A Case of Familial Cold Autoinflammatory Syndrome with De Novo NLRP3 Mutation

A 1-year-old Chinese boy presented with recurring urticaria and conjunctivitis associated with low fever (<38°C) since perinatal period (Fig. 1). He was first diagnosed as urticaria, while antihistamine drugs were ineffective. No trigger observed at first. Blood tests showed leukocytosis (17,360/μl) with neutrophilia (11,450/μl). No abnormal results were found on the ophthalmologic examination except for conjunctivitis. A skin biopsy showed moderate perivascular and periadnexal neutrophilic and lymphocytic infiltration, which also supported the diagnosis of chronic urticaria (Fig. 2). Then he was treated with methylprednisolone 4 mg bid. The severity and frequency of skin lesions were improved than before. But the side effects of glucocorticoids like obesity, hirsutism were significant, and the effectiveness was also declined as time went by. Further inquiry revealed that rashes were exacerbated when exposed in the cold environment. High fever (38.6°C) was once accompanied with severe skin rashes and conjunctivitis. Besides, the patient underwent whole exome sequencing. It revealed a heterozygous c.1064T>C transversion in exon 3 of the NLRP3 gene, which leads to the p.(Leu355Pro) missense variant in cryopyrin which has been previously reported in a case of FCAS. Genetic investigation of his parents didn’t detect the missense variant and supported the de novo nature of the patient’s mutation.

The differential diagnosis of urticarial eruption should include cold urticaria, familial mediterranean fever (FMF), pyrin-associated autoinflammation with neutrophilic dermatosis (PAAND), Majeed syndrome. Cold urticaria can be triggered...
by the cold, but mostly doesn’t accompany fever and is sensitive to antihistamines. \textit{NLRP3} mutation are also related to FMF and Majeed syndrome\textsuperscript{4}. The skin lesions of FMF and Majeed syndrome most commonly report erysipelas-like erythema. FMF is characterized as fever and short-term serositic attacks (peritonitis, pleuritis) while Majeed syndrome is characterized as bone pain and joint swelling. PAAND is commonly associated with \textit{MEFV} mutation, featured for fever, neutrophilic dermatosis and myalgia/myositis like FCAS. FCAS is characterized by increased interleukin (IL)-1 \textit{\beta} release due to the \textit{NLRP3} mutation, so early treatment against IL-1 \textit{\beta} like anakinra is essential\textsuperscript{5}. Diagnostic delay of FCAS is frequent since the early phase of clinical feature is not typical especially without family history like this patient. FCAS can turn into MWS or CINCA syndrome with systemic involvement like neurologic damage, arthritis and joint deformity, renal amyloidosis and failure. Chronic urticaria with conjunctivitis and fever insensitive to antihistamine agent is a reminder for CAPS, and further genetic testing to ensure \textit{NLRP3} mutation helps to make accurate diagnosis. We received signed consent form from the patient for the publication of all photographic images.

**CONFLICTS OF INTEREST**

The authors have nothing to disclose.

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Research data are not shared.

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4. Karacan İ, Balamir A, Uğurlu S, Aydın AK, Everest E, Zor S,
Dear Editor:

Hypertrichosis lanuginosa acquisita (HLA) is a rare disorder characterized by the appearance of fine hairs (lanugo), which are relatively long and slightly pigmented. Apart from the face, HLA occurs on the trunk, limbs, and axillae. HLA is frequently associated with various diseases but most commonly with cancer. Among the associated cancers, lung and colon cancers are the most common followed by breast cancer, uterine cancer, and lymphoma. In non-malignant conditions, HLA is often associated with endocrine or metabolic disorders including immunodeficiencies, anorexia nervosa, thyrotoxicosis, and porphyria cutanea tarda. In some cases, HLA may be due to the use of medications, such as phenytoin, streptomycin, cyclosporin, psolaren and minoxidil that cause hair growth1.

A 46-year-old female presented with hypertrichosis on her shoulder, back, neck, and face, which first appeared a year earlier (Fig. 1). The lanugo grew on her face and then spread to other parts of the body, where it became darker and coarser. She was not taking any medication and there was no history of disease. To find the disorder associated with HLA, complete blood count, biochemical, hormone level, and autoimmune antibody tests were performed. Biochemical testing revealed elevated serum aspartate aminotransferase (63 U/L, normal < 31 U/L), alanine aminotransferase (73 U/L, normal < 31 U/L), alkaline phosphatase (464 U/L, 42 < normal < 98 U/L), and gamma-glutamyl transferase (339 U/L, normal < 51 U/L) levels. Anti-nuclear (1:640, cytoplasmic pattern) and anti-mitochondrial antibodies tested positive. Serum immunoglobulin G levels reached the upper limit of normal at 1,626 mg/dl (reference, 680 ∼ 1,620 mg/dl). Viral markers for hepatitis tested negative. We observed a minimal diffuse increase in hepatic echogenicity on liver ultrasonography and core needle liver biopsy; these findings were consistent with autoimmune hepatitis (Fig. 2). Based on the above findings, the patient was diagnosed as having HLA with autoimmune hepatitis. She is taking hepatotonics and undergoing regular follow-up. Although her liver function has normalized over time, the lanugo has not reduced (Fig. 1).

So far, there is only one published case of HLA related to autoimmune hepatitis2, and the present report supports the association between HLA and autoimmune hepatitis. In this case, a liver biopsy was performed, and the patient

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