

Persistent urticarial rash in a newborn

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ABSTRACT

We presented the case of a 1-month-old girl with diffuse urticarial-like rash since birth. The initial evaluation showed elevated inflammatory markers. The response to treatment helped to narrow the diagnosis. In this case, we explored the differential diagnosis of rashes in this age group and the role of a therapeutic trial of medication as a diagnostic modality.

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CHIEF CONCERN

Urticarial-like rash

HISTORY OF PRESENT ILLNESS

A 1-month old white girl was referred to the allergy/immunology clinic due to a diffuse urticarial-like rash, which started within a few hours of birth and persisted thereafter. Individual lesions lasted several hours to several days and never disappeared completely. The infant did not have any other symptoms. There were no known sick contacts. The infant was exclusively breast-fed. She was born at full term *via* a repeat caesarean section. Prenatal laboratory test results were negative. Her mother had no infections during pregnancy or at the time of the infant's birth. The family history was negative for autoimmune disease, immunodeficiency disorders, and consanguinity.

PHYSICAL EXAMINATION

At initial presentation, she weighed 3.8 kg (25th percentile). Her weight gain had been stable since birth. Her temperature was 36.6°C, heart rate was 140 beats/minute, and the respiratory rate was 54 breaths/minute. The physical examination was significant for diffuse, blanching, erythematous patches, and plaques, most prominent on the face and scalp but sparing her soles (Fig. 1, A and B).

QUESTION 1

What Is the Differential Diagnosis?

Maculopapular and macular rashes that first appear in the newborn period can have various noninfectious and infectious etiologies (Table 1). The appearance of the rash may be atypical or vary throughout its course; thus, the rash should be evaluated in the context of the clinical presentation while keeping a broad differential diagnosis in mind. Benign noninfectious conditions include erythema toxicum neonatorum, transient neonatal pustular melanosis, neonatal cephalic pustulosis, and neonatal acne. These rashes usually have a pustular appearance, although can present as papules, especially at the onset.¹ At birth, our patient's rash was thought to be erythema toxicum neonatorum. Infections should be considered. The differential diagnosis of viral exanthems that present as maculopapular or macular rashes is broad.² Staphylococcal scalded skin syndrome, an exfoliative disease caused by *Staphylococcus aureus*, is a bacterial infection that may present with macular erythema early in its course.³ Although the incidence of congenital syphilis has been on the rise, this disorder mostly presents in infants born to women with a lack of prenatal care.⁴

Clinical stability and the absence of fever, despite persistence of rash, made infection less likely in our patient. Cutaneous manifestations frequently occur with food allergy, *e.g.*, cow's milk allergy.⁵ However, the patient was exclusively breast-fed, which made this diagnosis unlikely. A drug-induced rash was also unlikely because the only medication she had been on was cholecalciferol, which was started after the appearance of the rash. An etiology to consider was neonatal lupus. In neonatal lupus, congenital heart block, cutaneous annular lesions, and cytopenia are the most common clinical manifestations.^{6,7} Other rare causes in the neonatal period may include cryopyrin-associated periodic syndrome (CAPS), urticaria pigmentosa, hemo-

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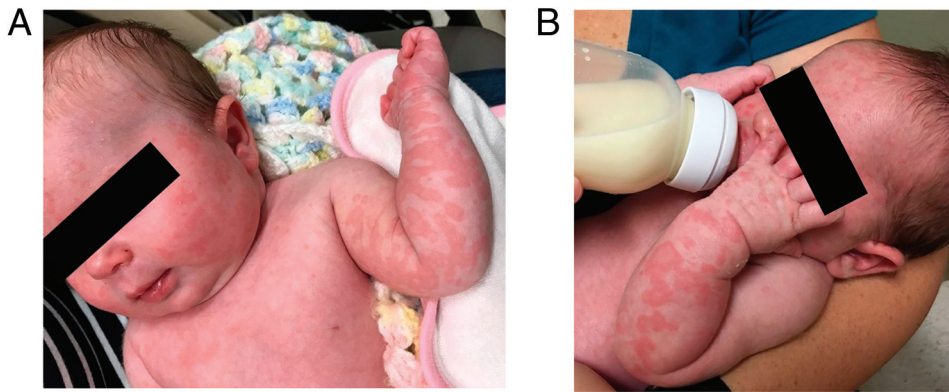


Figure 1. (A and B) Photographs, showing urticarial-like rash, taken at 1 month of age, before initiation of therapy.

Table 1 Differential diagnosis of maculopapular and macular rashes in newborns

Benign
Erythema toxicum neonatorum
Transient neonatal pustular melanosis
Neonatal cephalic pustulosis
Neonatal acne
Infectious
Viral exanthems
Neonatal syphilis
Staphylococcal scalded skin syndrome
Food allergy
Cow's milk allergy
Drug eruption
Malignancy
Langerhans cell histiocytosis
Other
Neonatal lupus
Cryopyrin-associated periodic syndrome
Urticaria pigmentosa
Hemophagocytic lymphohistiocytosis

phagocytic lymphohistiocytosis (HLH), and malignancies, *e.g.*, Langerhans cell histiocytosis.^{8–11}

Initial Laboratory and Diagnostic Findings

Laboratory results showed an elevated erythrocyte sedimentation rate of 58 mm/hour (reference range, 0–10 mm/hour), and elevated C-reactive protein level of 4.79 mg/dL (reference range, <0.50 mg/dL). A complete blood cell count with differential was normal (Table 2).

QUESTION 2

What Additional Laboratory Data or Investigations Would Be Helpful in Arriving at a Diagnosis?

In the setting of laboratory evidence of systemic inflammation, infection should be considered. Along with serologic testing, the workup usually involves

Table 2 Laboratory results

Test	Results (reference range)
WBC count, K/ μ L	11.60 (5.0–21.0)
Platelets, K/ μ L	382 (158–470)
ALT level, units/L	15 (0–33)
Total bilirubin value, mg/dL	0.2 (0.0–1.2)
ESR, mm/hr	58 (0–10)
CRP level, mg/dL	4.79 (<0.50)
ANA	<1:80 (<1:40)
Anti-RNP antibodies, units/mL	2.3 (<20)
Anti-SSA antibodies, units/mL	3.15 (<20)
Anti-SSB antibodies, units/mL	1.87 (<20)
CMV PCR result	Negative
Blood culture result	Negative
Ferritin level, ng/mL	622.4 (13.0–150.0)

WBC = White blood cell; ALT = alanine transaminase; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; ANA = antinuclear antibody; Anti-RNP = anti-ribonucleoprotein; Anti-SSA = anti-Sjögren's-syndrome-related antigen A; Anti-SSB = anti-Sjögren's-syndrome-related antigen B; CMV = cytomegalovirus; PCR = polymerase chain reaction.

ophthalmologic evaluation and imaging of the brain *via* a cranial ultrasound. Antinuclear antibody and anti-Sjögren's-syndrome-related antigen A and anti-Sjögren's-syndrome-related antigen B antibodies are valuable in evaluating for neonatal lupus. A ferritin level and liver function tests should be obtained if HLH is high on the differential diagnosis.¹² A tryptase level may be obtained if urticaria pigmentosa is suspected.¹⁰ A skin biopsy may be needed if the diagnosis is not arrived at by less-invasive diagnostic measures.

CLINICAL COURSE

Additional studies included antinuclear antibody, which was negative. Levels of anti-ribonucleoprotein, anti-Sjögren's-syndrome-related antigen A, and anti-Sjögren's-syndrome-related antigen B antibodies were normal. Blood culture and cytomegalovirus polymerase chain reaction results were negative. The ferritin level was elevated, at 622.4 ng/mL (reference range, 13.0–150.0 ng/mL) (Table 2). However, the patient did not have splenomegaly, fever, cytopenia, or liver function abnormalities, which are common features of HLH.^{11,12} Elevated inflammatory markers, a lack of other laboratory findings, and a persistent urticarial-like rash made us suspect an autoinflammatory disorder, *e.g.*, CAPS.

Radiographs of the extremities did not demonstrate periarticular soft-tissue swelling or abnormalities of the epiphyses. A cranial ultrasound showed normal parenchyma, without calcifications, ventriculomegaly, or hemorrhage. Audiologic and ophthalmologic evaluations were normal. Due to the high clinical suspicion for CAPS, anakinra was trialed at a starting dose of 2 mg/kg/day. The patient responded to the treatment; the rash resolved completely with the first dose. Subsequently, the rash reappeared but responded on increasing the dose of anakinra to 4 mg/kg/day. Several weeks later, inflammatory markers returned to normal: C-reactive protein of 0.27 mg/dL (reference range, <0.50 mg/dL), and erythrocyte sedimentation rate of 9 mm/hour (reference range, 0–10 mm/hour). An autoinflammatory syndromes genetic panel revealed a heterozygous mutation in the NLR family pyrin domain containing 3 (*NLRP3*) gene: c.911T>G.

DISCUSSION

Our patient's presentation was most consistent with CAPS. CAPS is a rare disorder characterized by episodic or chronic noninfectious systemic inflammation. It consists of three overlapping phenotypes, ranging from mild to severe: familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome, and neonatal-onset multisystem inflammatory disease (NOMID).¹³ The most common features among these phenotypes are recurrent fever, rash, arthralgias, and conjunctivitis. Patients typically present by 6 months of age, but some cases are not recognized until later in childhood or even adulthood.^{14–16} In FCAS, exposure to systemic cold precipitates symptoms. Complications such as renal disease and hearing loss are rare in FCAS.^{17,18} Patients with Muckle-Wells syndrome are more likely to develop sensorineural hearing loss and amyloidosis-induced renal disease after long-term disease.¹⁹ The most severe phenotype is NOMID, also known as chronic infantile neurological cutaneous and articular (CINCA)

syndrome. Patients with NOMID frequently experience central nervous, audiologic, ophthalmic, and skeletal involvement. Neurologic manifestations include chronic meningitis, cerebral atrophy, and, sometimes, mental retardation. Arthropathy that results from epiphyseal overgrowth of the long bones can be disabling.^{20,21} Some patients have features of all three phenotypes.²² Our patient's presentation did not fit into one category.

Mutations in the *NLRP3* gene, which are dominantly inherited or *de novo* gain-of-function mutations are now known to be the cause of CAPS.²³ The *NLRP3* gene, which is also known as cold-induced autoinflammatory syndrome-1-gene, encodes cryopyrin. Cryopyrin is involved in the formation of the *NLRP3* inflammasome, which leads to the activation of caspase-1 and release of interleukin (IL) 1 β .^{24,25} The majority of patients with CAPS have germline mutations in the *NLRP3* gene, detected either by Sanger sequencing or next-generation sequencing. Up to 70% of patients with "genotype negative" CAPS have evidence of somatic mosaicism, which may require more-advanced techniques, which complicates the process of diagnosis.^{15,26}

Our patient has a heterozygous mutation in the *NLRP3* gene: c.911T>G, which has not been reported in CAPS. The mutation is located on exon 3, which is the most common site for mutations in the *NLRP3* gene in association with CAPS.²³ This mutation may represent a pathogenic variant. Both parents had genetic testing performed, and neither carries this mutation, which suggests it is likely a *de novo* mutation. In this patient's case, a skin biopsy was not needed for a diagnosis, but a biopsy may be valuable in many cases. The rash associated with CAPS is migratory and urticarial-like, but it differs from urticaria histologically. The CAPS rash characteristically involves a perivascular neutrophilic infiltrate, without the evidence of vasculitis, which varies from the predominantly lymphocytic infiltrate of typical urticaria.^{27,28}

The severity of the disease and the complications are related to the specific mutation identified. In the setting of a novel mutation, close clinical monitoring is required to detect any evidence of persistent inflammation or development of hearing loss, uveitis, or arthropathy. The main treatment for CAPS is IL-1 blockade. Anakinra is a recombinant IL-1 receptor antagonist, which is administered daily as a subcutaneous injection. Results of studies have shown that anakinra can improve daily symptoms, decrease laboratory markers of inflammation, and decrease or even prevent the risk of long-term complications such as hearing loss, vision loss, and renal disease.^{14,29,30} Our patient had a quick response to anakinra. Although anakinra is considered safe, monitoring for adverse events, including surveillance for neutropenia and

thrombocytopenia, is an important part of clinical management.^{31–33} An increased risk of infection may be present, and patients should be carefully monitored.³³ Other treatments include rilonacept, a fusion protein of the IL-1 receptor, and canakinumab, a fully human anti-IL-1 β antibody.^{34,35} Anakinra has excellent central nervous system penetration and is thus favored over rilonacept and canakinumab for patients with evidence of central nervous system involvement.³⁶

Final Diagnosis

The final diagnosis was cryopyrin-associated periodic syndrome.

SUMMARY AND CONCLUSION

Urticarial-like rashes in pediatric patients can pose a diagnostic dilemma. When evidence of systemic involvement is present, a rare but serious cause, cryopyrin-associated periodic syndrome, should be considered. Early diagnosis and treatment are critical and may prevent serious sequelae. A therapeutic trial of medication can be a time-saving diagnostic modality, especially when clinical findings are few, and confirmation with genetic studies is not prompt or not entirely conclusive.

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