

Lifelong urticaria and multiple unexplained systemic symptoms

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Clinical findings

A 23-year-old man had a history of a recurrent, urticated, mildly itchy eruption since infancy, of myalgia and headaches since childhood, and an episode of aseptic meningitis at 14 years of age. Other

symptoms included mouth and genital ulceration, sensorineural deafness, and conjunctivitis. Sudden onset of visual blurring led to admission for neurological investigation. On physical examination, an urticarial eruption was seen on the trunk and arms (Fig. 1), with mild muscle weakness and bilateral papillo-oedema (Fig. 1). Erythrocyte sedimentation rate and C-reactive protein were raised (50 mm/h and 47 mg/L; normal ranges 0–15 mm/h and < 10 mg/L, respectively). Cerebrospinal fluid (CSF) examination was abnormal, with a raised white cell count ($41 \times 10^6/L$ and 60% polymorphs; normal $0-5 \times 10^6/L$ and no neutrophils), raised protein (0.7 g/L; normal 0.2–0.4 g/L) and increased CSF opening pressure. Nerve conduction studies, electromyography, and brain magnetic resonance imaging gave normal results.

Histopathological findings

On histopathological examination of a skin biopsy, a dermal perivascular lymphocytic infiltrate with eosinophils and mast cells was seen (Fig. 2).

What is your diagnosis?

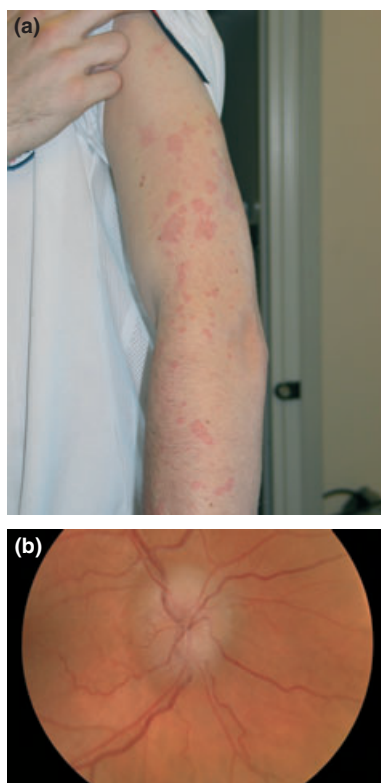


Figure 1 (a) Urticarial rash on left arm; (b) papillo-oedema showing blurred disc margins.

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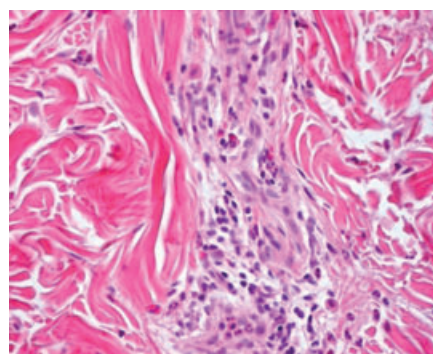


Figure 2 Perivascular infiltrate including lymphocytes, eosinophils and mast cells (haematoxylin and eosin, original magnification $\times 400$).

Diagnosis

Muckle–Wells syndrome (MWS).

Discussion

MWS is one of the cryopyrin-associated periodic syndromes (CAPS), a group of rare disorders of cytokine regulation. The group includes familial cold autoinflammatory syndrome (FCAS), the mildest phenotype, and neonatal-onset multisystem inflammatory disease (NOMID), the most severe phenotype. MWS has an intermediate severity phenotype.

These syndromes were originally thought to be distinct conditions, but are now regarded as a disease continuum with overlapping features. Common to all are recurrent episodes of multisystemic inflammation, and rash is a key symptom, which appears as a recurrent urticarial eruption that starts in early infancy. The eruption is usually accompanied by fever, joint problems, and eye problems including conjunctivitis and uveitis. The rash and systemic symptoms often follow a circadian rhythm, with a pattern of worsening symptoms in the evening,¹ although there was no clear diurnal variation in our patient. The typical histological finding is dermal neutrophilic infiltration involving small vessels and eccrine glands. Presence of a predominantly lymphocytic infiltrate, more in keeping with classic urticaria, was a very unusual feature in this case.

Neurological involvement in MWS is not commonly described, and headache and papillo-oedema are reported infrequently.² Sensorineural deafness occurs in 60–70% of cases of MWS and NOMID. The mechanism is unclear, although it has been suggested to arise as a consequence of cochlear nerve inflammation. Systemic amyloidosis, usually presenting with renal impairment and nephrotic syndrome, is the most severe complication of MWS, occurring in up to 25% of cases.²

CAPS are caused by gain-of-function mutations in the cryopyrin gene *CIAS1* (now known as *NLRP3*), and in our patient, genotyping revealed heterozygosity for the *NLRP3* T348M mutation. The encoded protein NALP3 (NACHT, leucine-rich repeat and pyrin domains containing protein 3) is thought to be an intracellular equivalent of a Toll-like receptor, and associates with other intracellular proteins to form the inflammasome. This is a molecular platform, which is critical in the innate immune response, and is activated by danger signals such as metabolic stressors and microbial pathogens. NALP3 activation starts a chain of molecular events that result in the activation

of the pro-inflammatory cytokines interleukin (IL)-1 β and interleukin-18.³

Therapeutic options for the cryopyrinopathies have until recently been very limited; however, the advent of IL-1 inhibitors has had a major effect on morbidity. Successful treatment of MWS with anakinra, a recombinant human IL-1 receptor antagonist, has been reported,^{4,5} and several other agents targeting the IL-1 pathway are in various stages of development.

After diagnosis, our patient presented to the National Amyloidosis Centre, where he was treated with a novel long-acting IL-1 β antagonist, canakinumab (previously ACZ885; Novartis Pharmaceuticals UK Ltd, Frimley, Surrey, UK) with dramatic clinical and biological results.⁶ Within 24 h of the first injection, the rash had completely resolved, and the headaches and myalgia significantly improved. Normalization of acute phase reactants occurred within 2 weeks, and the patient has had sustained remission with ongoing treatment. Our patient was funded to receive canakinumab through a clinical trial; however, the high cost of treatment (approximately £50 000 per patient annually) highlights the economic implications of long-term monoclonal antibody therapy in patients with CAPS.

This case exemplifies the value of astute dermatological assessment, which provided a unifying diagnosis for the debilitating symptoms and lifelong urticarial rash, and has resulted in profound clinical remission after treatment with a novel IL-1 β antagonist.

Learning points

- MWS is one of the CAPS or cryopyrinopathies, a group of rare autoinflammatory diseases characterized by recurrent episodes of systemic inflammation. Other members of the group are FCAS and NOMID, which represent the mild and severe ends of the disease spectrum, respectively. MWS has an intermediate severity phenotype.
- An urticarial rash appearing in birth or early infancy with systemic symptoms including fever, arthralgia and conjunctivitis should prompt further investigation and diagnostic consideration of a cryopyrinopathy.
- The cryopyrinopathies are caused by mutations of the same gene, *CIAS1* (*NLRP3*). This encodes NALP3, a pro-inflammatory protein that enhances the activation of IL-1 β , initiating an inflammatory cascade.

- Advances in the understanding of the molecular and immunological basis of this group of diseases has led to the successful use of novel therapies targeting the IL-1 pathway. Anakinra was the first anti-IL-1 therapy to be used, and other IL-1 inhibitors are in various stages of development.

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