Analysis on misdiagnosis of a case of novel variant of NLRP12

We had read with great interest the paper about undefined systemic autoinflammatory diseases (SAIDs) by Ter Haar *et al.*¹ We noticed heterogeneity of presentation in SAIDs, is difficult to diagnose, and there are no standard medications for the treatment. Here, we report a case with novel variant in NLRP12 was misdiagnosed as refractory systemic-onset juvenile idiopathic arthritis (sJIA) for 2 years.

A 9-year-old girl presented with arthralgia for 2 months and skin rash on her trunk and fever for 10 days, despite antibiotic therapy. The affected joints were both knees and wrists. She was admitted to our department for an initial evaluation in June 2016. Laboratory investigations include the blood count (white blood count (WBC) $9.03 \times 10^9/L$, platelet count (PLT) $508 \times 10^9/L$), inflammatory parameters (high C-reactive protein (CRP) 117.7 mg/L, erythrocyte sedimentation rate (ESR) 108 mm/hour, serum ferritin 628.6 ug/L, interleukin-6 (IL-6) 325.3 pg/L). Serum creatinine, transaminase and procalcitonin levels were within normal limits, whereas results for rheumatoid factor, antinuclear antibody, anti-cyclic-citrullinated peptide antibodies, and human leukocyte antigen (HLA) B27 tests were negative. The bone marrow smear and chest CT had no abnormal changes. MRI of the right hand demonstrated swelling in soft-tissues, and abnormal signs were seen in the subcutaneous and interstitial. Ultrasound of knee joint showed synovial thickening and patellar bursal effusion. Based on the clinical, laboratory and radiologic findings, the diagnosis of sJIA was made. After remission, the patient received prednisolone (1.5 mg/kg by mouth daily), methotrexate (10 mg/m² po weekly), folate (5 mg/m² po three times/week).

After 3 months, the patient presented with similar symptoms. Therefore, tocilizumab injection (12 mg/kg every 2 weeks for the first 3 months and per month subsequently) was given. She had no fever, and inflammatory parameters also returned to normal ranges. However, in the second half of 2017, when the prednisolone decreased to 0.5 mg/kg/day, elevation of inflammatory parameters and fever recurred, and repeated MRI of the right hand revealed minimal improvement of arthritis. The exome sequencing of immune genome revealed a novel mutation in the exon 4 of the NLRP12 gene (c.2129t>c:p.L710P). Sanger sequencing confirmed the mutation was inherited from her father, who denied any symptoms. It has not been reported in literature yet. Then, tocilizumab was discontinued, and changed to prednisolone (1.5 mg/kg by mouth daily) and methotrexate (10 mg/m² by mouth weekly) since 2018. At follow-up, her inflammatory parameters are still abnormal, but without any symptoms.

Our patient presented with fever, arthralgia in knees, wrists and skin rash is in accordance with clinical diagnosis criterion of sJIA, which is different from previous reports.²⁻⁴ But after a period of time of standard treatment were ineffective. Afterwards, in the first year, the addition of tocilizumab controlled

the progression to some extent. As soon as the dosage of steroid was decreased, she presented again fever and arthralgia. Genetic studies confirmed that she did not suffer from sJIA, but carried a novel mutation of NLRP12. Thus, we speculate that the recurrent symptom is due to the reduction of steroids, so we discontinued tocilizumab. Finally, it confirmed that she has a good response with steroids. More research is needed to see if patients with a regular pattern of febrile episodes will have a good response to steroids.¹ But our patient is still in low disease activity. Long-term prognosis still needs further follow-up. The non-specific clinical manifestations of the NLRP12 mutation may cause misdiagnosis. As more and more cases were found, it may increase the knowledge of NLRP12 and improve the diagnostic rate.

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