myalgia, CNS involvement, lymphadenopathy or arthritis, and fever (Table 3).

It should be noted that these may be very frequent symptoms, which when presented separately usually do not raise suspicion of an autoinflammatory disorder. However, a combination of symptoms (e.g. urticarial rash, recurrent fever of unknown origin and arthralgia) in addition to further hints including a positive family history or laboratory abnormalities (i.e. elevated inflammation markers) makes the diagnosis of autoinflammatory disease much more likely.

How to distinguish isolated chronic urticaria from autoinflammatory diseases by looking at skin lesions and other symptoms

The urticarial rash in patients with autoinflammatory syndromes may be, at first sight, indistinguishable from that of urticaria patients. However, a close clinical look, a detailed patient history, the assessment of treatment responses, laboratory findings and skin histopathology can provide valuable hints that can help to discriminate urticaria from autoinflammatory disorders (Table 4). The urticarial rash in patients with autoinflammatory syndromes has a broader spectrum of lesions than urticaria, namely flat wheals that may, at first sight, resemble erythematous patches but also more solid and stable lesions (Fig. 5). Also, the urticarial rash in autoinflammation patients is rather symmetrically distributed on the trunk and/or extremities, usually sparing the head. Children, however, may present a more generalized urticarial rash, less frequently affecting even the face. In contrast, isolated chronic urticaria is characterized by typical itchy wheal-and-flare-type skin reactions that are asymmetrically distributed and may occur anywhere on the body. The duration of single

Figure 3 Erythematous plaques on the dorsal hand and forearm of a patient with hyper-IgD syndrome.

Figure 4 Erythematous patches in a patient with TNF-receptor-associated periodic syndrome.

Table 3 Clinical signs and symptoms of selected autoinflammatory diseases and possible differential diagnoses

	Autoinflammatory disorder							
Clinical signs and symptoms	CAPS	Schnitzler's syndrome	NLRP12-associated FCAS	soJIA	AOSD	MKD	TRAPS	Differential diagnosis
Chronic urticarial rash	X	X	X	X	X	X	X	Urticaria (spontaneous or induced, e.g. cold contact urticaria) Urticarial vasculitis
Eye redness and pain	X			X				Allergic conjunctivitis Uveitis (autoimmune, infectious)
Periorbital oedema							X	Angioedema Allergic contact dermatitis
Serositis							X	Autoimmune connective tissue disorder
Stomatitis, aphthae						X		Allergy Autoimmune disorder Infection
Abdominal pain, diarrhoea						X	X	Food allergy Inflammatory bowel disease
Proteinuria	X					X	X	Autoimmune connective tissue disorder
Lymphadenopathy	X	X	X	X	X	X	X	Infection Malignancy Autoimmune connective tissue disorder
Myalgia	X	X				X	X	Infection Autoimmune connective tissue disorder
Arthralgia/arthritis	X	X	X	X	X	X	X	Rheumatoid arthritis JIA Reactive arthritis Autoimmune connective tissue disorder
Headache and other CNS symptoms	X					X	X	Migraine
Fever	X	X	X	X	X	X	X	Infection Malignancy Immunodeficiency Autoimmune connective tissue disorder

The clinical signs and symptoms represent a selection of common features and are found in other nonurticarial autoinflammatory diseases such as familial Mediterranean fever (FMF), periodic fever, aphthous stomatitis, pharyngitis and adenitis syndrome (PFAPA), Behcet's disease and others as well.

Table 4 Distinguishing criteria of chronic urticaria and autoinflammatory syndromes

Characteristics of urticarial rash	Chronic urticaria	Autoinflammatory syndrome
Appearance	Papular wheals Wheal-and-flare reaction	Flatter wheals, erythematous patches but also more solid and stable lesions No wheal with surrounding flare
Localization	Asymmetrical distribution common	Rather symmetrical distribution
Duration of single lesion	Transient (minutes or few hours)	Hours, up to 24 h
Pruritus	Severe	May be absent, rather burning or painful
Angioedema	Often associated	Rare
Skin histopathology	Dermal oedema; partly sparse inflammatory infiltrate of perivascular eosinophils, neutrophils and lymphocytes	No significant dermal oedema; dense neutrophil-rich perivascular and interstitial infiltrates, but can also be rather nonspecific
Start of symptoms	All ages	Childhood (hereditary fever syndromes) Adulthood (acquired complex disorders)
Disease duration	Few years	Usually life-long
Response to antihistamines	Moderate – good Dose dependent	Missing
Systemic symptoms	None	Recurrent fever, fatigue, arthralgia and others
Inflammation markers	Within normal range	(Continuously) elevated
Family history	Negative	Often positive

Figure 5 (A) Oedematous skin-coloured wheals with surrounding erythema in a patient with chronic spontaneous urticaria (CSU). (B) Erythematous flat wheals in a patient with cryopyrin-associated periodic syndrome (CAPS).

lesions, on average, is longer in autoinflammatory diseases (hours up to 24 h) as compared to chronic urticaria (minutes to hours) depending on the severity of the illness (4). Severe pruritus represents the most bothersome symptom for many patients with chronic urticaria (43). In autoinflammatory syndromes, pruritus may be absent (20) and is rarely more than minimally symptomatic, or skin lesions are described as eliciting a burning sensation. In addition, many patients with chronic urticaria frequently show angioedema, which is a rare finding in autoinflammatory disease (20). Skin histopathology in urticaria predominantly shows dermal oedema. Inflammatory infiltrates, if any, are limited to sparse perivascular eosinophils, neutrophils and lymphocytes. In many cases of autoinflammatory disease, dense neutrophil-rich perivascular and interstitial infiltrates are seen in lesional skin (44).

Systemic symptoms (i.e. fever, malaise and joint involvement) and repeatedly elevated inflammation markers such as C-reactive protein (CRP), serum amyloid A (SAA), erythrocyte sedimentation rate (ESR) and neutrophilic leukocytosis are characteristic for autoinflammatory disorders but not for chronic urticaria. Urticaria may occur at any age, and symptoms can reoccur for several years (43). In autoinflammatory diseases, first symptoms typically appear after birth or in childhood as in CAPS, or later in life as in SchS, which starts at the age of 50 on average. Finally, autoinflammatory disorders do not respond to 'classical' urticaria treatments such as antihistamines or combinations of antihistamines and H2 blockers and/or leukotriene antagonists. Response to glucocorticoids is variable in different autoinflammatory disorders. Cryopyrin-associated periodic syndrome and Schnitzler's syndrome, but not isolated chronic urticaria, respond poorly (or not at all) to glucocorticoids except at high doses of the order of a mg per kg (45). In HIDS, TRAPS, AOSD and soJIA however, oral glucocorticoids can be quite effective (7, 34, 40, 46).

Suspicion of autoinflammatory disease should prompt appropriate diagnostic measures to rule out or confirm CAPS, SchS or another autoinflammatory condition.

Table 5 Characteristics of cold-induced urticarial disorders

Characteristics	Cold contact urticaria	Systemic cold urticaria	FCAS (NLRP3- and NLRP12-associated)
Localization	Limited to cold-exposed area	Generalized rash	Generalized rash
Disease trigger	Cold contact (solid, liquid and air)	Cold humid air, change in temperature	Cold humid air, change in temperature
Ice cube test	Wheal-and-flare reaction within minutes	Negative	Negative
Systemic cold provocation	Generalized rash, angioedema and risk of anaphylaxis within minutes	Generalized rash within minutes, angioedema and anaphylaxis possible	Generalized rash, fever, malaise, arthralgia within 1–2 h

How to diagnose autoinflammatory syndromes

The laboratory work-up for diagnosing autoinflammatory syndromes should include basic inflammation markers (CRP, ESR), a differential blood count to screen for neutrophilia (neutrophils are often elevated in autoinflammatory disorders and during treatment with glucocorticoids), antinuclear antibodies to rule out autoimmune diseases and urinalysis to screen for proteinuria which raises the possibility of secondary AA renal amyloidosis. Although not routinely available in all countries, SAA should be included as an important inflammation marker and screening parameter for amyloidosis in autoinflammatory diseases. Serum amyloid A levels are elevated during disease attacks and correlate well with other acute phase proteins, namely CRP and ESR (47). Persistent high SAA levels are also associated with an increased risk of amyloidosis (48). For the detection of subclinical inflammation, the phagocyte-specific proteins S100A8/9 and S100A12 have been proposed as highly sensitive biomarkers in autoinflammatory syndromes (47, 49). However, these are currently limited to specialist centres. If the patient's history, clinical and laboratory findings are highly suspicious of autoinflammatory disease such as CAPS, a selected gene mutation analysis may confirm the diagnosis of hereditary periodic fever syndrome. However, it should be noted that mutational analyses are only performed by specialist centres, are usually expensive and may be negative in up to 40 to >50% of autoinflammatory disorders with typical clinical symptoms (50, 51). To increase the probability of positive results from genetic testing, the use of a clinical diagnostic score, which has recently been validated, may be helpful (52). In patients with adult-onset urticarial rash, systemic symptoms and elevated inflammation markers, a simple immune electrophoresis test is recommended to screen for paraproteins indicative of SchS. To establish a definitive diagnosis of SchS, the use of recently updated diagnostic criteria is recommended (21).

Special attention should be paid to cold-induced urticarial rashes. In cold contact urticaria as well as in FCAS1 and FCAS2, cold exposure is the only or major disease-triggering factor (Table 5). Without a detailed history and diagnostic testing, cold-induced autoinflammatory disorders may be overlooked. As a first step, a simple cold provocation test with a melting ice cube applied on the volar forearm in a thin polythene bag for 5 min is recommended (53). A negative test result (no wheal-and-flare reaction 15 min after provocation) rules out 'classical' cold contact urticaria and points to atypical cold urticaria including idiopathic and familial forms or cold-induced autoinflammatory disorders (53–55) (Table 5). Atypical idiopathic cold urticaria is not associated with systemic symptoms and develops within minutes. Also, in patients with CAPS, a transient rash may be seen within minutes after exposure to cool temperatures. However, a genuine cold-triggered CAPS attack with systemic symptoms including fever and malaise develops not before hours after cold provocation (56). In patients with a negative ice cube test result and no history of cold-induced anaphylaxis, a cold room provocation may be performed to distinguish atypical cold urticaria from FCAS.

Conclusion

Autoinflammatory syndromes are rare and severely debilitating chronic diseases with limited awareness. Thus, they are underdiagnosed and often recognized with a diagnostic delay of many years or even decades. Early diagnosis is of great importance to enable effective treatment and to prevent long-term complications such as amyloidosis. Urticarial rash is often the earliest and one of the most common and prominent symptoms in autoinflammatory disorders. Therefore, allergists and clinical immunologists should consider them as a potential differential diagnosis of chronic spontaneous urticaria. Thinking of autoinflammatory conditions and their clinical profiles is the most important step in detecting these diseases, which are readily diagnosed and treated.

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Author contributions

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manuscript and sent it back to the first authors. After a prefinal version was composed out of all of the changes, and a final review and approval was obtained from all contributing authors, the final version of the manuscript was submitted. K. Krause and M. Maurer: substantial contributions to (1) conception of manuscript, (2) drafting the article and (3) final approval of the version to be published. C.E. Grattan, C. Bindslev-Jensen, M. Gattorno, T. Kallinich, H.D. de Koning, H.J. Lachmann, D. Lipsker, A.A. Navarini, A. Simon and C. Traidl-Hoffmann: substantial contributions to (1) revising the article critically for important intellectual content and (2) final approval of the version to be published.

Conflict of interest

K. Krause, C. E. Grattan, C. Bindslev-Jensen, T. Kallinich, H. D. de Koning, H. J. Lachmann, D. Lipsker, A. A. Navarini, A. Simon, C. Traidl-Hoffmann declared that they have no conflict of interest. M. Gattorno: Consultancy fees and honoraria for meeting presentations from Novartis and SOBI Biovitrum. M. Maurer: Marcus Maurer is or recently was a Speaker and/or Advisor for Almirall Hermal, Essex Pharma, Genentech, Merckle Recordati, Novartis, Sanofi Aventis, Schering-Plough, Merck, MSD, UCB and Uriach.

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