Case Reports in Dermatology

Case Rep Dermatol 2025;17:86–90
DOI: 10.1159/000544705
Received: November 3, 2024
Accepted: February 6, 2025
Published online: February 25, 2025

© 2025 The Author(s).
Published by S. Karger AG, Basel
www.karger.com/cde

OPEN ACCESS

This article is licensed under the Creative Commons Attribution-NonCommercial 4.0 International License (CC BY-NC) (http://www.karger.com/Services/OpenAccessLicense). Usage and distribution for commercial purposes requires written permission.

Single Case

Recurrent Urticaria: A Rare Cryopyrin-Associated Periodic Syndrome – Muckle-Wells Syndrome

Richa Siddhi Gawhale

Department of Pediatrics, Dr. D.Y. Patil Medical College, Hospital and Research Centre, Pune, India

Keywords

Muckle-Wells syndrome · Cryopyrin-associated periodic syndrome · Autoinflammatory disorder · NLRP3 mutation · Anti-IL one medication

Abstract

Introduction: Muckle-Wells syndrome (MWS) is a rare cryopyrin-associated periodic syndrome (CAPS), an autoinflammatory disorder due to a loss of function mutation in the NACHT domain of the NLRP3 gene. The loss of cryopyrin activity brought on by this deficiency eventually causes dysregulated inflammation and increased release of the proinflammatory cytokine interleukin (IL)-1 beta. It has an autosomal dominant inheritance. ***Case Presentation:*** We present here an 8-year-old girl with recurrent fever, recurrent urticarial rash, sensorineural hearing loss, raised inflammatory markers and serum amyloid levels, which did not respond to the anti-histaminic drugs, was wrongly diagnosed as tuberculosis, which on further genetic evaluation was diagnosed as MWS. ***Conclusion:*** Despite being uncommon, treating clinicians should take MWS into consideration given the specific clinical presentation. With the availability of appropriate medications, future complications can be prevented, and the prognosis is better.

© 2025 The Author(s).
Published by S. Karger AG, Basel

Introduction

Dysregulated innate immune response without antigen is known as autoinflammatory disorders. The cytokine excess and inflammasome activation that follow are the cause. The clinical characteristics include elevated acute phase reactant, rash, serositis, lymphadenopathy, recurring flare-ups of systemic inflammation, and a chronic illness history. As a

Correspondence to:
Siddhi Gawhale, siddhigawhale99@gmail.com

Case Rep Dermatol 2025;17:86–90
DOI: 10.1159/000544705
© 2025 The Author(s). Published by S. Karger AG, Basel
www.karger.com/cde

subtype of autoinflammatory syndrome, cryopyrin-associated periodic syndrome (CAPS) is caused by mutations in the NACHT domain of NLRP3, which was formerly known as cryopyrin. It belongs to a distinct category of autosomal dominant diseases [1]. Neonatal onset multi-system inflammatory disorder (NOMID), Muckle-Wells syndrome (MWS), and familial cold autoinflammatory syndrome (FCAS) are its three distinct but frequently overlapping elements. The moderate versions of these disorders include FCAS and MWS, whereas NOMID is the most severe and often causes devastating neurologic consequences. These diseases sit along a phenotypic continuum with increasing levels of severity. The distinction of cryopyrinopathies may be aided by cutaneous, neurological, ophthalmologic, and rheumatologic symptoms. One of the main symptoms in all phenotypes is early-onset urticarial rash. The hallmark symptoms of MWS are urticarial rash, recurrent fever, progressive sensorineural hearing, visual loss, and the development of secondary amyloidosis. Up to 30% of MWS patients experience the latter. When hearing loss first affects high sound frequencies, it might not be identified until irreparable damage occurs [2]. Anti-IL-1 medications (anakinra, rilonacept, and canakinumab) are well-tolerated by these patients [3]. After obtaining written and informed consent, we discuss a pediatric case diagnosed clinically as MWS, though a rare entity, whose timely diagnosis and treatment would improve the clinical outcome and reduce undue parental stress due to its repetitive nature.

Case Presentation

The 8-year-old girl had complained of intermittent fever for the past year and rashes all over her body that started to appear at about 6 months of age. She experienced an oil massage at the age of 6 months, which resulted in the rapid emergence of well-defined elevated skin rashes across her entire body that vanished in minutes. The rashes began to appear every day. There was no connection between these rashes and the use of oil, no discernible pattern to the rash's onset, no disruption of sleep at night, and no prior history of fever, eczema, food, medication, or insect allergies. The rashes continued to appear without any specific pattern daily. They always resolved within one to 2 h without any medication, and they were not itchy. Their parents expected she would outgrow it with time; thus, no further doctor visits or follow-ups were done. At the age of 7 years, she developed high-grade intermittent fever, for which she required admission. But fever continued to appear often, without any specific pattern. After experiencing on-and-off fever for 4 months, a positive Mantoux test, and a chest X-ray revealing a hilar shadow, she was later started on antitubercular medications. GeneXpert sputum yielded negative results. Fever did not, however, go away entirely. She reported to us at this time that she had a daily history of intermittent fever, with most episodes occurring after dark. She exhibited good activity during the interfebrile phase and had a healthy appetite. Mother had a history of non-pruritic hives all over her body that were worse during a fever and when her skin was exposed. Hives were more common on exposed bodily parts. Antipyretics were used to treat fever and minor joint pain. There was no prior history of edema, redness, involvement of other joints, involvement of the eyes, or repeated hospitalizations. No significance was found in birth, developmental, or family history. Upon general examination, the patient had pallor and well-defined raised lesions over the body. She measured 125 cm (at the 50th centile) in height and 23 kg (25th to 50th centile). A systemic evaluation revealed no abnormalities. The results of the investigation showed neutrophilic leukocytosis (WBC: 22,740/μL, ANC: 16,470/μL) and iron deficiency anemia (Hb: 8.4 g/dL, serum iron: 30 μg/dL, TIBC: 500 μg/dL, transferrin saturation: 8%, ferritin: 15 ng/mL), high CRP of 70 mg/dL, and raised ESR (25 mm at 1 h). Pure tone audiometry revealed right-sided severe mixed hearing loss. Antineutrophilic antibody (ANA),

Case Rep Dermatol 2025;17:86–90
DOI: 10.1159/000544705
© 2025 The Author(s). Published by S. Karger AG, Basel
www.karger.com/cde

immunoglobulins, and interleukin levels were all within normal limits. Serum amyloid level was high (295 mg/L). The complaints above of hearing loss, elevated amyloid levels, and inflammatory markers led to the suspicion of Muckle-Wells syndrome. Germline mutations in the NLRP3 gene were detected by Sanger sequencing test. A pediatric rheumatologist advised following up a month after starting Colchicine empirically to prevent amyloidosis. There were fewer events still occurring, so the next plan was to begin Anakinra.

Discussion

The intermediate type of cryopyrinopathy, known as Muckle-Wells syndrome, is characterized by self-limiting, repeated episodes of fever, urticaria, arthralgia, myalgia, and conjunctivitis, in the absence of a specific trigger that begins in childhood with a median age of onset of 0.8 years [4]. Progressive sensorineural hearing loss and amyloidosis are examples of later consequences. The first sign to appear is a cutaneous eruption, defined by migratory, non-pruritic maculopapular rashes. There may be signs of developmental retardation, headache, and stomach pain. Serum C-reactive protein (CRP) and serum amyloid A (SAA) are raised with absolute neutrophilic leukocytosis [5]. In a recent study, including 164 cases of MWS patients, the following criteria for the diagnosis of CAPS were proposed: a specificity of 94% and a sensitivity of 81% [6]: raised inflammatory markers (CRP/SAA) (mandatory criteria). In addition, ≥2 of 6 CAPS have typical signs/symptoms: (1) urticaria-like rash, (2) cold/stress-triggered episodes, (3) sensorineural hearing, (4) loss musculoskeletal symptoms (arthralgia/arthritis/myalgia), (5) chronic aseptic meningitis, and (6) skeletal abnormalities (epiphyseal overgrowth/frontal bossing). Our patient had an adequate clinical history, fulfilled the above criteria, and was diagnosed as MWS. Between 40 and 80 percent of patients have severe exhaustion and persistent discomfort that lowers their quality of life [7]. Attacks may become more frequent at night, and they may be accompanied by general malaise, chills, perspiration, severe myalgia, a heaviness in the lower limbs, and, infrequently, edema. A non-pruritic urticarial rash appears during attacks, and rashes follow livedoid patterns. Lesions have a histologically neutrophilic preponderance [5]. Most attacks (48%) end after 24 h, although a significant number (36%) persist longer than 3 days. 40% of patients have more than 24 attacks annually, whereas half of patients are in pain. 90% of instances of migraine, intracranial hypertension, or chronic meningitis involve headache and irritation, which significantly impair day-to-day functioning [8]. Osteoarticular symptoms mainly consist of arthralgia and nail clubbing; the patient less frequently presents with an oral ulcer, folliculitis, or erythema nodosum [9]. While high-dose corticosteroids were somewhat helpful in the past, painkillers and antihistamines were not very useful. Three IL-1 inhibitors have shown efficacy in CAPS, including anakinra (a recombinant non-glycosylated form of human IL-1RA), rilonacept (a chimerical protein consisting of the IL-1-binding domains of IL-1RI and IL-1R accessory proteins fused to the Fc portion of human IgG1), and canakinumab (a fully human monoclonal IgG1 targeted at IL-1β). Anakinra and canakinumab have been approved for treatment with all CAPS phenotypes. With subcutaneous injections of anakinra, symptoms subsided fast, and levels of SAA and CRP returned to normal. According to clinical severity, anakinra may be administered in the above 8-month age group in the USA and Europe at a dose of 1–8 mg/kg/day, with a maximum of 300 mg [10].

Autoinflammatory syndromes must be considered in patients with recurring urticaria-like lesions and fever, and appropriate treatment should be initiated. Very few pediatric cases of cryopyrinopathies have been identified from the Indian subcontinent despite reports of the condition in the European population. We emphasize the clinical diagnosis, based upon the discussed criteria, and backing up with genetic test. Due to its rarity, we also stress the early

diagnosis and appropriate treatment with biological agents, which may prevent late complications and improve patients' quality of life. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000544705).

Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the parent of the patient for publication of the details of their medical case.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

No funding was available for the study.

Author Contributions

The first author was involved in conception and design of the case report; acquisition, analysis, and interpretation of work; drafting and reviewing it critically; and final version to be published. The second and corresponding author was involved in conception and design of the case report; acquisition, analysis, and interpretation of work; drafting and reviewing it critically; and final version to be published and communication with the journal and fulfilling journal's administrative requirements.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

References

1 Abdulla MC, Alungal J, Hawkins PN, Mohammed S. Muckle-Wells syndrome in an Indian family associated with NLRP3 mutation. J Postgrad Med. 2015;61(2):120–2. https://doi.org/10.4103/0022-3859.153107
2 Ahmadi N, Brewer CC, Zalewski C, King KA, Butman JA, Plass N, et al. Cryopyrin-associated periodic syndromes: otolaryngologic and audiologic manifestations. Otolaryngol Head Neck Surg. 2011;145(2):295–302. https://doi.org/10.1177/0194599811402296
3 Rowczenio DM, Trojer H, Russell T, Baginska A, Lane T, Stewart NM, et al. Clinical characteristics in subjects with NLRP3 V198M diagnosed at a single UK center and a review of the literature. Arthritis Res Ther. 2013;15(1):R30. https://doi.org/10.1186/ar4171
4 Tran T-A. MuckleWells syndrome: clinical perspectives. Open Access Rheumatol. 2017;9:123–9. https://doi.org/10.2147/OARRR.S114447
5 Almeida de Jesus A, Goldbach-Mansky R. Monogenic autoinflammatory diseases: concept and clinical manifestations. Clin Immunol. 2013;147(3):155–74. https://doi.org/10.1016/j.clim.2013.03.016

Case Rep Dermatol 2025;17:86–90
DOI: 10.1159/000544705
© 2025 The Author(s). Published by S. Karger AG, Basel
www.karger.com/cde

6 Kuemmerle-Deschner JB, Ozen S, Tyrrell PN, Kone-Paut I, Goldbach-Mansky R, Lachmann H, et al. Diagnostic criteria for cryopyrin-associated periodic syndrome (CAPS). Ann Rheum Dis. 2017;76(6):942–7. https://doi.org/10.1136/annrheumdis-2016-209686
7 Koné-Paut I, Lachmann HJ, Kuemmerle-Deschner JB, Hachulla E, Leslie KS, Mouy R, et al. Sustained remission of symptoms and improved health-related quality of life in patients with cryopyrin-associated periodic syndrome treated with canakinumab: results of a double-blind placebo-controlled randomized withdrawal study. Arthritis Res Ther. 2011;13(6):R202. https://doi.org/10.1186/ar3535
8 Levy R, Gérard L, Kuemmerle-Deschner J, Lachmann HJ, Koné-Paut I, et al. PRINTO and Euro fever. Phenotypic and genotypic characteristics of cryopyrin-associated periodic syndrome: a series of 136 patients from the Eurofever Registry. Ann Rheum Dis. 2015;74(11):2043–9. https://doi.org/10.1136/annrheumdis-2013-204991
9 Marzano AV, Tavecchio S, Venturini M, Sala R, Calzavara-Pinton P, Gattorno M. Urticarial vasculitis and urticarial autoinflammatory syndromes. G Ital Dermatol Venereol. 2015;150(1):41–50.
10 Koné-Paut I, Galeotti C. Current treatment recommendations and considerations for the cryopyrin-associated periodic syndrome. Expert Rev Clin Immunol. 2015;11(10):1083–92. https://doi.org/10.1586/1744666X.2015.1077702