Chronic urticarial plaques in a young woman

Suzanne C. Ward, MD, and Nathan W. Rojek, MD
Irvine, California

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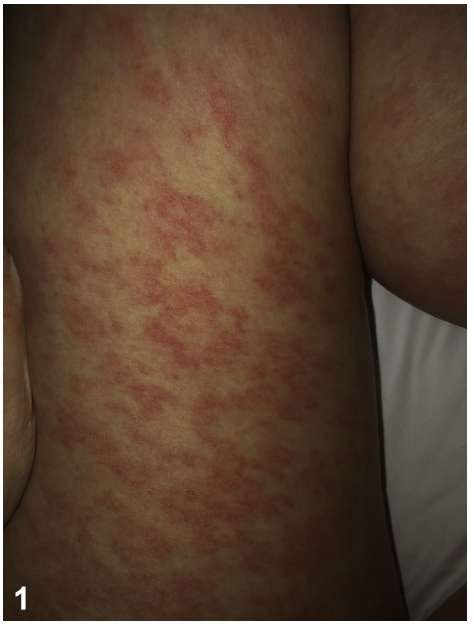

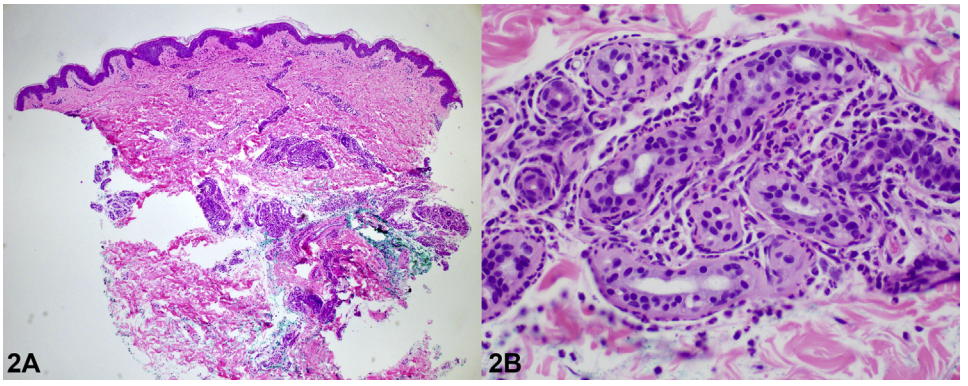

A 22-year-old woman presented with daily urticaria since infancy. Wheals were generalized, intensely pruritic, and individual lesions lasted less than 24 hours (Fig 1). She reported exacerbation by cold and windy weather and endorsed associated fevers, joint pain/stiffness, and conjunctivitis. She denied hearing loss. Her father had similar symptoms, though he had not been formally evaluated or treated. Laboratory evaluation revealed mild

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Correspondence to: Suzanne C. Ward, MD, Department of Dermatology, University of California Irvine, 118 Medical Surge I, Irvine, CA 92697-2400. E-mail: scward@hs.uci.edu.

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elevation in serum immunoglobulin E level (123 kU/L) but negative antinuclear antibody and histamine release assay. Treatments that failed included maximum recommended doses of oral antihistamines and a 9-month trial of omalizumab. At that time, prednisone had been the only effective treatment. Skin biopsy was obtained (Fig 2).

Question 1: What is the most likely diagnosis?

A. Chronic idiopathic urticaria (CIU)

B. Autoimmune urticaria

C. Schnitzler syndrome

D. Familial cold autoinflammatory syndrome (FCAS)

E. Deficiency of interleukin 36 receptor antagonist

Answers:

A. Chronic idiopathic urticaria (CIU) — Incorrect. While about 60% of cases of chronic urticaria are ultimately deemed idiopathic, the patient's onset in infancy and additional symptoms of cold sensitivity, fevers, arthralgias, and conjunctivitis suggest the presence of an underlying systemic disease.[1]

B. Autoimmune urticaria — Incorrect. Autoimmune urticaria is a common cause of chronic urticaria; however, it is less likely in this scenario given the patient's negative histamine release assay.[1]

C. Schnitzler syndrome — Incorrect. Schnitzler syndrome is a rare autoinflammatory condition associated with urticaria and systemic symptoms, often in the presence of underlying monoclonal gammopathy. In this case, it is less likely as it is an acquired condition and unlikely to present in infancy.

D. Familial cold autoinflammatory syndrome (FCAS) — Correct. FCAS is a rare genetic autoinflammatory syndrome. Diagnostic criteria for FCAS include the following features: (1) recurrent fever and rash after cold exposure, (2) positive family history, (3) age of onset prior to 6 months, (4) duration of flares less than 24 hours, (5) conjunctivitis, and (6) lack of other systemic symptoms including deafness, periorbital edema, lymphadenopathy, and serositis. Urticarial lesions may be burning in nature and generally spare the head.[2] Our patient met all clinical criteria for FCAS.

E. Deficiency of interleukin 36 receptor antagonist — Incorrect. Deficiency of interleukin 36 receptor antagonist is also an inherited autoinflammatory syndrome that presents with fever and cutaneous findings. However, it is not the best answer in this case as the cutaneous presentation resembles generalized pustular psoriasis rather than urticaria.[2]

Question 2: This condition is due to a mutation in which of the following genes?

A. *C1QA*

B. *NLRP3*

C. *STAT3*

D. *IL1RN*

E. *MEFV*

Answers:

A. *C1QA* — Incorrect. Homozygous pathogenic variants in *C1QA* cause deficiency of C1q, a rare autosomal recessive immunodeficiency with a systemic lupus erythematosus-like phenotype. Hypocomplementemic urticarial vasculitis may also be associated with acquired deficiency of C1q.

B. *NLRP3* — Correct. Pathogenic variants in *NLRP3* may be sporadic or autosomal dominant and are responsible for the cryopyrin-associated periodic syndromes, including FCAS. *NLRP3* encodes cryopyrin which serves as a scaffold for the NLRP3 inflammasome; aberrant inflammasome activity leads to overproduction of interleukin 1β.[2] Our patient was diagnosed clinically, though confirmatory genetic testing is pending.

C. *STAT3* — Incorrect. Deficiency in *STAT3* is the most common cause of autosomal dominant hyperimmunoglobulin E syndrome (previously known as Job syndrome). Autosomal dominant hyperimmunoglobulin E syndrome is associated with eczematous dermatitis and immunodeficiency but not chronic urticaria.[3]

D. *IL1RN* — Incorrect. *IL36RN* encodes the interleukin 36 receptor antagonist. Loss of function mutations leads to deficiency of interleukin 36 receptor antagonist, not FCAS.[2]

E. *MEFV* — Incorrect. *MEFV* encodes the pyrin gene. Disease-causing mutations in *MEFV* are associated with familial Mediterranean fever, not FCAS.[2] Familial Mediterranean fever is also an inherited autoinflammatory syndrome with fevers and joint

pain. However, the cutaneous lesions associated with familial Mediterranean fever typically resemble erysipelas rather than urticaria.

Question 3: Which of the following is the best treatment for this condition?

A. Prednisone

B. Mepolizumab

C. Omalizumab

D. Canakinumab

E. Dupilumab

Answers:

A. Prednisone — Incorrect. While prednisone may provide symptomatic relief, it is not ideal for long-term management of FCAS due to its significant side-effect profile.[4]

B. Mepolizumab — Incorrect. Mepolizumab is a fully-humanized antiinterleukin 5 monoclonal antibody used to treat severe asthma with eosinophilia, eosinophilic granulomatosis with polyangiitis, and hypereosinophilic syndrome. It has neither shown benefit in FCAS nor in CIU.[4]

C. Omalizumab — Incorrect. Omalizumab is a monoclonal antibody that binds the Fc receptor of immunoglobulin E. It is approved by the US Food and Drug Administration for asthma and CIU but not for FCAS.[4]

D. Canakinumab — Correct. Canakinumab is a fully human antiinterleukin 1β monoclonal antibody, administered subcutaneously every 8 weeks. It is approved by the US Food and Drug Administration for the treatment of FCAS as well as other periodic fever syndromes, hyperimmunoglobulin D syndrome, systemic juvenile idiopathic arthritis, and adult-onset Still disease.[4,5] Our patient was treated with canakinumab 150 mg administered every 8 weeks and experienced full resolution of symptoms after her first dose.

E. Dupilumab — Incorrect. Dupilumab is a monoclonal antibody to the interleukin 4 receptor α subunit, which binds interleukin 4 and interleukin 13. It is approved by the US Food and Drug Administration for atopic dermatitis, asthma, and chronic rhinosinusitis with nasal polyps and has been reported to be efficacious in treating CIU refractory to omalizumab; however, it is not indicated for the treatment of FCAS.[4]

Abbreviations used:

CIU: chronic idiopathic urticaria
FCAS: familial cold autoinflammatory syndrome

Conflicts of interest

None disclosed.

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