

LETTER TO THE EDITOR

Neutrophilic urticarial dermatosis (NUD) indicating Cryopyrin-associated periodic syndrome associated with a novel mutation of the *NLRP3* gene

Editor

A 33-year-old female with a 30-year history of recurrent arthralgia, tendovaginitis and fever episodes presented to our institute for recalcitrant generalized urticarial lesions which started at the age of 29. Her diagnosis was chronic spontaneous urticaria. Extensive allergy testing and searches for infectious foci had been negative. She had fully recovered from herpes meningitis some years earlier.

Urticaria persisted for more than 24 h with a maximum in the evening. The patient reported itching, chronic fatigue and intermittent pain of the ankles and small joints. Extensive laboratory and technical tests were inconspicuous, except for a mild elevation of antinuclear antibodies (1 : 640). Punch biopsies were classified as unspecific urticae. Differential diagnoses included

rheumatoid neutrophilic dermatitis, Sweet syndrome and systemic Lupus erythematosus (SLE).

For treatment of the then favoured diagnosis SLE, the patient received methotrexate and hydroxychloroquine leading to a marginal improvement of arthralgia. The urticarial episodes with fatigue and intermittent fever, however, increased in frequency and intensity. All available treatments for urticaria including high-dose antihistamines, systemic corticosteroids and omalizumab were unsuccessful. Laboratory tests now showed an inflammatory reaction, pronounced during urticarial episodes, with neutrophilia, increased levels of alpha-1-globulin, and CRP.

The patient was biopsied again and the old biopsies were reassessed. All specimens revealed the same histopathological pattern (Fig. 1). Based on recent literature^{1–3} the findings were now interpreted as neutrophilic urticarial dermatosis (NUD) as seen in Cryopyrin-associated periodic syndromes (CAPS) and Still's disease. Subsequent genetic testing revealed a novel heterozygous c.1942G>T (p.Asp648Tyr) mutation in exon 3 of the *NLRP3* gene, indicative of CAPS. The patient's father, the sister of her father and one of her brothers were found to carry the same mutation (Fig. 2). The patient's severe symptoms resolved within days upon initiation of daily anakinra injections. Several months later, the patient continues to be in full remission.

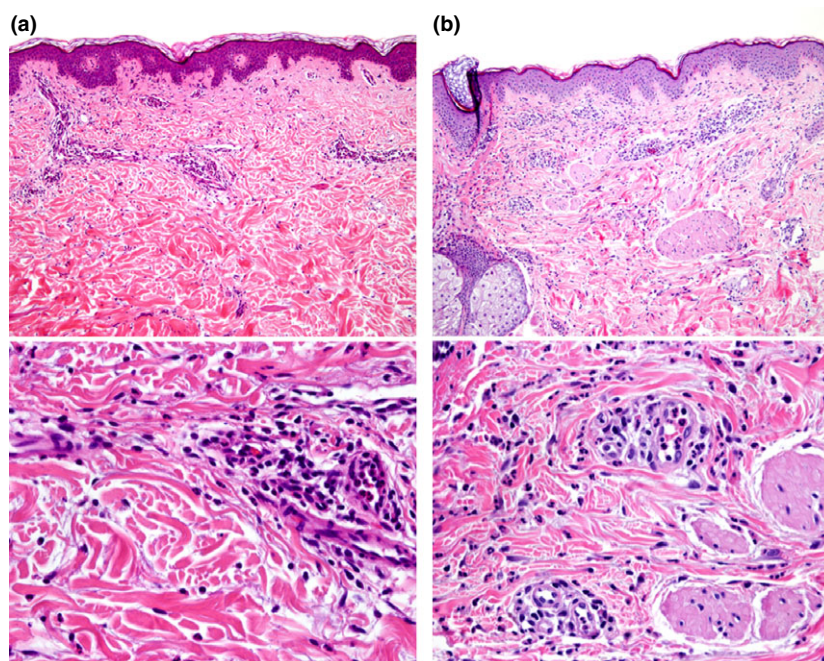


Figure 1 Histopathology. Biopsies taken at the time of first presentation 2007 (a) and in 2013 (b) demonstrate the same pattern of a perivascular and interstitial dermatitis devoid of epidermal changes or vascular damage. High magnifications of both specimens (bottom each) show that the infiltrate consists almost exclusively of intact neutrophils. Eosinophils, as expected in urticaria, or nuclear dust, as expected in early leucocytoclastic vasculitis, are lacking. The pattern and composition is typical of neutrophilic urticarial dermatosis (NUD).

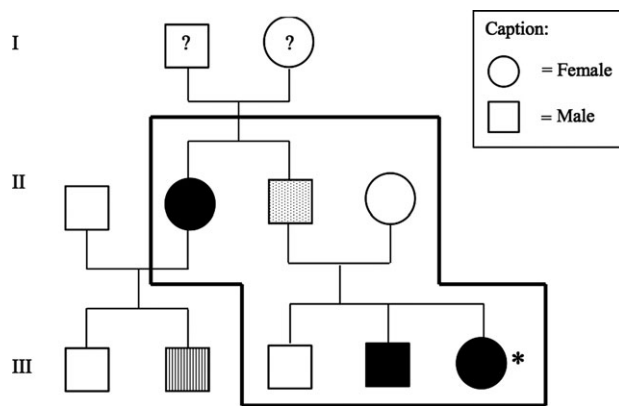


Figure 2 Pedigree. Encircled individuals were genetically tested. A star marks our patient in generation III. The other black symbols indicate her aunt and brother which are also heterozygous carriers of the c.1942G>T (p.Asp648Tyr) mutation and show symptoms probably related to Cryopyrin-associated periodic syndromes (CAPS). The dotted symbol indicates the patient's father who is a heterozygous carrier but has no clinical symptoms. Linear shades mark a relative with fatigue, periodic fever and arthralgia; however, no genetic testing has been performed so far.

CAPS include three phenotypes of rare autoinflammatory disorders that increase in disease severity from familial cold urticaria (FCAS) and Muckle-Wells syndrome (MWS) to chronic infantile neurological, cutaneous and articular syndrome/neonatal onset multisystem inflammatory disease (CINCA/NO-MID).^{4–6} Childhood-onset chronic recurrent episodes of fever, urticarial rash, arthralgia, elevated acute-phase reactants with or without neurological symptoms are suggestive of CAPS.⁶ All phenotypic variants are related to heterozygous mutations of the cryopyrin gene *NLRP3* that plays an important role in the induction of innate immune responses, specifically the regulation of interleukin-1 β (IL-1 β).^{4,5,7} CAPS patients carry gain-of-function mutations of *NLRP3* leading to an uncontrolled overproduction of IL-1 β , which explains the characteristic clinical response to anti-IL-1 drugs such as anakinra.^{5,8}

Diagnosis of CAPS is often delayed as clinical as well as histopathological findings may be interpreted as nonspecific. NUD, as seen in the present case, is a distinct clinicopathological pattern that has only recently been characterized as a hallmark of autoinflammation.^{1–3} Levels of acute-phase proteins such as CRP and serum amyloid A (SAA) are frequently elevated in CAPS. Prolonged elevations of SAA contribute to the development of systemic amyloidosis.⁶

From the clinical findings and the response to anakinra in our patient, we speculate that the detected mutation is responsible for CAPS in this case, but functional testing has not yet been

conducted. The absence of symptoms in the patient's father and the presence of only mild symptoms in her aunt are consistent with variable penetrance of the *NLRP3* variant. Identical amino acid substitutions related to *NLRP3* mutations are known to be sometimes associated with different phenotypes suggesting the involvement of additional genetic and environmental factors.^{5,9}

The presented case emphasizes the need to consider rare diseases such as CAPS in patients with recalcitrant urticaria and the requirement of interdisciplinary counselling including expert histopathologists and geneticists.

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