A 17-year-old girl was referred to our medical centre and received regular follow-up visit. She has suffered from monthly periodic fever and rash since the 40th day after birth. The frequency of fever was remarkably reduced after 8 years of age but relapsed after 16 years of age, when the maximum body temperature reached 38°C. Non-steroidal anti-inflammatory drugs were used to maintain normal temperature. In addition to fever, she had a recurrent runny nose, itchy throat, and irritating dry cough since childhood. Another major symptom was atopic dermatitis, which occurred at the ages of 5 months, 8 years and 14 years. The specific appearance included red papules on the trunk, limbs, and scalp, which was accompanied by itching and purulent appearance after scratching and desquamation (Fig. 1A). Dark red patches covered with greasy scales or scabs were found on the body by dermatoscope. Pain in multiple joints has occurred since 15 years of age, and it was accompanied by swelling of the bilateral knees and ankles, left elbow, and joints of the hands and toes. B-scan ultrasound showed joint effusion and synovial hyperplasia. Bone marrow oedema was revealed in hip joint and knee joint by magnetic resonance imaging (Fig. 1B-C). Swollen submandibular lymph nodes were found by ultrasound scan. Mild splenomegaly was detected through positron emission tomography. Test results of purified protein derivative skin test and T-SPOT.TB test were negative.

Dermoscopy examination did not find any bacterial or fungal infections. Skin biopsies were not performed because of the proband’s refuse. No abnormality was detected in blood culture test, Epstein-Barr virus DNA test, cytomegalovirus DNA test and chest computed tomography scan. These results excluded the possibility of infection. The complete blood count, basic metabolic panel and urinalysis were normal. The erythrocyte sedimentation rate and C-reactive protein were elevated, while autoantibody tests, including antinuclear antibodies, anti-neutrophil cytoplasmic antibodies, and anti-cyclic citrullinated peptide, were negative. The serum IgA level slightly decreased, while the serum levels of IgG, IgM, IgE, and complement were normal. Bone marrow examination found no evidence of haematological diseases. She did not have dental or endocrine system symptoms, and her growth was not affected.

The proband’s father had suffered from seborrhoeic dermatitis, polyarthralgia and low back pain since young. Strikingly, he developed a high fever and severe anaemia only one week before the proband was transferred and was then diagnosed with LGLL by bone marrow examination. The proband’s mother had no symptoms. Complete medical records, including the pedigree and disease histories of the kindred, were collected and documented. Genomic DNA was collected from both peripheral blood and cheek swabs of the proband and her parents, and whole-exome sequencing (WES) was performed with
DNA extracted from peripheral blood. This research was approved by the Institutional Review Board of Peking Union Medical College Hospital and performed according to the Declaration of Helsinki. Informed consent was obtained from the participants.

WES identified a STAT3 variant (NM_139276.3:c.454C>T; p.R152W) in exon 5 in both the proband and her father (Fig. 1D). Sanger sequencing with DNA from both peripheral blood and cheek swabs indicated existence of the STAT3 variant between the proband and her father (Fig. 1E). This variant was reported to be the genetic cause of ADMIO1 (1). Frequency of the STAT3 variant was not reported in the gnomAD and 1000 Genomes databases. In addition, it is predicted to be “probably damaging” or “damaging” by several in silico analysis tools, including SIFT, PolyPhen2, CADD, and REVEL, and was categorised as pathogenic in ClinVar. Based on the clinical manifestations, laboratory results and gene testing results, the proband was diagnosed with ADMIO1. The proband was given 0.5 mg/kg/d prednisone along with sulfasalazine (SASP), metothrexate and leflunomide. Her fever, proteinuria, dermatitis, and arthritis initially improved, although the symptoms recurred after prednisone was tapered off. SASP was then replaced by tofacitinib. And after 6 months of treatment, her symptoms and inflammatory markers were relieved, and the maintenance dose of prednisone was set at 10 mg per day.

ADMIO1 is caused by heterozygous variants in STAT3 and mainly manifests as lymphoproliferation and early-onset multisystem autoimmunity. Our patient presented with lymphadenopathy, hepatosplenomegaly, recurrent fever, polyarthritis, dermatitis, low IgA levels, and ruled out main causes of infection, which were consistent with the features of ADMIO1. Furthermore, Milner et al. (1) reported the same STAT3 c.454C>T variant that caused ADMIO1 in a 25-year-old male patient; however, the clinical manifestations were not identical and the patient of their case mainly presented as autoimmune haemolytic anaemia, autoimmune thrombocytopenia, insulin-dependent diabetes mellitus, alopecia, lung nodules, lymphadenopathy, and hepatosplomegaly. Our cases expanded the understanding of correlation between ADMIO1 clinical features and the STAT3 variant.

More importantly, in our study, the proband’s father shared the same variant in STAT3, they presented different clinical manifestations, which suggests the complexity of STAT3 variants. This study expands the phenotype spectrum of ADMIO1, explores the effect of tofacitinib in treatment, and emphasises the need for and potential usefulness of genetic testing in differential diagnosis.

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References
https://doi.org/10.1182/blood-2014-09-007263
https://doi.org/10.1182/blood-2014-04-570101
https://doi.org/10.1038/ng.3040
https://doi.org/10.1016/j.beha.2019.06.003
https://doi.org/10.1016/j.pdp.2017.10.001
https://doi.org/10.1016/j.semarthrit.2020.05.020
https://doi.org/10.1016/j.imunir.2012.03.014