Case Report

Late-Onset, Low-Penetrance NLRP3-Associated Autoinflammatory Disease Presenting with Urticaria-Like Lesions: A CAPS Spectrum Case

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Abstract

Cryopyrin-associated periodic syndromes (CAPSs) are rare autoinflammatory disorders caused by gain-of-function mutations in the *NLRP3* gene, resulting in dysregulated interleukin-1–mediated inflammation. Although traditionally classified into three clinical subtypes according to disease severity and systemic involvement, increasing evidence supports the concept of CAPS as a continuous phenotypic spectrum. Low-penetrance NLRP3 variants may present with milder and atypical phenotypes, creating diagnostic challenges. A 19-year-old male patient presented with a three-month history of recurrent urticaria-like lesions triggered by cold exposure, accompanied by intense pruritus and burning sensation. The lesions appeared on the trunk and extremities, resolved within 24 hours without residual pigmentation, and were not associated with angioedema. The patient denied systemic symptoms such as fever, arthralgia, myalgia, fatigue, or weight loss. Family history was unremarkable. Initially diagnosed with chronic urticaria, he showed no significant response to high-dose second-generation antihistamines. Laboratory investigations during disease flares demonstrated neutrophilia and elevated C-reactive protein and serum amyloid A levels. Skin biopsy revealed superficial and deep perivascular neutrophilic infiltration without evidence of vasculitis. Genetic analysis identified a disease-associated NLRP3 variant, c.592G > A (p.Val198Met), supporting the diagnosis of CAPS. Following initiation of anakinra (100 mg/day), complete remission of cutaneous symptoms was achieved within two months. This case highlights an atypical CAPS presentation characterized by late onset and skin-limited inflammation without systemic manifestations. The findings support a spectrum-based understanding of CAPS and emphasize that isolated cutaneous phenotypes associated with low-penetrance NLRP3 variants should be considered in patients with antihistamine-resistant urticaria-like eruptions accompanied by neutrophilic inflammation and elevated acute-phase reactants.

Keywords: Cryopyrin-associated periodic syndrome, NLRP3, autoinflammatory disease, urticaria-like eruption, interleukin-1

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Introduction

Cryopyrin-associated periodic syndromes (CAPS) are a group of rare autoinflammatory disorders caused by gain-of-function mutations in the *NLRP3* gene, leading to dysregulated interleukin-1 (IL-1)–mediated inflammation. Traditionally, CAPS has been classified into three clinical subtypes—familial cold autoinflammatory syndrome, Muckle-Wells syndrome, and neonatal-onset multisystem inflammatory disease—based on age of onset, disease severity, and extent of systemic involvement. However, accumulating evidence indicates that these subtypes represent points along a continuous phenotypic spectrum rather than discrete clinical entities.

Case Report

A 19-year-old male patient presented with a three-month history of recurrent urticaria-like lesions triggered by cold exposure, accompanied by intense pruritus and a burning sensation. The patient denied systemic symptoms such as fever, arthralgia, myalgia, fatigue, and weight loss. There was no history of recent infection, drug exposure, or known allergic triggers. The family history was unremarkable. Physical examination during symptomatic periods revealed erythematous, edematous plaques distributed over the trunk and extremities (Figure 1). The lesions appeared and resolved spontaneously within 24 hours without residual pigmentary changes. No accompanying angioedema was reported.

Initially, the patient was thought to have chronic urticaria; however, despite treatment with second-generation antihistamines at up to four times the standard daily dose, he reported no significant improvement in either the frequency or severity of the lesions. Laboratory investigations during disease flares demonstrated neutrophilia and elevated levels of C-reactive protein and serum amyloid A. The combination of unresponsiveness to antihistamines, neutrophilia, and elevated acute-phase reactants raised suspicion of an autoinflammatory disorder rather than chronic spontaneous urticaria, prompting further diagnostic evaluation. A skin biopsy of an active lesion demonstrated no evidence of vasculitis but revealed perivascular neutrophilic infiltration in the superficial and deep dermis, accompanied by a mixed inflammatory infiltrate. Analysis of an autoinflammatory disorders gene panel revealed a heterozygous pathogenic variant in the *NLRP3* gene, c.592G > A (p.Val198Met), classified as Class 2 (possible pathogenicity, 95-99%), supporting the diagnosis of CAPS. Family screening was not performed.

Following the diagnosis, anakinra (100 mg/day subcutaneously), an IL-1 receptor antagonist, was initiated. After two months of treatment, the patient achieved complete resolution of cutaneous symptoms, with no recurrence of urticarial attacks.

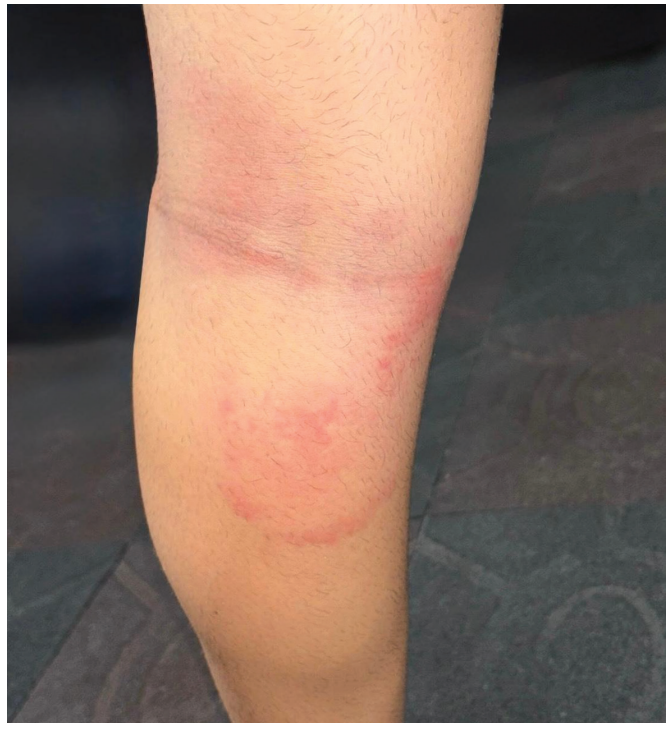

Figure 1. Urticaria-like plaques on the back of the leg

Discussion

The present case illustrates an atypical CAPS presentation characterized by delayed disease expression and inflammation confined to the skin, highlighting the diagnostic challenges posed by non-classical phenotypes. Such presentations expose the limitations of rigid subtype-based classifications and support a spectrum-based understanding of CAPS rather than strict categorical definitions.[1-3]

Accumulating clinical and genetic evidence indicates that CAPS represents a continuous phenotypic spectrum. Within this spectrum, low-penetrance NLRP3 variants are frequently associated with milder disease courses, later onset, and restricted organ involvement.[2-4] Patients carrying these variants may lack hallmark systemic inflammatory manifestations, which can delay recognition of CAPS, particularly when cutaneous findings dominate the clinical presentation.[3]

At the molecular level, CAPS is driven by dysregulated activation of the NLRP3 inflammasome, resulting in excessive production of IL-1β, a key mediator of inflammation across the CAPS spectrum.[1,4-6] While robust systemic IL-1 signaling underlies severe CAPS phenotypes, lower-intensity or compartmentalized inflammasome activation may preferentially manifest in the skin. In such cases,

IL-1–mediated neutrophilic inflammation can present as recurrent urticaria-like lesions that are poorly responsive to antihistamine therapy, reflecting cytokine-driven rather than mast cell-mediated inflammation.[4,7,8]

Within this framework, the absence of overt systemic inflammatory manifestations should not be interpreted as exclusion from the CAPS spectrum but rather as a consequence of variable genetic penetrance and tissue-specific inflammatory expression.[2-4] The complete and sustained response to IL-1 blockade provides functional confirmation of inflammasome-mediated disease activity and supports classification of this presentation as a skin-limited CAPS phenotype within the broader CAPS spectrum.[5,6]

Conclusion

Taken together, this case supports an expanded conceptualization of CAPS that includes late-onset, skin-limited phenotypes associated with low-penetrance NLRP3 variants, and it highlights the biological plausibility of isolated cutaneous involvement within the CAPS spectrum.

Footnotes

Informed Consent: Written informed consent was obtained from the patient for publication of the clinical images and clinical information included in this article.

Authorship Contributions

Surgical and Medical Practices: M.E.U., Ç.Y., Concept: M.E.U., E.G., Design: M.E.U., E.G., İ.Ü., Data Collection or Processing: M.E.U., E.G., B.Y., Analysis or Interpretation: M.E.U., E.G., Literature Search: E.G., Ç.Y., Writing: M.E.U., E.G.

Conflict of Interest: One of the authors, Ece Gökyayla, is a member of the Associate Editor of the Turkish Journal of Dermatology. However, she was not involved in any stage of the editorial decision-making process for this manuscript. The manuscript was evaluated independently by editors from other institutions. The other authors declare no conflicts of interest.

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