Patient Oriented Problem Solving (POPS) Case Report

Prolonged urticaria and fever in a toddler

Lori Broderick, M.D., Ph.D.,[1] Adriana H. Tremoulet, M.D.,[2] Jane C. Burns, M.D.,[2] and Hal M. Hoffman, M.D.[1,2,3]

ABSTRACT

We describe a 14-month-old girl who initially presented with 8 days of fever, conjunctival injection, rash, and irritability, admitted with a presumptive diagnosis of Kawasaki disease. Further history revealed intermittent urticarial-like rash since 3 months of age and pathological evaluation showed a perivascular infiltrate of neutrophils and lymphocytes. Here, we discuss the key points surrounding her diagnostic workup and our therapeutic approach.

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CASE PRESENTATION

Chief Complaint

Persistent urticaria and fever in a previously healthy child.

History of Present Illness

Our patient is a 14-month old girl, product of a full-term, fraternal twin gestation, who was initially hospitalized for 8 days with fever and rash with a presumptive diagnosis of Kawasaki disease. Evaluation revealed significantly elevated levels of acute-phase reactants and serum inflammatory markers without evidence of underlying infection. She received i.v. immunoglobulin (IVIG; 2 g/kg) initially, followed by a second dose of IVIG and subsequently infliximab (5 mg/kg), with only temporary resolution of fever, conjunctival injection, and rash. The allergy and immunology service was consulted for evaluation of persistent urticaria and fever.

Medical History

Review of our patient's history revealed that she had experienced an intermittent rash since 3 months of age, which was initially treated as dermatographism. Two months before her presentation, her parents noted recurrence of the rash with associated conjunctivitis. The rash was associated with fever and was unique in that it appeared to worsen during the day and have near complete resolution overnight. It was described as nonpruritic and nondistressing to the patient and was accentuated in exposed areas of skin with some sparing of areas covered by clothing (Fig. 1, A and B). Antibiotics and antihistamines had no impact on either the fever or the dermatologic symptoms.

There was no history of significant infections or prolonged illness. She met her developmental milestones appropriately but was generally noted to be smaller in size than her fraternal twin. She tolerated routine vaccinations without incident.

Family History

There is no family history of urticaria, immunodeficiency, autoimmune disease, or recurrent fevers. Her parents, as well as her fraternal twin, are healthy.

Physical Examination

She initially presented as an irritable child, with weight at the 43rd percentile for age and height at 70th percentile for age. At our initial evaluation, her temperature was 40.1°C (104.1°F), and she was tachycardic. Physical exam was notable for cervical and inguinal lymphadenopathy, mild hepatosplenomegaly and multiple erythematous, blanchable macules, and patches of an urticarial nature, mostly coalescing on the upper and lower extremities, face, and torso, with minimal involvement of the palms and soles (Fig. 1, A

Figure 1. Urticarial-like rash. (A and B) Photographs were taken at the peak of rash development, before initiation of any therapies. (C and D) Histological examination of skin with perivascular inflammatory infiltrate.

Table 1 **Laboratory evaluation**

Laboratory	Result (normal range)	Infectious Disease Evaluation—Negative Studies	
WBC	$21.9 \times 10^3/\mu L$ (6–$14 \times 10^3/\mu L$)	Pre-IVIG serologies	Cultures
Platelets	$697,000/\mu L$ (140–$440 \times 10^3/\mu l$)	Epstein-Barr virus	Blood
CRP	22 mg/L (0–3 mg/L)	Coccidioides	Urine
ESR	43 mm/hr (0–20 mm/hr)	Toxoplasma	
D-dimer	>5000 ng/mL (<400 ng/mL)	Bartonella	ELISA
Fibrinogen	163 mg/dL (160–425 mg/dL)	Enterovirus	Mycoplasma
LDH	1901 IU/L (500–950 IU/L)		
ANA	<1:40 (<1:40)	Direct fluorescent antibody	
C3	121 mg/dL (74–127 mg/dL)	Influenzae A and B	
C4	16 mg/dL (18–47 mg/dL)	Respiratory syncytial virus	
CH50	>60 U/mL (30–75 U/mL)	Parainfluenzae 1, 2, and 3	
Urinalysis	Normal	Adenovirus	

ANA = antinuclear antibody; CRP = C-reactive protein; ELISA = enzyme-linked immunosorbent assay; ESR = erythrocyte sedimentation rate; IVIG = i.v. immunoglobulin; LDH = lactate dehydrogenase; WBC = white blood cell.

and *B*). There was no evidence of skin excoriation, oral findings, or skin peeling of the fingers.

Laboratory and Other Diagnostic Findings

Laboratory evaluation revealed elevated levels of acute-phase reactants and serum inflammatory markers, including C-reactive protein at 22 mg/L (reference range, 0–3 mg/L), erythrocyte sedimentation rate of 43 mm/hour (reference range, 0–20 mm/hour), and platelets of 697,000/μL (reference range, 140–440 $\times$ $10^3/\mu$L). Cultures and diagnostic tests were negative for an infectious etiology (Table 1). Multiple echocardiograms documented normal coronary artery internal dimensions.

QUESTIONS

What Is the Differential Diagnosis?

The differential diagnosis for fever and urticaria in a child is extensive, and includes infectious causes, medication reactions (especially antibiotics), autoimmune diseases, vasculitides, and autoinflammatory disorders including the cyropyrin-associated periodic syndromes (CAPS).[1,2] The length of fever (>5 days), history of conjunctivitis, and presence of cervical lymphadenopathy is also concerning for Kawasaki disease, as initially diagnosed in this patient, although she did not meet the other criteria. For a diagnosis of classic Kawasaki disease, she would require at least two additional symptoms such as oral mucosal changes, polymorphous rather than urticarial rash, erythema/edema of palms/soles, or desquamation of fingertips/toes.[3] Table 2 summarizes a more complete list of differential diagnoses.

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

Complex urticaria, as suggested by lack of responsiveness to antihistamines, association with fever, or other indications of a systemic process, should be biopsied.

Table 2 Differential diagnosis of fever and urticaria

Immunologic/Autoimmune		Infectious	Autoinflammatory	Other Considerations
Urticarial vasculitis	Macrophage activation syndrome	Respiratory virus	CAPS	Kawasaki disease
SCLE/SLE	HLH	HIV	Familial Mediterranean fever	Malignancy
Systemic onset juvenile idiopathic arthritis	Schnitzler syndrome	Parasitic infection		Medications (penicillin and other β-lactam antibiotics)

CAPS = cryopyrin-associated periodic syndromes; HIV = human immunodeficiency virus; HLH = hemophagocytic lymphohistiocytosis; SCLE = subacute cutaneous lupus; SLE = systemic lupus erythematosus; URI = upper respiratory infection.

Evaluation of the inflammatory infiltrate may identify rare but serious syndromes marked by urticaria, including the vasculitides and CAPS. Immunohistochemical identification of specific cell types, such as regulatory T cells (observed in cases of chronic urticaria), can guide diagnosis and management decisions.[4] Additional histological studies such as immunofluorescent antibody staining of the tissue may provide further information regarding antibody deposition as seen in subacute cutaneous lupus.[5]

Clinical Course

Treatment with IVIG at 2 g/kg led to only a temporary improvement in the fevers and inflammatory markers, but minimal impact on her rash. Subsequent treatment with infliximab at 5 mg/kg as well as a second course of IVIG (2 g/kg), gave similar results.

Given the failure of sustained improvement in her inflammatory symptoms and persistence of the urticarial rash, a skin biopsy of affected skin was performed, which showed a perivascular inflammatory infiltrate comprised of lymphocytes, neutrophils, and rare eosinophils without evidence of leukocytoclastic vasculitis. Some of the mixed inflammatory infiltrate also surrounded a few adnexal structures, suggestive of CAPS[6,7] (Fig. 1, C and D).

A therapeutic trial with subcutaneous anakinra (2 mg/kg per day) resulted in partial resolution of symptoms, and increasing the dose to 4 mg/kg per day led to complete resolution of her physical symptoms as well as normalization of inflammatory markers (Fig. 2). There was no evidence of papilledema, such as blurred optic margins or hemorrhage near the optic disk on ophthalmologic exam, and laboratory studies have consistently indicated normal renal function. Additional workup revealed normal bone studies, but minimal leptomeningeal enhancement on MRI as observed in neonatal-onset multisystem inflammatory disorder.[8] Her dose requirement and clinical findings characterize her as a more severe phenotype on the spectrum of

CAPS. Sequencing of all *NLRP3* coding exons failed to show a mutation.

She continues to be asymptomatic on anakinra at 4 mg/kg per day, with serum inflammatory markers at the lower limits of detection: C-reactive protein at 0.02 mg/L (reference range, 0–3 mg/L) and erythrocyte sedimentation rate at 1 mm/hour (reference range, 0–20 mm/hour). Attempts at reducing her dose to every other day administration have resulted in return of clinical symptoms. She has met developmental milestones appropriately, and her growth has improved with height and weight now surpassing those of her fraternal twin sister. Therapy with anakinra has been well tolerated and she has not experienced any injection site reactions or serious infections.
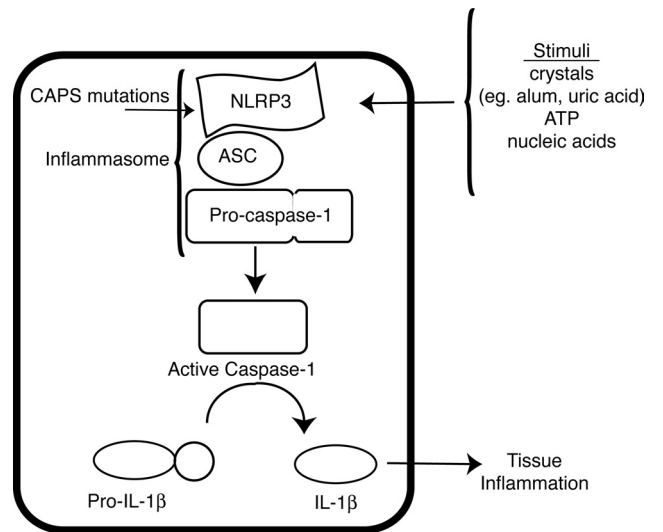
DISCUSSION

The pattern of symptoms and clinical findings, as well as response to anakinra, was consistent with a diagnosis of CAPS. CAPS are a spectrum of autosomal dominant disorders, characterized by intermittent or continuous symptoms of fever, rash, conjunctivitis, and musculoskeletal pain.[9,10] The mildest form, familial cold autoinflammatory syndrome, uniquely displays episodes of inflammation after mild generalized cold exposure.[11] Muckle-Wells syndrome is similarly characterized by inflammatory episodes, which occur more frequently but without a defined inciting factor. Chronic inflammation in Muckle-Wells syndrome leads to the development of progressive sensorineural hearing loss and systemic amyloidosis in a subset of patients.[12] In the most severe phenotype, neonatal-onset multisystem inflammatory disorder, patients present early with chronic inflammation including an urticarial rash and fever. Later, they develop signs of central nervous system inflammation (increased intracranial pressure, chronic aseptic meningitis, seizures, and uveitis) as well as sensorineural hearing loss and progressive arthropathy.[8] Although classified as dis-
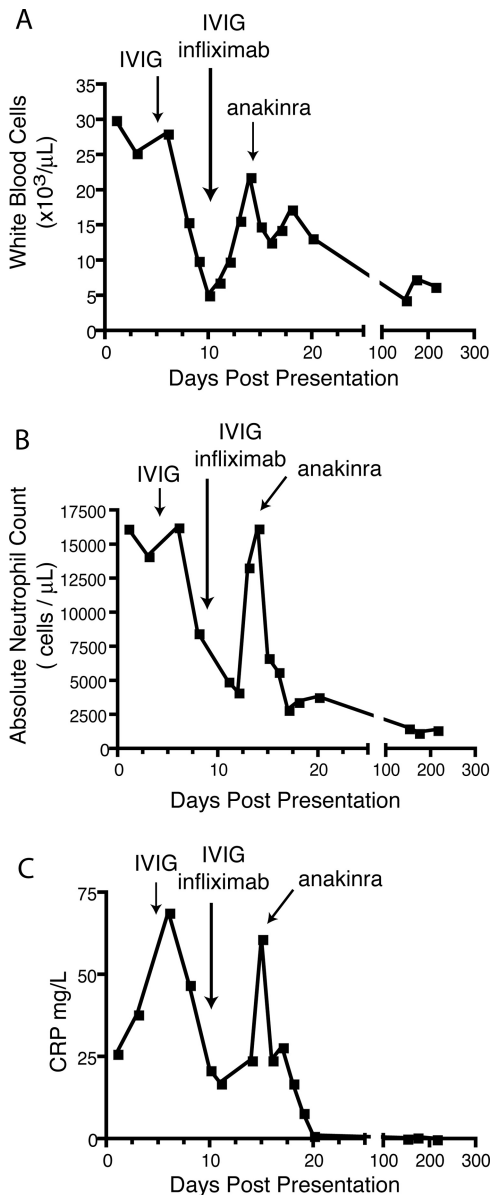
Figure 2. Select laboratory markers and response to therapy. (A) Total white blood cell count. (B) Absolute neutrophil count. (C) C-reactive protein (CRP). IVIG, i.v. immunoglobulin.

Figure 3. NLRP3 Inflammasome. Cyropyrin-associated periodic syndrome (CAPS)–associated mutations in NLRP3 lead to inflammasome hyperactivity, independent of known clinically relevant sterile inflammatory stimuli. Inflammasome activation results in pro–caspase-1 cleavage, caspase-1 activation, and IL-1β production leading to inflammation.

tinct disorders, many patients display overlapping symptoms, as we observed in our patient.

The majority of CAPS patients present within the first few weeks to months of life, consistent with the inherited nature of this systemic innate immune inflammatory disorder. However, there are several cases in which significant symptoms are not observed until after the neonatal period as was seen in our patient. This is also true for several of the other hereditary fever disorders, suggesting a role for an environmental trigger, such as microbial exposure. These autoinflammatory disorders are characterized by dysregulation of innate immunity or aberrant pattern recognition sensing, with a predominance of activated neutrophils and mono-

cytes, rather than the antigen-specific T cells and high-titer autoantibodies observed in autoimmune diseases.

Most but not all CAPS patients have a mutation in *NLRP3* which encodes cryopyrin.[13] The identification of mutation-negative patients with a classic CAPS phenotype suggests the involvement of additional genes in the same or related pathways. Additionally, considerable evidence now exists for the presence of somatic mosaicism in *NLRP3* in many CAPS patients initially thought to be mutant negative,[14,15] but this still has not been evaluated in our patient. Cryopyrin associates with apoptosis-associated speck-like protein containing a caspase recruitment domain and procaspase-1 to form the NLPR3 inflammasome driving IL-1β and IL-18 production. Persistent activation of the inflammasome in CAPS leads to up-regulation of IL-1β and the symptoms observed in CAPS (Fig. 3).[16]

Therapies for CAPS primarily target IL-1 and include anakinra (recombinant IL-1 receptor antagonist),[17,18] rilonacept (fusion protein of IL-1 receptor and IL-1 receptor accessory protein),[19,20] and canakinumab (humanized monoclonal antibody to IL-1β).[21] Studies with IL-1 blockers have consistently shown reduction of symptomatic periods and inflammatory markers in patients with CAPS, similar to the results observed in our patient. Additionally, anti–IL-1 therapy has often shown substantial improvement of progressive and long-term complications of CAPS, including hearing loss and renal disease due to amyloidosis, as well as improvement in quality-of-life measurements.[22–24] The success of IL-1–targeted therapy in CAPS and other neutrophilic skin disorders such as Sweet syndrome[25] and Schnitzler syndrome[26]

suggest that it may have a role in the therapy of chronic urticaria with neutrophilic pathology.

Currently, rilonacept and canakinumab are Food and Drug Administration approved for CAPS, whereas anakinra is only approved for the treatment of rheumatoid arthritis. All three drugs are injectable and have established life-changing results for these patients but primarily differ in their recommended frequency of administration. IL-1–targeted therapy may be associated with increased risk of nonopportunistic infection, and patients should be monitored appropriately and treated accordingly.

Final Diagnosis

Final diagnosis was cryopyrin-associated periodic syndrome.

SUMMARY AND CONCLUSIONS

This patient with mutation-negative CAPS emphasizes the broad differential diagnosis of fever and rash in a young child and the variable clinical presentation of the CAPS spectrum. This case also illustrates the usefulness of biopsy for urticarial-like lesions that are minimally responsive to conventional therapy. It also suggests that there is a role for a therapeutic trial of anakinra in the diagnostic workup of CAPS as well as long-term maintenance therapy.

ACKNOWLEDGMENTS

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