

Neonatal urticaria as a symptom of a multisystem inflammatory disease

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Urticaria is rare in neonates, and within the first months of life it is most often associated with food allergy, drug eruptions, or infection.¹ We report a case of a child who at the first hour of life had urticaria resulting from an underlying systemic inflammatory disorder.

CASE HISTORY

The patient was the term product of an uneventful pregnancy, labor, and delivery. At 1 hour of age a typical generalized urticarial rash developed and was present daily thereafter. The rash was maculopapular, erythematous, and blanching. It was migratory, with individual lesions lasting several hours, then fading without any residual skin discoloration. It occurred diffusely, including rarely on the palms and soles, and did not seem to itch.

The infant was exclusively breast-fed until age 13 months. At 2 months RASTs to milk, soy, egg, wheat, and several other foods were negative. At 3 months his mother began a "hypoallergenic" diet for 2 weeks, but the rash did not change and was also unresponsive to diphenhydramine. The infant was referred to our clinic for allergy consultation at 3 months, where physical examination including growth parameters and development was normal except for the urticarial rash. Skin prick testing to hypoallergenic formulas (Alimentum [Ross, Columbus, Ohio] and Neocate [SHS North America, Gaithersburg, MD]) and a panel of common foods was negative. Complete blood cell count was normal except for an elevated total white blood cell count (WBC) of 18,500 cells/ μ L with a normal differential, and an elevated sedimentation rate of 42 mm/h. Chemistry panel, antinuclear antibody, and evaluation for congenital infections were all negative. The patient's diet was changed to exclusively Neocate formula with no clinical improvement.

He was re-evaluated at 14 months, and in the interim the rash persisted daily. An upper respiratory infection with wheezing had been treated with glucocorticoids with complete but transient clearing of the urticaria. At re-examination the rash was unchanged, but mild developmental delay and increased head circumference (95th percentile) disproportionate to weight and length were noted. CT of his head showed mild ventriculomegaly and cerebral atrophy. At 16 months he refused to bear weight on his right leg, and examination

Abbreviations used

CINCA: Chronic infantile neurologic, cutaneous, and articular syndrome
CNS: Central nervous system
CSF: Cerebrospinal fluid
NOMID: Neonatal-onset multisystem inflammatory disease
WBC: White blood cell count

revealed thickened synovium in the right knee. Plain radiographs and a nuclear bone scan were normal. He was begun on naproxen, after which his weight bearing increased. At 18 months he was seen by a pediatric rheumatologist. Ophthalmologic evaluation revealed bilateral papilledema and he was admitted for further evaluation.

In the hospital, sedimentation rate and peripheral WBC remained elevated. MRI confirmed cerebral atrophy with no hydrocephalus, and CT of the chest abdomen and pelvis were normal. Lumbar puncture had an elevated opening pressure and cerebral spinal fluid (CSF) pleocytosis (CSF WBC 18 cells/mL with 66% neutrophils). Extensive evaluation of the CSF for infection was negative, as were CSF protein electrophoresis and synthesis. Serum Igs, complement levels, and 24-hour urine histamine levels were normal, and tests for multiple autoantibodies and antibodies against HIV were negative. A single-photon emission technetium-99 brain scan showed a perfusion abnormality involving the right motor strip area. A skin biopsy specimen is shown in Fig 1. On the basis of the constellation of symptoms and laboratory tests and the exclusion of other conditions, the diagnosis of neonatal-onset multisystem inflammatory disease (NOMID) was made. High-dose glucocorticoid therapy was begun, with subsequent resolution of the rash, synovitis, papilledema, and aseptic meningitis.

DISCUSSION

A multisystem inflammatory disorder of neonatal onset, NOMID, also termed "chronic infantile neurologic cutaneous and articular syndrome" (CINCA) was first described by Lorber in 1973² and subsequently in multiple reports. Fewer than 100 cases have been reported to date. Clinical features include a triad of dermatologic, articular, and central nervous system (CNS) symptoms beginning within hours or weeks from birth. No laboratory tests are diagnostic, but signs of systemic inflammation, such as an elevated sedimentation rate or elevated C-reactive protein, are almost universal. Frequently patients have hematologic abnormalities such as anemia, thrombocytosis, and an elevated peripheral WBC. Tests for autoantibodies are negative. No specific etiology has been demonstrated, although some reports speculate that intrauterine infections may be a factor, and a familial component has been noted.³

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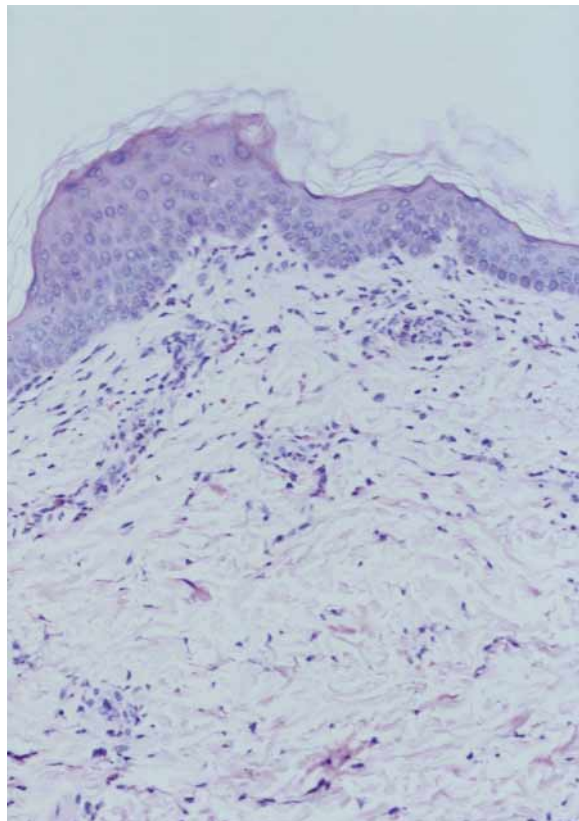


FIG 1. Skin biopsy specimen showing sparse, superficial, and deep perivascular infiltrate of lymphocytes, neutrophils, and occasional eosinophils and scattered inflammatory cells in interstitium. Normal epidermis and no evidence of leukocytoclasia or vasculitis.

A rash is often the first symptom and is usually urticarial, although erythema marginatum has also been described. Of particular note is that the urticaria often starts at a very early age, even on the first day or within the first several days of life, as in our patient.³ The rash is chronic and fluctuates irregularly. It can be nonpruritic and is unresponsive to antihistamine therapy. Skin biopsy findings show a polymorphonuclear cell infiltrate but no evidence of vasculitis or mast cell proliferation.⁴

Articular symptoms range from transient arthropathies to severe deforming polyarthritis.³ Joint symptoms are often progressive and can lead to significant, often pathognomonic radiographic changes.⁵ Guillet et al⁶ reported a

biphasic course with the onset of an urticarial rash 1.5 years before the development of articular symptoms.

The CNS component is also variable, with reports of patients without neurologic involvement.⁶ Neurologic symptoms include chronic CSF pleocytosis in the absence of any identifiable infection, papilledema sometimes with optic nerve atrophy or uveitis, and macrocephaly with brain atrophy. Developmental delay is almost universal and is sometimes progressive, and deafness and seizures can also be seen.

Food allergies are a common cause of urticaria in young infants. Although in utero sensitization to food proteins has been described and could explain urticaria on the first day of life, there was no evidence of food hypersensitivity in this patient. No infection, another common cause of urticaria, could be demonstrated and there was no evidence of an autoimmune process. Congenital C1 esterase inhibitor deficiency and mastocytosis have been reported in neonates but were ruled out in this case by a normal C1 esterase level and function and skin biopsy. Our patient had multiple features consistent with the diagnosis of NOMID and we feel this was the only explanation for his urticaria.

Allergists are often consulted for chronic urticaria and may be the first physician to begin a diagnostic evaluation. No reports of NOMID exist in the allergy literature. NOMID should be considered in any child with very early onset of urticaria, and signs of systemic inflammation or CNS and articular symptoms should be specifically sought in such patients.

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