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Infantile-Onset Fever and Urticaria

Sukesh Sukumaran, MD; Vini Vijayan, MD



Figure. Erythematous macular and urticarial lesions with areas of confluence on back and lower extremities.

A 5-year-old white girl presented with a history of recurrent fevers and urticaria since 2 months of age. The child had fevers (maximum temperature, 40°C) that lasted 3 to 5 days. Her mother reported that the fevers resolved spontaneously but continued to recur almost every month. The fever symptoms were associated with bilateral conjunctivitis, arthralgias, and irritability. The hivelike, nonpruritic urticaria did not improve with antihistamine medication and there were no known precipitating or aggravating factors. The child did not attend day care. Family history was noncontributory and her parents denied consanguinity.

The child was hospitalized on multiple occasions during infancy for the fevers, and she had comprehensive sepsis evaluations, including lumbar punctures, with negative results. Findings from chest and abdominal imaging and bone marrow aspiration with biopsy were negative for a malignant process. Despite extensive evaluation, a definitive source for the fevers was not identified, and the patient was referred to our institution.

On physical examination, the patient was febrile (temperature, 39°C) and appeared fussy. Growth measure findings were normal. Skin examination confirmed nonpruritic, macular and urticarial lesions on the face, back, and lower extremities (**Figure**). Bilateral conjunctival hyperemia without drainage was noted. There was neither swelling nor redness of the joints. Her right ankle and knee examination showed limited active and passive range of motion secondary to pain symptoms. Findings from the remainder of physical examination were normal.

WHAT IS YOUR DIAGNOSIS?

- A. Chronic urticaria
- B. Familial cold autoinflammatory syndrome
- C. Muckle-Wells syndrome
- D. Neonatal-onset multisystem inflammatory disorder

Diagnosis

C. Muckle-Wells syndrome (MWS)

Discussion

Laboratory tests showed normal complete blood cell count, erythrocyte sedimentation rate of 40 mm/h, and C-reactive protein of 153 mg/L (to convert to nanomoles per liter, multiply by 9.524). Urinary-

sis, serum amyloid, and audiometric test results were normal. Ophthalmologic examination revealed an absence of papilledema and uveitis. The patient underwent an evaluation for cryopyrin-associated periodic syndromes because of the presence of fever, arthritis, and urticaria as an infant. Genetic analysis revealed a T348M mutation of the *NLRP3* (formerly *CIAS1*) gene. The child was diagnosed with MWS (OMIM #191900).

The cryopyrin-associated periodic syndromes or cryopyrinopathies are a group of rare, inherited, autoinflammatory disorders of interleukin 1-associated regulation.¹ These syndromes occur because of genetic mutations in the *NLRP3* gene (OMIM *606416), which encodes cryopyrin, a protein that regulates inflammation. Mutations in this gene result in unregulated production of interleukin 1, leading to symptoms of inflammation such as fever and arthralgias.^{1,2}

Cryopyrinopathies include the following 3 subtypes: MWS, familial cold autoinflammatory syndrome, and neonatal-onset multisystem inflammatory disorder.^{1,2} Familial cold autoinflammatory syndrome is characterized by intermittent urticaria, fever, and arthritis triggered by exposure to cold temperatures. Neonatal-onset multisystem inflammatory disorder has the most severe phenotype and presents in infancy as a systemic inflammatory condition with fever, arthritis, urticaria, and central nervous system disease.^{1,2}

First described in 1962, MWS is inherited as an autosomal dominant trait with variable penetrance. Symptoms start in infancy and early childhood, and the disease is characterized by recurrent non-pruritic urticaria with periodic fevers. Fevers occur at irregular intervals every few weeks, last 24 to 48 hours, and resolve spontaneously. Symptoms can be precipitated by stress, exercise, and cold or heat exposure. Arthralgia can affect any joint, but bony destruction is not usually seen. Conjunctivitis occurs with flares of the disease.^{1,2}

The main complications of MWS include sensorineural hearing loss (SNHL) and progressive amyloidosis. Inflammation within the cochlea or leptomeninges may be related to SNHL. Bilateral SNHL has been described in up to 85% of patients with MWS. The SNHL

begins during early adolescence and often starts at high frequencies but can rapidly progress to profound hearing loss.^{3,4} Deposition of amyloid in the kidneys and liver also contributes to the MWS morbidity.^{1,2}

Confirmation of the diagnosis is achieved through genetic testing and identification of an *NLRP3* mutation. Studies have detected cases of somatic mosaicism of the *NLRP3* gene in individuals with clinical findings of cryopyrin-associated periodic syndromes, without evidence of the genetic mutation on the standard genetic tests.⁵ Histopathologic analysis of skin lesions shows perivascular and interstitial, mixed-inflammatory infiltrate of plasma cells, histiocytes, eosinophils, and mast cells.⁶

Currently, there is no cure for the cryopyrinopathies. Treatment involves use of agents that target interleukin 1, such as rilonacept, canakinumab, and anakinra.^{7,8} Most patients have a normal life span, and the development of complications such as amyloidosis and SNHL is rare with treatment. However, routine audiological monitoring is recommended for all patients with MWS; early detection and management of hearing loss is important for speech, language, and social development. Traditional screening pediatric audiograms test for standard frequencies only. Hence, comprehensive otolaryngologic assessments should include testing of high-frequency hearing thresholds.^{4,5} Our patient was successfully treated with anakinra injection medication and has been doing well. She currently has no disease complications.

This case highlights the importance of investigating MWS as a possible diagnosis for infants with recurrent fevers and urticaria. Delay in diagnosis can result in irreversible and profound medical and developmental complications.

ARTICLE INFORMATION

Author Affiliations: Division of Pediatric Rheumatology, Department of Pediatrics, Arkansas Children's Hospital, Little Rock (Sukumaran); Division of Pediatric Infectious Diseases, Department of Pediatrics, Arkansas Children's Hospital, Little Rock (Vijayan).

Corresponding Author: Vini Vijayan, MD, Division of Pediatric Infectious Diseases, Department of Pediatrics, Arkansas Children's Hospital, 1 Children's Way, Slot 4, 512-2, Little Rock, AR 72202 (vvijayan@uams.edu).

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