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CASE REPORT

From Urticaria to Correct Diagnosis: A Case Report of Cryopyrin-Associated Periodic Syndromes

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Abstract: Cryopyrin-associated periodic syndrome (CAPS) is a rare autoinflammatory disorder often misdiagnosed as urticaria or urticarial vasculitis, thereby delaying treatment for patients. This report presents a large CAPS pedigree. The proband was a 57-year-old man with recurrent urticaria-like rash, fever, and arthralgia for more than 50 years and hearing loss for 28 years. Sixteen of his relatives had similar symptoms. One-generation sequencing revealed a c.778C>T; p.(Arg260Trp) variant in the NLRP3 gene, confirming the diagnosis of CAPS. The aim of this case report is to raise awareness of CAPS and its various clinical manifestations, highlighting that urticaria may be a presentation of autoinflammatory diseases, thereby improving diagnostic accuracy.

Keywords: cryopyrin-associated periodic syndromes, case report, urticaria, large family

Introduction

Cryopyrin-associated periodic syndrome (CAPS) is a rare autoinflammatory disease caused by mutations in the *NLRP3* gene.[1,2] This condition is characterized by recurrent episodes of systemic inflammation with diverse clinical manifestations.[3] CAPS encompasses three clinically overlapping phenotypes: familial cold-induced autoinflammatory syndrome (FCAS, OMIM #120100),[4] Muckle-Wells syndrome (MWS, OMIM #191900),[5] and chronic inflammatory neurologic cutaneous and articular syndrome (CINCA, OMIM #607115).[6] Various triggers can precipitate disease manifestations, including cold exposure, fatigue, stress, infections, trauma, and sleep deprivation. In some cases, episodes may occur spontaneously.[7] While the reported global prevalence of CAPS ranges from 2.7 to 5.5 cases per million, these figures likely underestimate the true prevalence due to challenges in diagnosis and recognition.[7] This is particularly evident in China, where CAPS remains poorly recognized, leading to frequent misdiagnosis. In this report, we present a large CAPS pedigree consisting of 17 affected individuals. The proband, a 57-year-old male, has been experiencing recurrent episodes of an urticaria-like rash, fever, and arthralgia for the past 51 years. In addition, he has suffered from progressive hearing loss over the last 27 years. Significantly, similar clinical manifestations have been observed in sixteen of his relatives.

Case Presentation

The proband is a 57-year-old man who presented with recurrent urticaria-like rash (without itching, Figure 1A and B), arthralgia, and fever beginning at the age of six. Cold was a common trigger, and attacks usually lasted 2–3 days. At the age of 23, the patient visited the hospital for the first time because of severe arthralgia. The diagnosis at that time remained unknown. After intravenous injection of penicillin and dexamethasone, the patient's symptoms improved for a while, but recurrent attacks continued thereafter. At the age of 30, the patient reported a progressive deterioration in auditory function, although medical consultation was not pursued. By the age of 45, his symptoms had worsened, and he was diagnosed with urticaria vasculitis after a skin biopsy at another hospital. After receiving penicillin and

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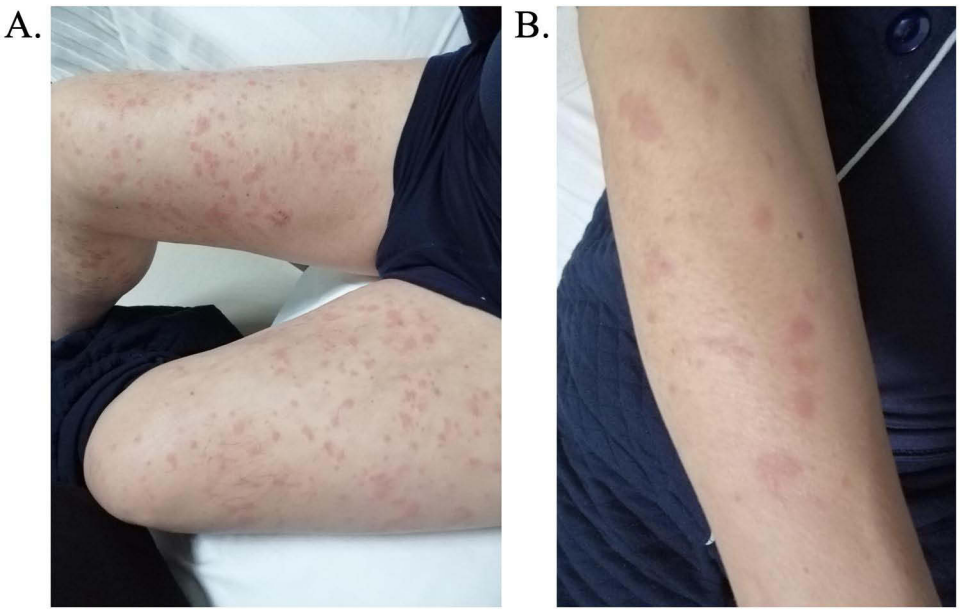


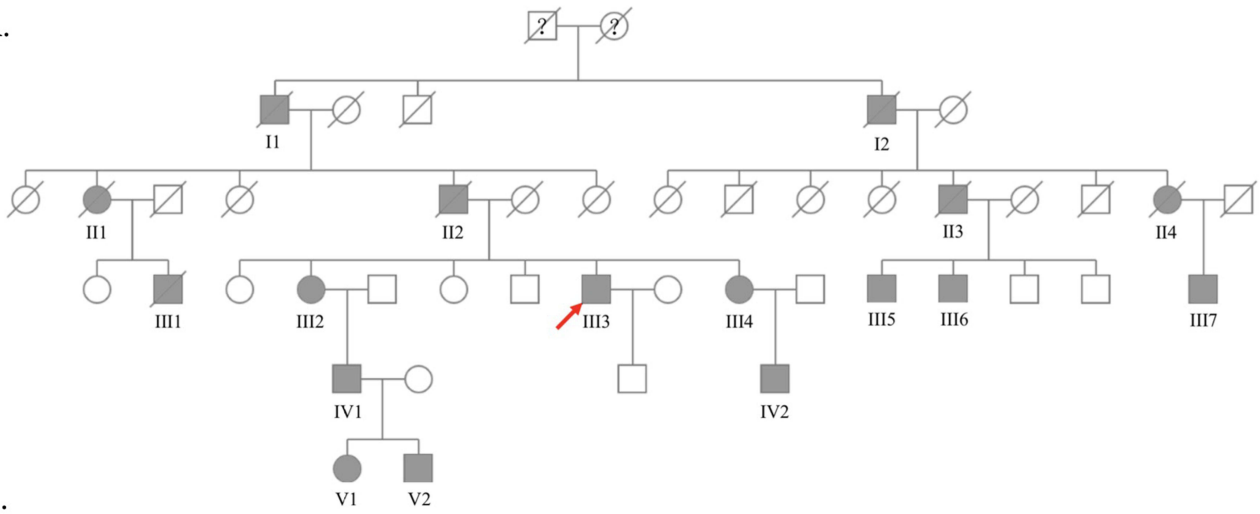
Figure 1 (**A**) and (**B**) Urticaria-like rash on legs and right arm.

dexamethasone again, the patient's symptoms improved temporarily. At the age of 57, the patient experienced frequent tightness and shortness of breath after exercise. Based on electrocardiogram and coronary CT angiography, he was diagnosed with unstable angina and underwent percutaneous coronary intervention (PCI). After PCI, the patient's rash and arthralgia worsened again. The patient received methotrexate 10 mg once a week and tofacitinib citrate 5 mg twice a day for one week. However, there was no improvement in his symptoms. The treatments were discontinued due to diarrhea. The patient has a positive family history, with 17 affected members in the pedigree, 10 of whom are currently alive (Figure 2A). Most affected individuals exhibited symptoms including urticaria-like rash, fever, arthralgia, ocular involvement, and hearing loss (Figures 2B). Due to the inconclusive initial diagnosis, the patient was referred to our hospital for further evaluation and expert consultation.

Upon admission, we performed a comprehensive laboratory workup. Hematological tests revealed significantly elevated inflammatory markers: interleukin-6 (IL-6) levels were 9.9 pg/mL (reference range: <5.9 pg/mL); high-sensitivity C-reactive protein (hsCRP) was markedly elevated at 26.53 mg/L (reference range: <3.00 mg/L); erythrocyte sedimentation rate (ESR) was increased to 47 mm/h (reference range: <15 mm/h); and tumor necrosis factor-alpha (TNF-α) measured 9.7 pg/mL (reference range: <8.1 pg/mL). ANA17 profile: Positive for anti-nuclear antibodies (IgG, 1:80) and weakly positive for anti-Jo-1 (34). All others negative. Audiological evaluation suggested sensorineural hearing loss. X-rays showed osteoporosis and osteoarthritis of the hands, wrists, and knees. The skin biopsy demonstrated a perivascular inflammatory infiltrate in the superficial and mid-dermis, composed of lymphocytes, neutrophils, and mast cells. No fibrinoid degeneration or other features suggestive of vasculitis were observed. The findings are consistent with a perivascular inflammatory pattern associated with autoinflammatory disorders, rather than primary vascular inflammation (Figure 3A). In addition, genetic testing was performed. We identified the c.778C>T; p.(Arg260Trp) variant in exon 3 of the *NLRP3* gene (Figure 3B), a mutation known to cause FCAS or MWS. Based on the clinical symptoms: urticaria-like rash, cold-triggered episodes, sensorineural hearing loss, and arthralgia; laboratory tests: elevated hsCRP; and the genetic variant, the patient was diagnosed with CAPS.[2]

IL-1 inhibitors are the primary treatment for CAPS.[8] However, at the time of the patient's consultation, these medications were not available in China. The patient's symptoms improved significantly with warmth. Therefore, he did not use IL-1 inhibitors. We suggest that young affected family members consider the use of IL-1 inhibitors to forestall organ damage.

A.



B.

Patient	Age/sex	Urticaria-like rash	Fever	Arthralgia/ arthritis	Ocular involvement	Hearing loss	Cardiac involvement
III2	67y/F	+	+	+	+	+	-
III3	57y/M	+	+	+	+	+	+
III4	57y/F	+	+	+	+	+	+
III5	61y/M	+	+	+	+	+	-
III6	57y/M	+	+	+	+	+	-
III7	52y/M	+	+	+	+	+	-
IV1	40y/M	+	+	+	+	+	-
IV2	30y/M	+	+	+	+	+	+
V1	13y/F	+	+	+	-	-	-
V2	4y/M	+	+	+	+	-	-

Figure 2 (**A**) The pedigree of the patient, red arrow represents the proband; (**B**) The clinical manifestations observed in affected family members.

Discussion

In this study, we report a CAPS pedigree, which to our knowledge is the largest CAPS pedigree reported to date. CAPS includes 3 clinical entities. FCAS has the mildest clinical manifestations and is typically characterized by a systemic inflammatory response triggered by cold exposure, including fever, urticaria, and arthralgia. MWS is the more severe clinical entity, characterized by recurrent fever, headache, urticaria, arthralgia or arthritis, as well as sensorineural deafness and type AA amyloidosis. NOMID/CINCA is the most severe form of CAPS and presents with urticaria, fever, arthralgia, growth retardation, facial deformities (eg, proptosis and saddle-nose), chronic meningitis, sensorineural deafness, cerebral atrophy, uveitis, enlarged lymph nodes, and hepatosplenomegaly. These symptoms can be easily confused with a variety of common illnesses; therefore, increasing physicians' awareness of CAPS will help in the early diagnosis and treatment of CAPS.

CAPS is caused by mutations in the NLRP3 gene that encodes cryopyrin.[9] Cryopyrin is a key component of the NLRP3 inflammasome, which plays a critical role in innate immunity. The NLRP3 inflammasome activates potent pro-inflammatory cytokines such as IL-1β and IL-18 by interacting with caspase-1 to cleave their inactive precursors.[10] Additionally, the NLRP3 inflammasome can activate gasdermin D, a protein that forms pores in the cell membrane, facilitating the release of pro-inflammatory cytokines into the extracellular environment and inducing pyroptosis.[11] Beyond its intracellular functions, activated macrophages can release the NLRP3 inflammasome, which further amplifies the inflammatory response by activating extracellular and neighboring phagocytic cells to produce IL-1β. Point mutations

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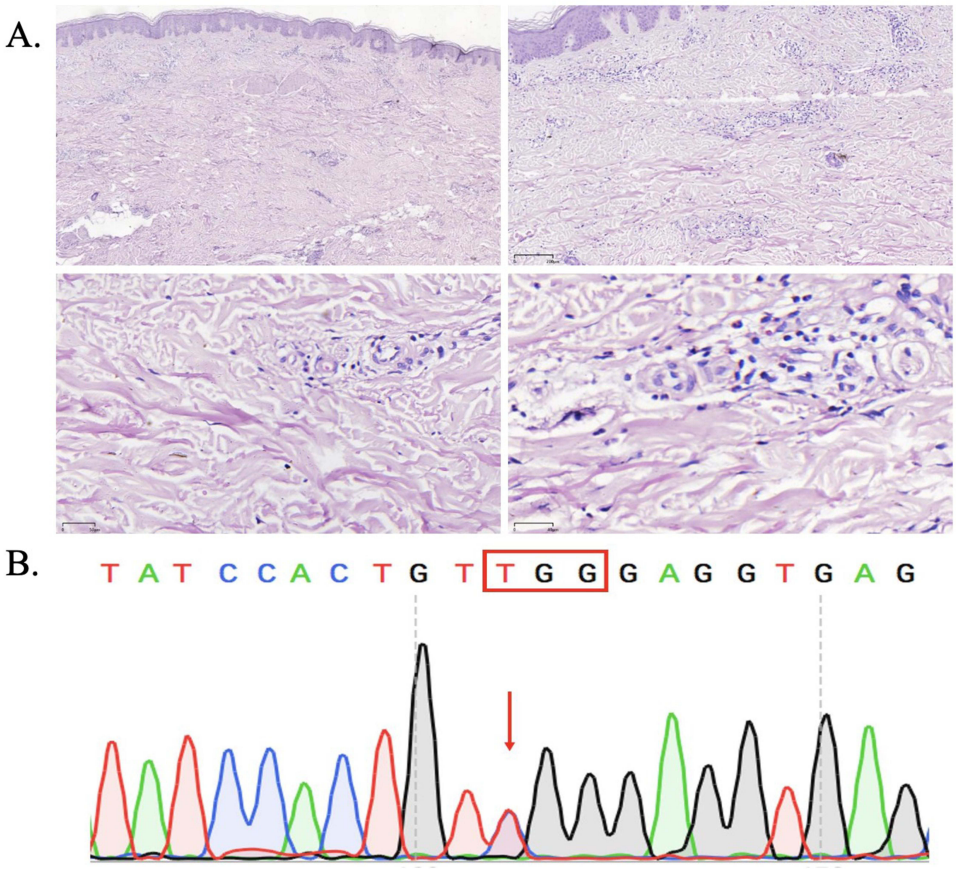

Figure 3 (**A**) the skin biopsy; (**B**) A c.778C>T; p.(Arg260Trp) variant in exon 3 of the NLRP3 gene, red arrow represent mutation sites.

in the NLRP3 gene enhance abnormal formation of the inflammasome and dysregulated activation of IL-1β, leading to a cascade of inflammatory responses.

As recommended in the 2021 EULAR/American College Guidelines, rapid disease control with IL-1 blockers is essential to prevent the development of irreversible organ damage, avoid inappropriate treatment-related side effects, and optimize health-related quality of life. Recent case reports further support these recommendations. Wei et al reported on a patient with CAPS who presented with persistent fever, rash, swollen joints, recurrent cerebral infarctions, growth retardation, and hearing loss from the age of 6 months.[12] This patient was treated with prednisone, leflunomide, thalidomide, and anakinra, which helped control disease activity initially. However, as the disease progressed, the patient developed renal failure and uremia, ultimately requiring a kidney transplant. Post-transplant, the patient continued anakinra therapy and the disease stabilized. In contrast, another report presented a patient with CAPS who underwent renal transplantation for renal insufficiency caused by amyloidosis.[13] This patient received only traditional immunosuppressive therapy before the transplant and did not receive anakinra post-surgery. Seventeen months after the transplant, her renal function deteriorated again, and a renal biopsy revealed secondary amyloidosis. These cases highlight the critical role of IL-1 inhibitors in the early management of CAPS, particularly in preventing irreversible organ damage.

Conclusion

This case highlights the importance of a comprehensive clinical evaluation when a patient presents with recurrent fever, joint pain, and an urticaria-like rash, as these symptoms may indicate an underlying autoinflammatory disease such as CAPS. In cases where IL-1 mediated autoinflammatory diseases are suspected, it is crucial to measure specific biomarkers of systemic inflammation, including CRP, ESR, and, when possible, serum amyloid A protein and S100 proteins. Genetic testing plays an important role in both confirming and ruling out the diagnosis. Once IL-1 mediated

autoinflammatory diseases, such as CAPS, are diagnosed, Initiating IL-1 blocker therapy is crucial to prevent irreversible organ damage and enhance the patient's quality of life. Early and accurate diagnosis, along with timely treatment, are key to managing this rare disease effectively and preventing long-term complications.

Abbreviations

CAPS, cryopyrin-associated periodic syndrome; FCAS, familial cold-induced autoinflammatory syndrome; MWS, Muckle-Wells syndrome; CINCA, chronic inflammatory neurologic cutaneous and articular syndrome; hsCRP, high-sensitivity C-reactive protein.

Consent for Publication

Written informed consent for publication was obtained from all family members whose details are included in Figure 2. The case details are open access and can be browsed without institutional approval. The proband described in this Case Report provided written informed consent for the case details and images to be published.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Booshehri LM, Hoffman HM. CAPS and NLRP3. *J Clin Immunol*. 2019;39(3):277–286. doi:10.1007/s10875-019-00638-z
2. Romano M, Arici ZS, Piskin D, et al. The 2021 EULAR/American College of Rheumatology points to consider for diagnosis, management and monitoring of the interleukin-1 mediated autoinflammatory diseases: cryopyrin-associated periodic syndromes, tumour necrosis factor receptor-associated periodic syndrome, mevalonate kinase deficiency, and deficiency of the interleukin-1 receptor antagonist. *Ann Rheum Dis*. 2022;81(7):907–921. doi:10.1136/annrheumdis-2021-221801
3. Gupta A, Tripathy SK, Phulware RH, Arava S, Bagri NK. Cryopyrin-associated periodic fever syndrome in children: a case-based review. *Int J Rheum Dis*. 2020;23(2):262–270. doi:10.1111/1756-185X.13772
4. Mohite RS, Kotecha U, Bhattad S. Familial Cold Autoinflammatory Syndrome Type 1. *Indian J Pediatr*. 2021;88(8):834. doi:10.1007/s12098-021-03805-6
5. Liu J, Zhang R, Yi Z, Lin Y, Chang H, Zhang Q. Identification of a variant in NLRP3 gene in a patient with Muckle-Wells syndrome: a case report and review of literature. *Pediatr Rheumatol Online J*. 2023;21(1):15. doi:10.1186/s12969-023-00795-x
6. Finetti M, Omenetti A, Federici S, Caorsi R, Gattorno M. Chronic Infantile Neurological Cutaneous and Articular (CINCA) syndrome: a review. *Orphanet J Rare Dis*. 2016;11(1):167. doi:10.1186/s13023-016-0542-8
7. Welzel T, Kuemmerle-Deschner JB. Diagnosis and Management of the Cryopyrin-Associated Periodic Syndromes (CAPS): what Do We Know Today? *J Clin Med*. 2021;10(1):128. doi:10.3390/jcm10010128
8. Terreri MT, Bernardo WM, Len CA, et al. Guidelines for the management and treatment of periodic fever syndromes: cryopyrin-associated periodic syndromes (cryopyrinopathies - CAPS). *Rev Bras Reumatol Engl Ed*. 2016;56(1):44–51. doi:10.1016/j.rbr.2015.08.007

9. Kone-Paut I, Galeotti C. Anakinra for cryopyrin-associated periodic syndrome. *Expert Rev Clin Immunol*. 2014;10(1):7–18. doi:10.1586/1744666X.2014.861325
10. Molina-Lopez C, Hurtado-Navarro L, Garcia CJ, et al. Pathogenic NLRP3 mutants form constitutively active inflammasomes resulting in immune-metabolic limitation of IL-1beta production. *Nat Commun*. 2024;15(1):1096. doi:10.1038/s41467-024-44990-0
11. Hooftman A, Angiari S, Hester S, et al. The Immunomodulatory Metabolite Itaconate Modifies NLRP3 and Inhibits Inflammasome Activation. *Cell Metab*. 2020;32(3):468–478e467. doi:10.1016/j.cmet.2020.07.016
12. Wei W, Wang F, Wang S, Wu H, Liu S, Wang G. Renal transplantation in patients with cryopyrin-associated periodic syndrome: a case report and literature review. *Int Immunopharmacol*. 2025;146:113879. doi:10.1016/j.intimp.2024.113879
13. Imaizumi R, Ishii Y, Miki K, et al. A case of cryopyrin-associated periodic syndrome with kidney transplant failure. *CEN Case Rep*. 2015;4(1):1–5. doi:10.1007/s13730-014-0129-y