Allergology International. 2010;59:321-322
DOI: 10.2332/allergolint.10-LE-0224

LETTER TO THE EDITOR

Dear Editor

Exanthem with Cryopyrin Associated Periodic Syndromes and Consideration of IL-1 Targeted Therapy for Neutrophilic Predominant Urticaria

The article by Kambe *et al*.[1] is an excellent review on the potential role of the inflammasome in skin disorders. As one of the investigators involved in the discovery of the cryopyrin mutation, I felt compelled to comment on the exanthem associated with cryopyrin-associated periodic syndromes (CAPS), i.e. Familial Cold Auto-Inflammatory Syndrome, Muckle-Wells Syndrome, and Neonatal Onset Multi-System Inflammatory Disorder, referred to as NOMID. This exanthem is not true urticaria[2] as: (1) it is erythematous, macular-papular; (2) it is non-pruritic; (3) it can remain in situ for more than 24 hours; (4) it has dermal infiltration primarily with neutrophils; (5) it has no histo-pathological evidence of mast cell degranulation; and (6) it is non-responsive to anti-histamines. I suggest that typical urticaria is not a manifestation of CAPS, and in lieu of this terminology, I would recommend use of nomenclature, such as macular-papular exanthem or urticaria-like exanthem, to differentiate from true urticaria associated with vasoactive mediator release secondary to mast cell degranulation.

The authors make an important commentary that the cytoplasm of mast cells contain the NLRP-3 inflammasome. The NLRP-3 inflammasome can be stimulated by pathogen-associated molecular patterns (PAMPs) and danger associated membrane patterns (DAMPs), such as urate crystal formation, free ATP, hypokalemia that can develop from catabolic tissue injury. PAMPs and DAMPs can in turn stimulate a cascade of events leading to extracellular secretion of IL-1 cytokines. These cytokines can cause neutrophilic chemotaxis by various immune pathways[3] that could explain skin biopsy proven perivascular neutrophilic predominant urticaria, as described by Tharp.[4] This particular type of urticaria is often less responsive to anti-histamines. Assuming the inflammasome is involved, there may be rationale to consider IL-1 targeted therapy in conjunction with optimal antihistamine treatment for management of these conditions. Moreover, clinicians frequently witness outbreaks of urticaria in association with viral infections and consequently this aforementioned inflammasome mediated mechanism may explain some of the pathobiology associated with infectious-induced urticaria.

Alan A. Wanderer[1]
[1]Clinical Professor of Pediatrics, Allergy, and Clinical Immunology, University of Colorado Health Sciences Center, Denver, CO, USA
Email: aw@aacmt.com

REFERENCES

1. Kambe N, Nakamura Y, Saito M, Nishikomori R. The inflammasome, an innate immunity guardian, participates in skin urticarial reactions and contact hypersensitivity. *Allergol Int* 2010;**59**:105-13.
2. Wanderer AA, Hoffman HM. The spectrum of acquired and familial cold-induced urticaria/urticaria-like syndromes. *Immunol Allergy Clin North Am* 2004;**24**:259-86.
3. Wanderer AA. Ischemic-reperfusion syndromes: Biochemical and immunologic rationale for IL-1 targeted therapy. *Clin Immunol* 2008;**128**:127-32.
4. Tharp MD. Chronic urticaria: pathophysiology and treatment approaches. *J Allergy Clin Immunol* 1996;**98**:S325-30.

The Authors Respond

We appreciate the comments by Wanderer to our recent review on the role of the NLRP3 inflammasome in the pathogenesis of skin disorders,[1] especially his comments regarding the terminology of skin eruption observed in cryopyrin-associated periodic syndrome (CAPS). We agree with his clarification that examthema observed in CAPS is not true uticaria (Fig. 1). As he pointed out, the eruption in CAPS is an erythematous, non-pruritic rash that is not responsive to antihistamines. Histopathologically the eruption does not show evidence of mast cell degranulation, rather infiltration of neutrophils without vasculitis. In contrast, the eruption in CAPS patients disappears without remaining pigmentation, suggesting the absence of epidermal attack. Unlike typical urticaria, the molecular mechanism underlying CAPS is based on mutation of the *NLRP3* gene. Aberrant activation of the NLRP3 inflammasome results in excessive cleavage of pro-IL-1β and accumulation of active IL-1β in dermal mast cells, a phenotype observed in skin specimens from CAPS patients.[2] Thus, the eruption associated with CAPS varies both in genetic etiology and histopathology from ordinary urticaria and therefore may also be referred to as pseudourticaria.[3]

However, for us, as practicing dermatologists who observe skin eruption at the bedside or the clinic, the rash in CAPS still appears to visually resemble typical urticaria. In the past, clinicians have classified the eruption observed in familial cold autoinlammatory syndrome (formerly known as familial cold urticaria) and Muckle-Wells syndrome, both now recognized as CAPS, as a form of urticaria, without knowledge of the function of NLRP3. We believe that preserving the classification of CAPS as a urticaria-like examthema will be beneficial to patients, their families and some physicians who are not familiar with these diseases. By retaining this classification system, those interested in researching the characteristic

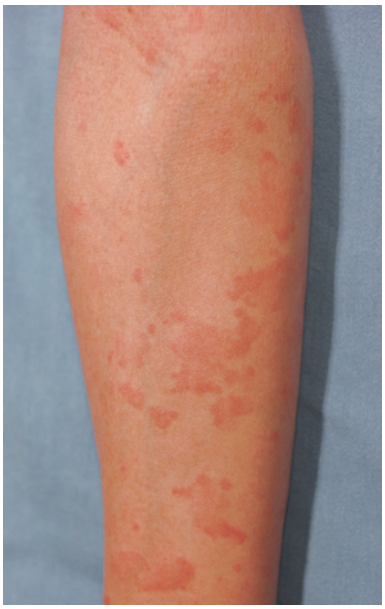

Fig. 1 The urticaria-like exanthema in CAPS. The eruption is erythematous, non-pruritic rash that is not responsive to antihistamines.

autoinflammatory symptoms observed in CAPS, such as skin rash, will be directed to the appropriate information, thereby aiding in self or clinical diagnosis.

NLRP3 is the intracellular receptor for the molecular recognition of specific patterns associated with pathogen or endogenous danger signals. We believe that urticaria represents an essential host defense mechanism, whereby the recognition of harmful agents by NLRP3 evokes a urticarial reaction to wash out unfavorable molecules to the lymphovessels where specific immuno-corresponding cells lay in wait. Therefore, we hope that further analysis of the "urticaria-like exanthema" observed in CAPS, now known to depend on the constitutively active status of NLRP3 and resulting inflammasome activation, will lead to a greater understanding of antihistamine refractory urticaria.

We thank Dr. Aaron P. Burberry (The University of Michigan) for English editing.

Naotomo Kambe[2] and Yuumi Nakamura[2,3]
[2] Department of Dermatology, Chiba University Graduate School of Medicine, Chiba, Japan and [3]Department of Pathology and Comprehensive Cancer Center, The University of Michigan, Medical School, Ann Arbor, MI, USA
Email: nkambe@faculty.chiba–u.jp

REFERENCES

1. Kambe N, Nakamura Y, Saito M, Nishikomori R. The inflammasome, an innate immunity guardian, participates in skin urticarial reactions and contact hypersensitivity. *Allergol Int* 2010;**59**:105-13.
2. Nakamura Y, Kambe N, Saito M *et al*. Mast cells mediate neutrophil recruitment and vascular leakage through the NLRP3 inflammasome in histamine-independent urticaria. *J Exp Med* 2009;**206**:1037-46.
3. Neven B, Prieur AM, Quartier dit Maire P. Cryopyrinopathies: update on pathogenesis and treatment. *Nat Clin Pract Rheumatol* 2008;**4**:481-9.