Autoantibodies in NLRP3-associated autoinflammatory disease: a case report

Sirs,

NLRP3-associated autoinflammatory disease (*NLRP3*-AID), formerly called cryopyrin-associated periodic syndrome (CAPS), is a monogenic systemic autoinflammatory disease (SAID) with autosomal dominant inheritance caused by *NLRP3* mutation, leading to enhanced activation of the NLRP3-inflammasome and overproduction of interleukin (IL)-1β (1, 2). Its diagnostic criteria contain high inflammatory markers and characteristic clinical features such as recurrent fever, urticaria-like rash and non-infectious inflammation in central nervous system (3). The presence of pathogenic *NLRP3* mutations is confirmatory, but is not necessary. According to the definition, SAIDs are caused by defect or dysregulation of the innate immune system, and are lack of autoantibodies or antigen-specific T lymphocytes (2). We presented the first case of *NLRP3*-AID with high-titer ANA and antiphospholipid antibodies.

A 38-year-old Chinese woman presented with cold-triggered episodes of rash (Fig. 1A) and fever since the age of 2. She also had recurrent arthritis of both knees, oedema of bilateral legs (Fig. 1B), and lymphadenopathy in recent years. The pathology of lymph node showed reactive hyperplasia. Over the last 3 years, she suffered from hearing loss with the diagnosis of binaural sensorineural deafness. She had recurrent conjunctivitis (Fig. 1C) for several years and had complained of blurred vision in the last 6 months. Fundus examination demonstrated bilateral papilledema (Fig. 1D). The cerebrospinal fluid test showed evidences of chronic non-infectious meningitis (intracranial pressure: 300 mmH_2O, leukocytes: 19 cells/mm^3, normal levels of protein and glucose, and negative results for bacterial, fungal, acid-fast smear and antibodies to TORCH). MRI of brain showed several subcortical lacunar infarcts in the frontal and parietal lobes (Fig. 1E).

The complete blood count, biochemistry panel and urine analysis were normal. ESR and CRP were elevated. She had a positive ANA (1:160, nucleolar pattern), a positive anti-β2GPI antibody of IgM (54-68 AU/ml, cut-off < 20 AU/ml), and a positive lupus anticoagulant (LA) (1.24-1.29, cut-off ≤1.2) for several times at least 12 weeks apart. Other autoantibodies including anti-ENA, Coombs' test, ANCA, and ACL were negative. She also had hyperglobulinemia of IgG (28 g/L, normal range 7-17g/L), yet serum levels of C3 and C4 were normal.

Pedigree analysis (Fig. 1F) showed that her twin 3-year-old daughters had cold-induced urticarial, without arthritis, hearing loss or blurred vision. The proband's parents and her three sisters had no symptoms. Genetic testing identified a pathogenic *de novo* heterozygous *NLRP3* mutation (NM_001243133.1: exon3: c.1043C>T, p.T348M) in the proband. Her twin daughters had the same mutation.

Based on the clinical manifestations, laboratory results and gene testing result, she was diagnosed as *NLRP3*-AID complicated with antiphospholipid syndrome (APS). Since IL-1 inhibitors were unavailable in China, and she refused other biological agents due to a financial difficulty, prednisone was given with 1mg/kg per day, accompanied with mycophenolate mofetil 0.75g twice a day and aspirin 100mg once a day. After three-month treatment, her symptoms and inflammatory markers relieved except for high intracranial pressure, papilledema and hearing loss.

The patient could be diagnosed as APS because of lacunar infarcts and positive APLs more than twice at least 12 weeks apart. However, only *NLRP3*-AID could explain all of her manifestations rather than APS or SLE. Through thorough literature review, we have not found autoantibodies reported in patients with *NLRP3*-AID so far. Whereas, in familial Mediterranean fever (FMF), the most common monogenic SAID also due to activation of inflammasome, positive ANA with incidence of 6% (4), RF with incidence of 4-4.8% (4, 5), anti-CCP with incidence of 0-14.5% (4-6), and occasionally LA (7) had been reported. The results of autoantibody prevalence in FMF patients are conflicting (8). However, our case with

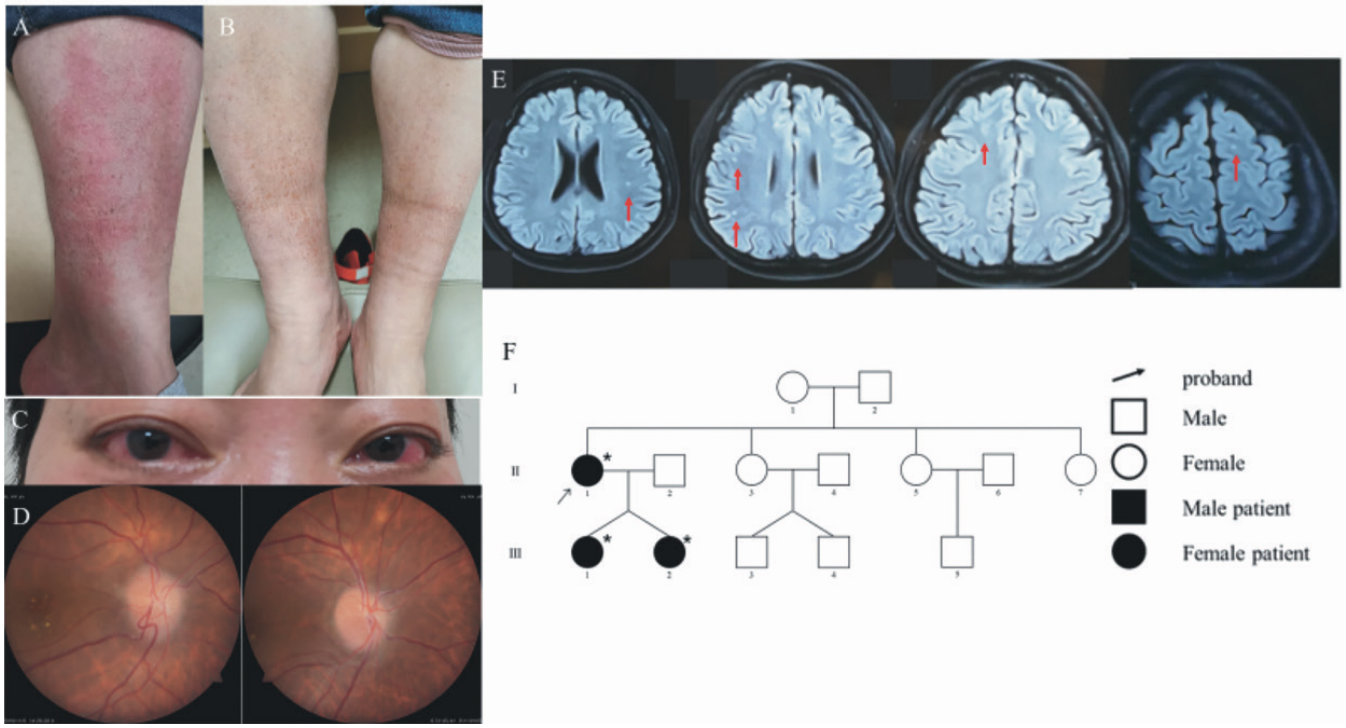

Fig. 1. Clinical manifestations of a Chinese adult *NLRP3*-AID patient with high-titer autoantibodies.
A: Urticaria-like rash; **B**: Oedema of lower extremities; **C**: Bilateral conjunctivitis; **D**: Color fundus photo showed bilateral elevation and blurred margin of the optic disc which is consistent with papilledema; **E**: MRI of brain showed several subcortical lacunar infarcts in the frontal and parietal lobes (red arrows); **F**: Pedigree of the patient.
The black arrow indicates the proband. The asterisks indicate the individuals who carried the *NLRP3* T348M variant.

literature review implies that SAIDs and autoantibodies could co-occur by chance and are not absolutely mutually exclusive.

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