

BRIEF REPORT

Neonatal urticaria: Could it be CAPS?

Abstract

A neonatal boy presented with a persistent urticarial rash. Initial investigations showed raised inflammatory markers and evidence of systemic inflammation. A working diagnosis of cryopyrin-associated periodic syndrome (CAPS) was made, and the patient responded extremely well to Anakinra. Molecular genetic testing revealed a somatic mutation (affecting 12.5% of cells) in the NLRP3 gene, accounting for the persistent inflammatory state but milder phenotype as seen in our patient.

1 | CASE REPORT

A Caucasian boy developed a fixed urticarial rash 7 hours after birth and was urgently referred to dermatology. Initial investigations were indicative of an inflammatory cause; a neutrophilia ($3.54 \times 10^9/L$), elevated inflammatory markers; C-reactive protein (135 mg/L), erythrocyte sedimentation rates (35 mm/h), and ferritin. His autoimmune profile, serum tryptase, and amyloid were negative. A lumbar puncture and septic screen were also negative. There was no improvement after antihistamines and antibiotics. Despite the rash, he seemed a lively and well baby (Figure 1).

A skin biopsy showed a sparse neutrophilic infiltrate with no significant spongiosis within the epidermis. There was moderate dermal edema associated with a perivascular neutrophilic infiltrate. Acute inflammation was seen around adnexal structures in the deep dermis, with no evidence of lupus or cutaneous vasculitis (Figure 2).

Features were consistent with a neutrophilic urticaria, and an autoinflammatory condition was suspected; specifically CAPS, a rare multisystem, autoinflammatory syndrome. Fundoscopy revealed bilateral elevated disc suggestive of early bilateral papilloedema. A cranial ultrasound was requested due to an increasing head circumference (50th-70th centile), this showed minor asymmetry between the lateral ventricles. A noncontrast CT brain, MRI brain, and hearing tests showed no abnormality. To further investigate for a diagnosis of CAPS, molecular genetic testing was performed. This revealed a somatic mutation in NLRP3 exon 3 c.1691 G>A p.G564D in 12.5% of cells.

Given the ongoing systemic symptoms, Anakinra (2 mg/kg/d), an interleukin 1 (IL-1) antagonist, was commenced. A dramatic response was noted clinically and biochemically. Within 24 hours, the urticarial rash had disappeared; this rapid resolution of symptoms following Anakinra further supported the diagnosis of CAPS.

2 | DISCUSSION

Autoinflammatory syndromes (Table 1) result in aberrant secretion of IL-1 and manifest clinically as recurrent episodes of fever and inflammation affecting multiple organ systems.¹ CAPS encompasses three overlapping, autoinflammatory syndromes: familial cold autoinflammatory syndrome, Muckle-Wells syndrome, and chronic infantile neurologic cutaneous and articular syndrome (CINCA).² All three syndromes frequently present with persistent urticaria.

Patients with CINCA develop neurologic involvement (raised intracranial pressure, chronic aseptic meningitis, papilloedema) and



FIGURE 1 Generalized urticarial eruption

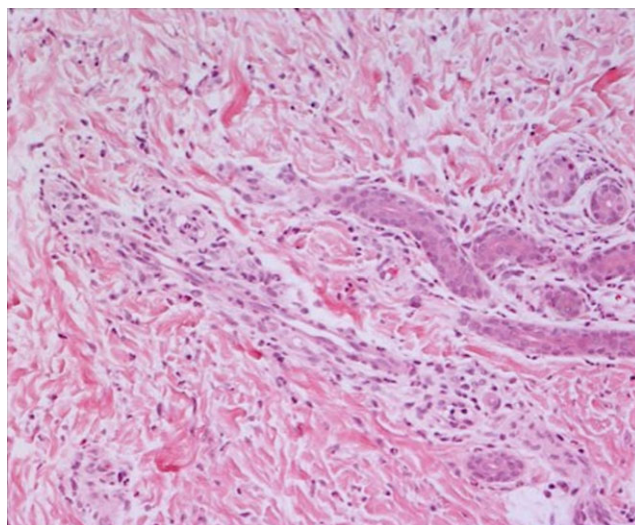


FIGURE 2 Scattered eosinophils seen throughout dermis

TABLE 1 Autoinflammatory syndromes

Disease	Gene/chromosome
Periodic/recurrent fevers	
Familial Mediterranean fever	MEVF 16p13.3
Mevalonate kinase deficiency	MVK 12q24
TNF receptor-associated periodic syndrome	TNFRSF1A 12p13
NALP12-associated periodic fever	NLRP12
Cryopyrinopathies	
Familial cold syndrome	NLRP3 1q44
Muckle-wells syndrome	NLRP3 1q44
CINCA	NLRP3 1q44
Granulomatous	
Blau's syndrome	CARD15/NOD2 16q12
Pyogenic disorders	
Papa syndrome	PSTPIP1
Majeed's syndrome	LPIN2 18p
DIRA	IL1RN 2q

epiphyseal overgrowth of the long bones.³ These disorders are associated with mutations in the NLRP3 gene on chromosome 1 which encodes the protein cryopyrin. Cryopyrin forms part of the Nalp3 inflammasome and is an activator of IL-1 β . Gain of function mutations of the NLRP3 gene, cause overactivation of the NLRP3 inflammasome, resulting in uncontrolled upregulation of interleukin-1 β .⁴ In our patient, a somatic mutation was present in NLRP3 exon 3 c.1691 G>A p.G564D in 12.5% of cells. This may have accounted for the milder phenotype exhibited, as the neonate remained relatively well throughout.

The IL-1 antagonist, Anakinra, is approved for the treatment of CAPS. Anakinra inhibits both IL-1 α and IL-1 β by competitive binding to IL1-R1, downregulating uncontrolled release of IL-1 β . Administration of Anakinra results in rapid improvement both clinically and biochemically as reported by Neven et al.⁵ This can aid as a diagnostic tool. Prior to the introduction of Anakinra, patients with CAPS faced a grave prognosis; the introduction of IL-1 β has

undoubtedly led to a massive improvement in quality of life for these patients.

Keywords

Anakinra, autoinflammatory, cryopyrin-associated periodic syndrome, urticaria

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REFERENCES

1. Gabay C, Lamacchia C, Palmer G. IL-1 pathways in inflammation and human diseases. *Nat Rev Rheumatol*. 2010;6(4):232-241.
2. Ombrello MJ, Kastner DL. Autoinflammation in 2010: expanding clinical spectrum and broadening therapeutic horizons. *Nat Rev Rheumatol*. 2011;7(2):82-84.
3. Shinkai K, McCalmont TH, Leslie KS. Cryopyrin-associated periodic syndromes and autoinflammation. *Clin Exp Dermatol*. 2008;33(1):1-9.
4. Cook GP, Savic S, Wittmann M, et al. The NLRP3 inflammasome, a target for therapy in diverse disease states. *Eur J Immunol*. 2010;40(3):631-634.
5. Neven B, Marvillet I, Terrada C, et al. Long-term efficacy of the interleukin-1 receptor antagonist anakinra in ten patients with neonatal-onset multisystem inflammatory disease/chronic infantile neurologic, cutaneous, articular syndrome. *Arthritis Rheum*. 2010;62(1):258-267.