

INSTRUCTIVE CASE

Chronic urticaria of neonatal onset: A potential sign of autoinflammationSam Mehr,^{1,2} Kristi J Jones,³ Davinder Singh-Grewal,^{2,4} Ivona Aksentijevich⁵ and Alyson Kakakios¹

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Abstract: We present a 6 year old boy with chronic urticaria of neonatal onset associated in childhood with features of neurological and joint inflammation. Genetic analysis confirmed the diagnosis of neonatal onset multi-inflammatory disorder (NOMID). Daily subcutaneous anti-IL-1 receptor antagonist therapy resulted in a dramatic and sustained amelioration of systemic inflammation. NOMID must be considered in any child with chronic urticaria of neonatal/infantile onset, particularly if associated with joint and/or neurological inflammation.

Key words: anakinra; chronic infantile neurological; cutaneous and articular syndrome; NOMID.

Case

A 5 years and 7 months old boy, the only child of non-consanguineous Australian-born parents, was referred to immunology outpatients of The Children's Hospital at Westmead by his general paediatrician with chronic urticaria of neonatal onset. The child was born at 35 weeks following a pregnancy complicated by poor fetal growth and pre-eclampsia. Six hours following delivery, the child developed an urticarial-like rash (Fig. 1). By 48 h of age, the rash resolved but subsequently re-emerged and became persistent by 6 weeks of age. The urticaria was migratory, generally non-pruritic and present



Fig. 1 Urticarial-like rash on limbs and face at day 1 of life.

Key Points

- 1 Cryopyrinopathies, such as neonatal onset multi-inflammatory disorder (NOMID), are rare autoinflammatory syndromes that result from overproduction of interleukin-1 and 18.
- 2 NOMID/chronic infantile neurological, cutaneous and articular syndrome must be considered in any child with a chronic urticarial-like rash of neonatal/infantile onset, particularly if associated with joint and/or neurological inflammation.
- 3 Prompt recognition and treatment of NOMID with anti-interleukin-1 receptor antagonist therapy is imperative to avoid permanent end organ inflammatory damage and amyloidosis.

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on a daily basis, and no specific triggers were identifiable. From 4 years of age, the child began to experience chronic frontal headaches, periodic fevers (up to 40°C, occurring every 4 weeks and lasting <12 h) and intermittent episodes of knee and ankle arthritis.

At initial evaluation at age 5 years and 7 months, examination was unremarkable apart from evidence of growth failure (height and weight on the first percentile). A full blood count, performed when the child was afebrile, revealed elevated white cell (WCC; $19.2 \times 10^9/L$, normal 5.0–14.5) and platelet counts ($633 \times 10^9/L$, normal 150–600 $\times 10^9/L$). His erythrocyte sedimentation rate (ESR) was 30 mm/h (normal <20 mm/h). Previous WCCs and ESRs had also been elevated (Fig. 2). C3, C4 and ferritin levels were within normal limits, and anti-nuclear antibody was negative. His urticaria persisted despite daily antihistamines. Daily oral prednisolone (1 mg/kg) was prescribed for 3 months, resulting in resolution of urticaria and periodic fever, but only partial resolution of headaches and arthritis. All

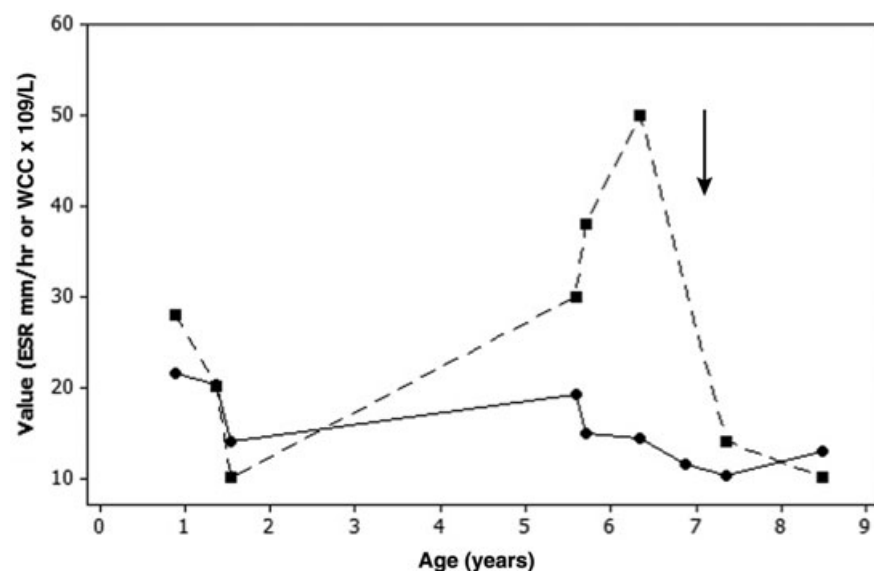


Fig. 2 White cell count (WCC) and erythrocyte sedimentation rate (ESR) pre- and post-anti-interleukin-1 receptor antagonist therapy. (●) WCC ($\times 10^9/L$); (■) ESR (mm/h); arrow, date anti-interleukin-1 receptor antagonist commenced.

features reoccurred once steroids were ceased, and prednisolone (1 mg/kg/day) was restarted but stopped 2 months later because of concerns about side effects. Cyclosporine was then prescribed for 2 months, but failed to control symptoms.

At 6 years and 4 months of age, because of persistent symptoms, the child was re-evaluated. His parents were now concerned about his hearing. Examination revealed hepatomegaly (9 cm liver span), a small right knee effusion and bilateral papilloedema. His WCC and ESR remained elevated (Fig. 2). A skin biopsy of an urticarial lesion demonstrated dermal perivascular infiltration with neutrophils. X-ray of the knees revealed bilateral hypoplastic patellae. A brain magnetic resonance imaging demonstrated mild bilateral white matter loss with lateral ventricular dilatation. Lumbar puncture resulted in a dry tap. Otoacoustic emissions were present bilaterally at low frequencies (<2000 Hz) but essentially absent at high frequencies (2000–8000 Hz).

On the basis of the clinical and laboratory features, a diagnosis of neonatal onset multi-inflammatory disorder (NOMID) was considered, and mutational analysis of the cold-induced autoinflammatory syndrome 1 (*CIAS1*) gene confirmed the patient to have a NOMID/Muckle-Wells-associated mutation T348M in exon 3 of *CIAS1*. Both parents were mutation negative.

Daily subcutaneous injections (1 mg/kg) of anti-interleukin-1 receptor antagonist (anti-IL1Ra; anakinra) were commenced. Within 24 h of starting anti-IL1Ra, his urticaria disappeared. Local pain at the site of injection was the only side effect reported. After 6 months on therapy, papilloedema was no longer evident, otoacoustic emissions had normalised and a brain magnetic resonance imaging showed no further white matter loss. Follow-up hearing tests 12 and 18 months post-therapy were normal. Since commencement of anti-IL1Ra, the child has had no further episodes of urticaria, arthritis or chronic headache, and repeat WCCs and ESRs have all been within normal limits (Fig. 2).

Discussion

NOMID, also known as chronic infantile neurological, cutaneous and articular syndrome, is a rare autoinflammatory syndrome caused by *de novo* or, less commonly, dominantly inherited mutations of *CIAS1*.^{1,2} *CIAS1* encodes cryopyrin, which interacts with other intracellular proteins to form a macromolecular complex involved in innate immunity, termed the inflammasome.^{1,2} Activated by intracellular danger signals (e.g. bacterial toxins/RNA, uric acid crystals), the inflammasome triggers a cascade of events, resulting in the production of pro-inflammatory IL-1 β and IL-18.^{1,2} Molecular models suggest that *CIAS1* mutations result in a gain of cryopyrin function, thereby leading to overproduction of IL-1 β and IL-18.^{1,2} As in our case, the mutations in NOMID are usually sporadic, missense and, in all except for a couple of patients, have clustered within exon 3. In approximately 50% of NOMID cases, no detectable *CIAS1* mutation is identifiable, suggesting genetic heterogeneity.¹

CIAS1 mutations are also associated with two milder cryopyrinopathy syndromes, known as familial cold autoinflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS). The distinction between the syndromes is predominantly made on clinical grounds. In FCAS, the mildest of the phenotypes, attacks of urticaria, fever and arthropathy are typically precipitated by exposure to cold temperatures. Sensorineural (SNL) deafness is uncommon, and neurological involvement is absent.^{1,2} In MWS, SNL deafness is common, but unlike NOMID, attacks of inflammation tend to be episodic rather than constant, neurological involvement is generally not described and sporadic mutations are rare.^{1,2} However, the clinical distinction between the syndromes is not always clear cut, and some patients exhibit overlapping clinical features (e.g. FCAS/MWS and MWS/NOMID). Some degree of phenotype-genotype correlation exists, such that, to date, mutations found in NOMID have not been reported in those with FCAS and *vice versa*.²

Table 1 Differentials, apart from NOMID, to consider in a child with chronic urticaria of infantile onset

Condition	Useful discriminating features
Systemic juvenile rheumatoid arthritis	Fever tends to be persistent rather than periodic Rash relapsing/remitting Absence of neurological inflammation
Neonatal lupus	Heart block (if present) Cutaneous features transient (i.e. usually resolve by 6 months) ANA positive (mother and infant) Anti-Ro/La positive (mother and infant)
Urticarial vasculitis	Leukoclastic vasculitis on skin biopsy
Cutaneous mastocytosis	Pigmented macules/papules ($\pm$ blistering of lesions) Generalised flushing Darier sign positive (i.e. lesions urticate on rubbing) Dermal mast cells infiltration on skin biopsy

ANA, anti-nuclear antibody; NOMID, neonatal onset multi-inflammatory disorder.

A chronic migratory non-pruritic urticarial-like rash of neonatal/infantile onset is the hallmark of NOMID. Although episodes of fever may also present during this time, other features of systemic inflammation tend to present later.¹ In one series, all children with NOMID developed urticaria by 3 months of age, with two-thirds developing it within the first few hours of life.³ Other differentials (and their discriminating features) to consider in a child presenting with a chronic urticarial-like rash during infancy is presented in Table 1.

Joint arthropathy and/or neurological disease, such as chronic aseptic meningitis, cognitive delay and seizures, is almost invariably present in NOMID.^{1–3} Other typical features include prematurity, growth retardation and SNL deafness in 70–80% of cases.^{1–3} Leukocytosis and elevations of ESR are also frequent findings.³ Amyloidosis is a feared complication that can result after years of untreated systemic inflammation.⁴ Our patient exhibited many features typical of NOMID, although the presence of hypoplastic patellae has not been previously reported. Radiological examination of affected patellae typically shows irregular borders and enlargement rather than hypoplasia.⁵

The use of anti-IL1Ra has revolutionised management of NOMID. Prior to its availability, control of disease was difficult, systemic immunosuppression was required and 20% of patients died before reaching adulthood.⁴ Anti-IL1Ra was reported in an open label study of NOMID patients to induce rapid symptom resolution, stabilisation of brain white matter loss, reversal of SNL hearing loss in some cases and biochemical inflammation quiescence.⁴ Our patient demonstrated all these therapeutic benefits.

NOMID must be considered in any child with chronic urticaria of neonatal/infantile onset, particularly if there is associated evidence of neurological and/or joint inflammation. Indeed, in our case, the delay in diagnosis for 6 years resulted in frequent school absenteeism because of ill health, chronic pain secondary to headaches and arthritis, and cosmetic embarrassment because of the presence of daily urticaria. Because genetic confirmation is currently not possible in 50% of patients, and response to anti-IL-1Ra does not appear to be dependent on the presence of a mutation,⁴ if clinical suspicion of NOMID remains high, a therapeutic trial of anti-IL1Ra is recommended.

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