

CASE REPORT

An unusual urticarial eruption: Familial cold autoinflammatory syndrome

Rebecca Nguyen,¹ Aaron Robinson,¹ Katherine Nicholls,^{1,2} George Varigos¹ and Con Dolianitis¹

¹Royal Melbourne Hospital, and ²Dorevitch Pathology, Melbourne, Victoria, Australia

ABSTRACT

This is a case of a 26-year-old Caucasian woman with a lifelong history of an episodic urticaria associated with arthralgia, precipitated by exposure to cold. She had no other significant past medical history. She reported several family members with a history of very similar episodic eruptions without definitive diagnoses. An examination showed an urticarial eruption over her limbs with no other systemic findings. A baseline full blood examination, serology and autoimmune screen were normal. A skin biopsy was consistent with urticaria, with dermal oedema and a perivascular infiltrate. Following genetic testing, she was found to be heterozygous for a mutation, p.Ala439Val in the *NLRP3* gene, known to cause familial cold autoinflammatory syndrome (FCAS), which typically presents with urticaria, conjunctivitis and arthralgia, as described in this patient. FCAS is one subtype of a group of conditions known as cryopyrin-associated periodic syndromes (CAPS). CAPS are rare, autosomal dominant inherited conditions with a spectrum of phenotypes, characterised by increased interleukin-1 β release with subsequent local and systemic proinflammatory and pyrogenic effects.

Key words: anakinra, autoinflammatory, canakinumab, cold, familial, FCAS, urticaria.

INTRODUCTION

This is a case of a 26-year-old Caucasian woman who presented with episodes of urticaria associated with arthralgia,

which were precipitated by cold exposure. This patient described a lifelong history of episodes of small erythematous, blanching papules, which coalesced to form larger plaques several centimetres in diameter on the limbs and trunk. These eruptions were associated with a painful burning sensation, chills and polyarthralgia, involving her wrists, hands, elbows, knees and ankles. These episodes were exacerbated by cold temperature and tiredness, with more frequent episodes occurring in winter than in summer, and after long hours in an airconditioned office. These symptoms were relieved within hours by hot showers and sleep, though after particularly severe episodes she reported residual erythematous patches the following day. The pain associated with these episodes was on occasion so severe that she was unable to work.

This patient's past medical history included mild asthma and benign colonic polypectomy. She had no other dermatologic conditions. Her regular medications included salbutamol as required and the combined oral contraceptive pill (levonorgestrel 0.15 mg, ethinyl estradiol 30 μ g). There was no known allergic history. She worked as a lawyer, at times spending long hours in an airconditioned office.

Her family history was significant, with many members of her family reporting a history of very similar episodic urticaria associated with arthralgia, with no definitive diagnosis. A family pedigree is shown in Fig. 1. Informed consent for the case report and photographs were obtained from the patient.

On examination, this patient had an eruption of urticarial plaques on the posterior aspects of her forearms, lower legs and dorsa of her feet bilaterally (see Figs 2 and 3 for clinical photographs). There was no lymphadenopathy, joint effusions or joint deformities. An oral mucosa examination was normal. The investigations performed are listed in the tables, giving the normal and abnormal results (Tables 1 and 2).

Correspondence: Dr Rebecca Nguyen, 18 Savannah Place, Chadstone, Vic. 3148, Australia. Email: bec.nguyen@gmail.com
Rebecca Nguyen, MBBS (Hons). Aaron Robinson, MBBS. Katherine Nicholls, FRACP. George Varigos, FACD. Con Dolianitis, FACD.
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Abbreviations

CAPS	cryopyrin-associated periodic syndromes
FCAS	familial cold autoinflammatory syndrome
Ig	immunoglobulin
Interleukin	IL

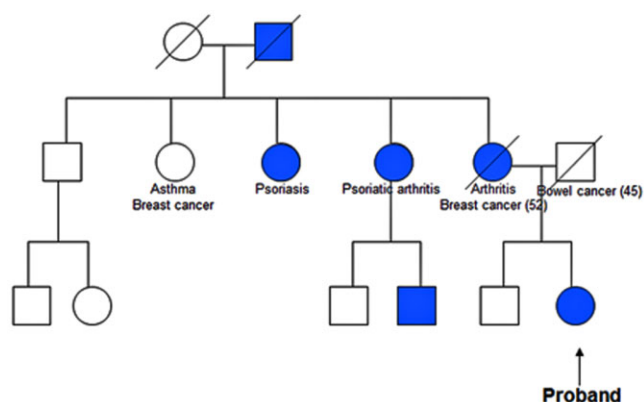


Figure 1 Family pedigree. ●, affected female, episodic urticarial rashes and arthralgia; ■, affected male; ○, unaffected female; □, unaffected male.



Figure 2 Clinical photographs of arm rash.

Histology from the skin biopsy was consistent with urticaria with an intact epidermis showing no spongiosis, exocytosis or apoptosis. There was dermal oedema with a perivascular infiltrate of lymphocytes, histiocytes, eosinophils and neutrophils. There was also a light interstitial infiltrate throughout the dermis and subcutaneous fat. Nuclear debris was not a feature and there was no fibrinoid necrosis (see Figs 4 and 5). No significant immune reactants were observed on direct immunofluorescence, or with staining for immunoglobulin (Ig)A, IgG, fibrin, C3c or C1q. Only faint IgM granular staining of the basement membrane zone was observed. These results excluded urticarial vasculitis, lupus and immunobullous diseases as differential

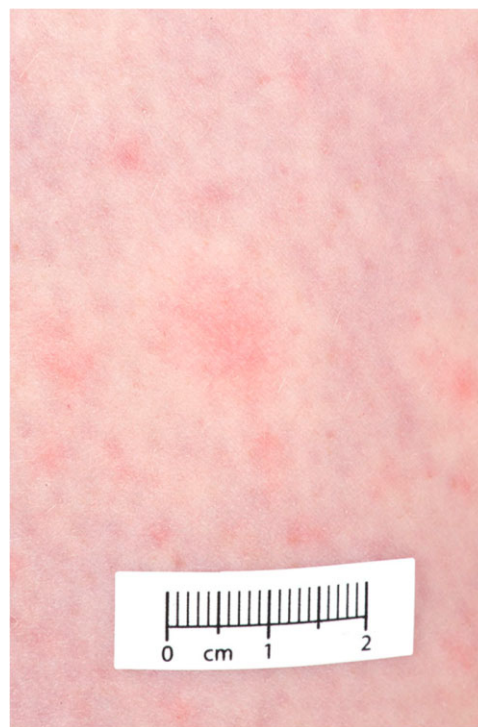


Figure 3 Clinical photographs of arm rash.

Table 1 Patient's normal results

Full blood count
Urea and electrolytes
Liver function tests
Coagulation studies
Complement studies
Immunoglobulin subtypes
Urinary protein
Anti-nuclear antibodies: negative
Extractable nuclear antibodies: negative
Cryoglobulins: negative
Urine microscopy and culture was negative for casts and red cells and had only traces of protein

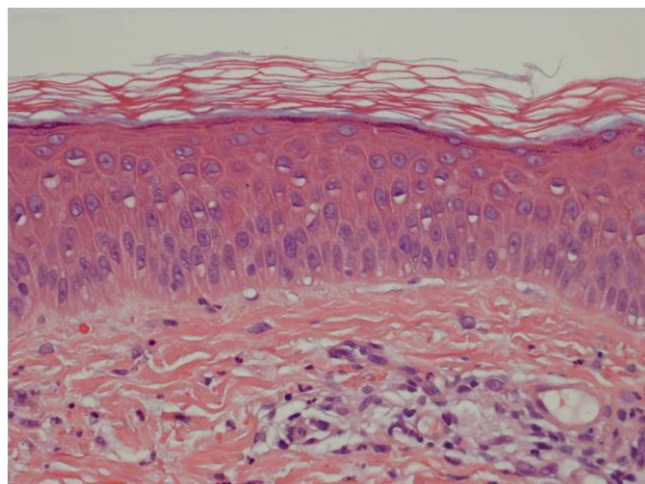
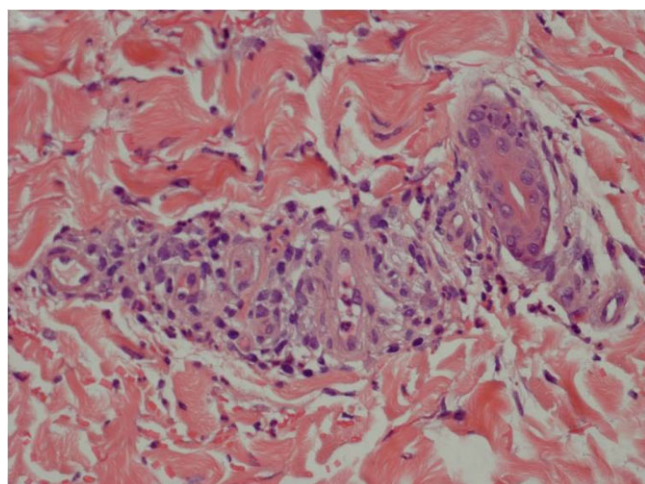
diagnoses. Mast cells were not noted, which excluded urticaria pigmentosa as a cause for her symptoms.

This patient was initially treated with cetirizine 10 mg twice daily and ibuprofen as required for her joint pains, with minimal improvement. She then trialed colchicine 0.5 mg twice daily, which subjectively reduced the severity (but not frequency) of the episodes but was ceased due to gastrointestinal side-effects.

Due to her significant family history with several members with similar episodic urticarial eruptions that were exacerbated by the cold, a referral to a clinical geneticist was made to look for an inherited group of conditions, known as cryopyrin-associated periodic syndromes (CAPS), which are associated with the *NLRP3* gene. *NLRP3* gene sequencing from DNA collected from peripheral blood showed a heterozygous p.Ala439Val (A439V) substitution in exon 3, which is a mutation reported in familial cold

Table 2 Patient's abnormal results

C-reactive protein (mg/mL)	25 (<5)
Erythrocyte sedimentation rate (mm in 1 h, range)	16 (2–12)
Serum protein electrophoresis (g/L, range)	
Alpha-1-globulin	2.8 (0.8–2.0)
Alpha-2-globulin	9.0 (5.4–8.9)
Beta-globulin	1 g(4.2–6.8)
	No detectable monoclonal protein
Serum amyloid (mg/mL)	34.5 (0.0–6.4)

**Figure 4** Histology with HE x40.**Figure 5** Histology with HE x40.

autoinflammatory syndrome (FCAS).^{1–5} Molecular karyotype analysis using a single nucleotide polymorphism microarray was normal. At the time of publication, an application for funding of anakinra treatment was awaiting approval.

DISCUSSION

CAPS are a group of conditions representing a spectrum of phenotypes, including FCAS, Muckle–Wells syndrome (MWS) and chronic infantile neurological cutaneous and articular (CINCA) neonatal onset multisystem inflammatory disease.^{1–3} See Table 3 for further details on the clinical phenotypes.^{4–6}

This patient demonstrated symptoms of an episodic urticarial eruption with polyarthralgia, which was exacerbated by the cold. The eruption would usually resolve in 24 h. These are all features of FCAS. The diagnosis of FCAS-1 was confirmed by sequencing of the *NLRP3* gene (*CIAS1* gene). Other pathogenic mutations in the *NLRP3* gene identified on exon 3 include V198M, R260W, G301D, L305P, A353V, L353P, A439V, R488K, E627G and A439V.^{1–5}

The *NLRP3* gene encodes a protein expressed primarily in peripheral blood leukocytes, which acts as the backbone of the NLRP3 inflammasome, a component of the innate immune system. In response to whole pathogen, pathogen-associated or damage-associated molecular signals, (exogenous signals indicating infection or environmental irritants or endogenous signals indicating injury), NLRP3 changes conformation to allow the assembly of the NLRP3 inflammasome, initiating a cascade of intracellular signalling involving caspase-1 activation, which culminates in the release of interleukin-1 beta (IL1 β). Mutations in the *NLRP3* gene in FCAS result in the inappropriate activation of the NLRP3 inflammasome in response to cold, by a mechanism not well understood. In FCAS, increased IL-1 β release subsequently has a local and systemic proinflammatory and pyrogenic effect, resulting in the urticaria and arthralgia, as described in this patient.^{7–9}

Though it is an autosomal dominant disorder, the degree of penetrance is unknown, so genetic counselling is recommended to all patients. Monitoring of renal function is also recommended due to the risk of amyloid-induced renal failure. This more commonly occurs in MWS but has been reported in cold familial urticaria.^{2,10,11}

Traditionally, symptomatic treatment with nonsteroidal anti-inflammatory drugs was the primary treatment available for arthralgia. High-dose corticosteroid treatment acts to decrease NF κ B signalling, thus downregulating the production of pro-IL-1 β production and in turn reducing IL-1 β release, but this approach has significant long-term side-effects.^{12,15}

As our understanding of the molecular pathogenesis of FCAS has improved, targeted anti-IL1- β agents have now been used to excellent effect in these conditions. Isolated case series, and more recently a larger multicentre trial on a larger cohort of CINCA patients, show the benefit of anakinra, an IL-1 receptor antagonist.¹⁴ IL-1 blockade has been shown to not only prevent recurrent attacks but also decrease the inflammatory response leading to amyloidosis. Another study reported a case treated with canakinumab, (an anti-IL-1 β human monoclonal antibody) with complete remission following therapy.¹⁵ Further studies into which is the most effective agent in these patients are needed.

Table 3 Clinical subtypes of cryopyrin-associated periodic syndromes

Familial cold autoinflammatory syndrome (FCAS) 3 subtypes: all have same phenotype, different gene affected FCAS-1 (<i>NLRP3</i>) FCAS-2 (<i>NLRP12</i>) FCAS-3 (<i>PLCG2</i>) Milder phenotype Urticarial rash Polyarthralgia Exacerbated by cold – within 1–2 h Resolved within 24 h	Muckle–Wells syndrome Urticarial rash Polyarthralgia Precipitated by cold Sensorineural hearing loss Amyloidosis	Chronic infantile neurological cutaneous and articular/neonatal onset multisystem inflammatory disease More severe phenotype with earlier presentation Urticarial rash Polyarthralgia Can be a continuous rash Chronic meningitis Long-term neurological sequelae
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