

CASE REPORT

Erythema nodosum in an adolescent patient with cryopyrin-associated periodic syndrome

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Key Clinical Message

Cryopyrin-associated periodic syndrome (CAPS) is a monogenetic auto-inflammatory disorder with systemic manifestations. Innate immune system aberrance is seen in both CAPS and erythema nodosum and this case may point to a previously unknown association. In pediatric patients with EN and systemic features, the possibility of underlying CAPS should be considered.

KEYWORDS

auto-inflammation, chronic infantile neurological, cryopyrin-associated periodic syndrome, cutaneous and articular syndrome, erythema nodosum, Muckle-Wells syndrome

1 | INTRODUCTION

The cryopyrin-associated periodic syndromes (CAPS) are monogenic auto-inflammatory conditions caused by mutations in NLRP3 (NOD-like receptor 3) which occurs either de novo or via a dominant inheritance pattern with variable penetrance with a prevalence between 1 and 5.5 per million children. Many of those children suffer from a delayed diagnosis.¹ We report an unusual case of biopsy-proven erythema nodosum occurring in a 16-year-old girl on maintenance canakinumab with CAPS with an overlapping MWS/NOMID phenotype. This may indicate an association between the two conditions which are both underpinned by aberrance of the innate immune system which may lead to earlier CAPS in the future.

Cryopyrin-associated periodic syndrome have a varying degree of severity: ranging from the severe phenotype presenting in the neonatal period-chronic infantile neurological, cutaneous, and articular syndrome (CINCA); the intermediate form-Muckle-Wells Syndrome (MWS), presenting in childhood with recurrent fever and urticarial rash, arthralgia, and myalgia; as well as the mildest form-familial cold

autoinflammatory syndrome (FACS).^{2,3} CINCA includes all the symptoms observed in MWS with added features of bone deformation, debilitating arthropathy, and central nervous system (CNS) involvement including chronic meningitis and mental retardation. The mildest form of CAPS is familial cold auto-inflammatory syndrome (FCAS) which is characterized by episodes of fever, rash, and joint pain following cold exposure. There is some degree of genotype, phenotype correlation, but overlap syndromes are increasingly reported.¹⁻⁴

Erythema nodosum is the commonest form of pediatric panniculitis and has been viewed as a cutaneous marker for a number of monogenic auto-inflammatory diseases such as Familial Blau Syndrome.⁴ However, it has not previously been reported to be associated with CAPS.

2 | CASE REPORT

A 16-year-old girl with known mutation in NLRP3 (c.1307 > T p.(Thr436Ile)), who was diagnosed with CAPS at 10 years of age presented with a six-month history of bilateral erythematous plaques on her lower limbs. There were no



FIGURE 1 Bilateral pretibial erythema and induration on review in clinic after 2 wk of indomethacin therapy (A) Right lower leg (B) Left lower leg

associated coryzal symptoms, fever, weight loss, or arthralgia. On examination, she had multiple warm, tender, and indurated erythematous plaques located anteromedially on the left lower leg. Similar erythematous patches were seen on the right anterior shin (Figure 1).

In terms of CAPS treatment, she had responded well to anakinra (Interleukin-1 receptor antagonist) at initial diagnosis; however, she had a significant disease flare which did not respond to escalating doses of anakinra. She was then changed to canakinumab 50 mg (Interleukin-1 beta antagonist) subcutaneous injection every 8 weeks, which stabilized her symptoms, with normal vision and hearing approximately 10 months prior to the presentation of the leg symptoms.

Laboratory investigation at presentation of her leg symptoms revealed an elevated C-reactive protein (CRP; 17 mg/dL) and erythrocyte sedimentation rate (ESR; 41 mm at 1 hour). Cell differentials, renal function, liver function, electrolytes, and hemoglobin A1c were within normal limits. The serum amyloid protein level was stable and low at 17 mg/L. An autoimmune screen did not detect any antinuclear antibody, extractable nuclear antigen antibody or antineutrophil cytoplasmic antibodies.

Histology of the 6 mm punch skin biopsy revealed septal panniculitis with inflammation within the mid- and deep dermis. The inflammatory infiltrate was predominantly lymphohistiocytic but also included some neutrophils (Figure 2). A diagnosis of erythema nodosum was made with clinicopathological correlation.

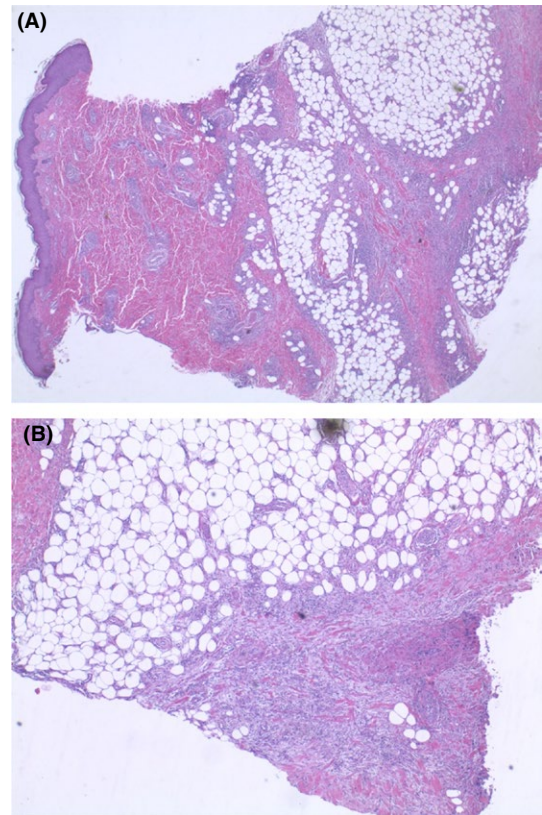


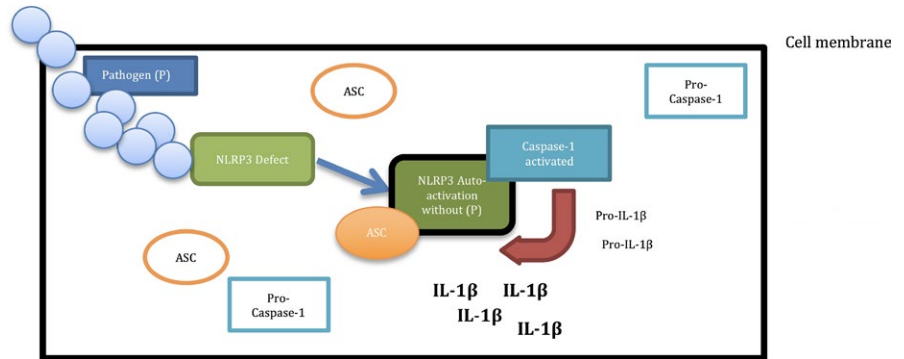
FIGURE 2 Histology of incisional biopsy showing predominantly septal panniculitis, suggesting erythema nodosum. A, Septal panniculitis; B, Deep septal inflammation with reactive changes

The patient was commenced on indomethacin 25 mg three times per day and advised to elevate both legs. On follow-up in 2 weeks' time, her pain had completely resolved although there was still residual warmth and induration on examination. After a further 2 weeks of Indomethacin 25 mg twice daily, her clinical examination was entirely normal with no ongoing symptoms.

3 | DISCUSSION

Muckle-Wells and CINCA Syndromes are moderate and severe clinical phenotypes of the cryopyrin-associated period syndrome (CAPS), respectively. Although the phenotypical distinction is helpful for clinicians, there is increasing recognition of phenotype/genotype overlaps between MWS and CINCA.³ The *NLRP3* gene codes for the NALP3 protein, also known as cryopyrin-a receptor protein of the inflammasome- which is significantly involved in autoinflammation.^{2,3} MWS characteristically manifests during early childhood with recurrent febrile episodes associated with nonpruritic urticarial rash, arthralgia, abdominal pain, myalgia, and conjunctivitis. If left untreated, a progressive sensorineural hearing loss often results in complete deafness by adolescence. Secondary amyloidosis affects 25% of patients and can lead

FIGURE 3 Schematic illustrating pathogen-derived signal activation of NLRP3 inflammasome, consisting of caspase-1 and adaptor protein ASC which leads to activated IL-1. In MWS, due to the mutated domain of NLRP3, the inflammasome assembles in the absence of pathogen signals leading to clinical disease



to chronic renal failure.⁴ Symptoms in CINCA appear immediately after birth with patients experiencing chronic symptoms and periods of exacerbation. Patients display a triad of nonpruriginous urticarial/polymorphic rash, severe arthropathy, and central nervous disorders. Mortality is 20% in untreated CINCA.²⁻⁴ The diagnosis can be made using a diagnostic model derived from a study involving 287 CAPS patients [Table 1].⁵

Autoinflammatory diseases are clinical disorders characterized by abnormally increased de novo inflammation, which is mediated predominantly by activation of innate immune system.⁶ The aberrant control of the innate immune response is predominantly mediated via interleukin (IL)-1-mediated pathways with lymphocytes, neutrophils, and macrophages as the key effector cells. This differs from autoimmunity, where disease is predominantly mediated by antibodies and aberrant T-cell responses. In auto-inflammatory processes, inflammasome complexes are important cytoplasmic proteins that regulate standard innate immune response. In the normal state, microbial and cytoplasmic toxins stimulate and activate specific cytoplasmic receptors, leading to the assembly of the inflammasomes. Examples of these receptors include the NOD-Like receptor (NLR) family of receptors, such as NLRP3, NLRP1, and MEFV. Assembly of inflammasomes leads to activation of the IL-1 β precursor and production of pro-inflammatory cytokine IL-1 β . Mutations in the genes of the inflammasomes components lead to dysregulation of the IL-1 inflammatory cascade and results in monogenic auto-inflammatory diseases.^{2,3} The various mutations of the *NLRP3* gene lead to a gain of function, causing abnormal IL-1 activation (Figure 3). Therefore, CAPS patients display dramatic responses to IL-1 inhibitors such as anakinra, canakinumab, and riloncept, with resolution of most symptoms and normalization of C-reactive protein (CRP).^{1-4,6}

Erythema nodosum (EN) has a prevalence of 1-5 per 100 000 persons and it is the most common type of panniculitis in children.⁷⁻⁹ It typically presents as tender, warm, erythematous subcutaneous nodules on pretibial areas and evolves into bruise-like, nonscarring lesions over 2-8 weeks. EN is often accompanied by fever, malaise, arthritis, and arthralgia, which can occur as a prodrome prior to cutaneous

TABLE 1 Diagnostic Criteria for Cryopyrin-associated periodic syndrome (CAPS)⁶

1. Major/mandatory criteria	Raised inflammatory markers (CRP or serum amyloid A protein)
2. Plus ≥ 2 of 6 Minor Criteria -CAPS typical signs/symptoms	Cold/stress- triggered episodes Rash: urticarial-like Sensorineural hearing loss Musculoskeletal symptoms including arthralgia/arthritis/myalgia Chronic aseptic meningitis Skeletal abnormalities: epiphyseal overgrowth/frontal bossing

manifestation.^{7,10} This condition is more common in younger women during the second and fourth decades of life.¹⁰

The pathogenesis of EN is still poorly understood, and 72% of cases are still classified as idiopathic.^{7,8,10} It has been hypothesized that activated neutrophils play a key role in causing the characteristic tissue inflammation.^{7,10-12} EN is commonly associated pediatric immunopathological disorders including inflammatory bowel disease, Behcet's disease, and sarcoidosis.¹³ The diagnosis of EN is established clinically, although histology may assist in atypical presentations. Histological examination will reveal septal panniculitis with infiltrates composed of mixed inflammatory cells (predominantly neutrophils in early lesions).^{7,8,10} The inflammation is primarily seen in the perivascular region within the septa but may spill into the lobules. The mainstay of treatment is identifying and removing the underlying trigger and symptomatic treatment; for the disease is usually self-limiting. However, new lesions may occur up to 2 months from initial onset and recurrence is not uncommon (30%-49%).¹⁰ Nonsteroidal anti-inflammatory medications, potassium iodide, and colchicine are commonly prescribed for symptomatic relief. Colchicine exerts its anti-inflammatory properties through impairing neutrophil chemotaxis and suppressing inflammasome-driven caspase 1 activation. Bed rest and leg elevation above the level of the heart twice per day for 30 minutes are highly recommended as adjuvant therapies.¹⁰

To the best of our knowledge, there have been no reports of EN in association with CAPS. The simultaneous occurrence in this case report is unique as CAPs is not a known immunopathic trigger for EN. Given that other monogenic diseases such as hyperimmunoglobulinemia with periodic fever syndrome have been reported to be associated with EN, this case may point to a previously unreported association of EN with MWS.^{4,6}

Like CAPS, EN is often associated with systemic symptoms of fever, arthritis, and arthralgia. Furthermore, patients with EN have shown to have elevated serum levels of innate immunity cytokines IL-6, IL-8, and TNF alpha as well as a fourfold higher percentage of primed neutrophils.^{7,10} Similarly, IL-6 and IL-8 were found in 100-fold higher concentrations among the skin supernatants of EN patients' lesional skin as compared to control.⁷ In both serum and skin samples, the highest expressed cytokines were those involved in neutrophil recruitment and activation. In addition, a case series found positive association between IL-1 β +3963 gene polymorphisms with the presence of erythema nodosum in Behcet's disease, implicating the role of IL-1 β in EN.¹¹ A similar correlation was observed by Volker et al, who described the association of erythema nodosum-like lesions in 13 individuals with NLRC4 mutation induced auto-inflammatory disorders.¹⁴ Although the pathogenesis of EN remains unclear, high levels of circulating innate immunity cytokines, serum neutrophilia, and neutrophils on histology suggest an underlying auto-inflammatory dysfunction.⁸

Thus, CAPS and EN are both associated with innate immunity aberrance-driven inflammation predominantly through IL-1 and IL-8. The association between the two conditions may not have been reported due to a low incidence of CAPS. There may be an increased likelihood of EN in MWS/CINCA overlap phenotypes—such as with our patient. EN in CAPS may have a more prolonged course similar to our patient due to aberrant auto-inflammation leading to an exaggerated immune response.

In conclusion, we present a 16-year-old girl with CAPS on treatment, with otherwise stable disease, who developed biopsy-proven erythema nodosum on bilateral lower limbs. The case report may be the first to indicate an association between these two conditions and should encourage further studies to explore their potential relationship. A clear association may be able to be established with future reports which could lead to increased clinician awareness and screening for cryopyrin-associated periodic syndromes in EN patients with suggestive systemic symptoms.

CONSENT FOR PUBLICATION

All three authors give their consent.

AUTHORSHIP

LC: contributed to the design of the manuscript, acquisition, and analysis of the data, drafted revision of the article, provided final approval of the version for publication and agrees to be accountable for all aspects of the work. DC: substantially contributed to the conception and design of the study, interpretation of the data, drafted parts of the manuscript, provided critical revision of the article, approved final version of the article and agrees to be accountable for all aspects of the work. AM: substantially contributed to the conception and design of the study, acquisition, and interpretation of the data, provided critical revisions of the article, approved final version of the article and agrees to be accountable for all aspects of the work.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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REFERENCES

1. Mehr S, Allen R, Boros C, et al. Cryopyrin-associated periodic syndrome in Australian children and adults: epidemiological, clinical and treatment characteristics. *J Paediatr Child Health*. 2016;52:889-895.
2. Murthy AS, Leslie K. Autoinflammatory skin disease: a review of concepts and applications to general dermatology. *Dermatology*. 2016;232:534-540.
3. Tran TA. Muckle-Wells syndrome: clinical perspectives. *Open Access Rheumatol*. 2017;9:123-129.
4. Moreira A, Torres B, Peruzzo J, Mota A, Eyerich K, Ring J. Skin symptoms as diagnostic clue for autoinflammatory diseases. *An Bras Dermatol*. 2017;92:72-80.
5. Kuemmerle-Deschner JB, Ozen S, Tyrrell PN, et al. Diagnostic criteria for cryopyrin-associated periodic syndrome (CAPS). *Ann Rheum Dis*. 2017;76:942-947.
6. Ciccarelli F, De Martinis M, Ginaldi L. An update on autoinflammatory diseases. *Curr Med Chem*. 2014;21:261-269.
7. De Simone C, Caldarola G, Scalfaferrri F, et al. Clinical, histopathological, and immunological evaluation of a series of patients with erythema nodosum. *Int J Dermatol*. 2016;55:e289-e294.
8. Wasson S, Govindarajan G, Folzenlogen D. Concurrent occurrence of Sweet's syndrome and erythema nodosum: an overlap in the spectrum of reactive dermatoses. *Clin Rheumatol*. 2006;25:268-272.
9. Kakourou T, Drosatou P, Psychou F, Aroni K, Nicolaidou P. Erythema nodosum in children: a prospective study. *J Am Acad Dermatol*. 2001;44:17-21.

10. Gilchrist H, Patterson JW. Erythema nodosum and erythema induratum (nodular vasculitis): diagnosis and management. *Dermatol Ther.* 2010;23:320-327.
11. Ozcimen AA, Dilek K, Bingol U, et al. IL-1 cluster gene polymorphisms in Turkish patients with Behcet's disease. *Int J Immunogenet.* 2011;38:295-301.
12. Ginarte M, Toribio J. Sweet's syndrome and erythema nodosum: two neutrophilic dermatoses? *Clin Rheumatol.* 2007;26:1215-1216.
13. Moraes AJ, Soares PM, Zapata AL, Lotito AP, Sallum AM, Silva CA. Panniculitis in childhood and adolescence. *Pediatr Int.* 2006;48:48-53.
14. Volker-Touw C, Koning H, Giltay JC, et al. Erythematous nodes, urticarial rash and arthralgias in a large pedigree with NLR4-related autoinflammatory disease, expansion of the phenotype. *Br J Dermatol.* 2017;176:244-248.

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