To the Editor: Childhood splenectomy exposes patients to increased risk of bacterial infections. Appropriate vaccination and education have helped combat these; however, insufficient attention is paid to viral infections after splenectomy. Herein, we report a case of cold agglutinin disease (CAD) caused by recurrent viral infections after splenectomy to treat childhood immune thrombocytopenic purpura (ITP). Antiviral and immunostimulant therapies were administered, resulting in an improved general condition.

The patient had suffered from recurrent epistaxis and skin hemorrhagic spots since he was 10 years old. A complete blood count and smear revealed thrombocytopenia; the lowest platelet count was 1 × 10^9/L. Bone marrow analysis indicated a diagnosis of ITP. He was administered corticosteroids and intravenous immunoglobulins subsequently; however, they were ineffective. Therefore, the patient underwent splenectomy to treat ITP at the age of 11 years. Postsplenectomy, his platelet count increased to an average of 500 × 10^9/L with a highest recorded count of 840 × 10^9/L. Mutations of JAK2/V617F, JAK2 exon 12, MPL W515L/K, and CALR were negative. Verruca first developed on his big toes, one year after splenectomy, and spread to all four limbs and the trunk thereafter [Figure 1]. Skin biopsy revealed verrucous proliferation, confirming this diagnosis. He received immunostimulant drugs, interferon, Chinese medicine, and cryotherapy, but with no efficacy. He also had acute posterior ganglionitis a year after the splenectomy, which was controlled with antiviral treatment.

This 24-year-old Chinese man was referred to our hospital in May 2016, with a chief complaint of dizziness and fatigue for one year. A complete blood picture revealed the followings: erythrocyte, 0.28 × 10^12/L; hemoglobin, 73 g/L; mean corpuscular volume, 114.3 fl; mean corpuscular hemoglobin, 260.7 pg; mean corpuscular hemoglobin concentration, 2.281 g/L; reticulocytes, 6.2%; leukocyte, 7.14 × 10^9/L; neutrophil, 5.06 × 10^9/L; lymphocyte, 1.51 × 10^9/L; and platelets, 798 × 10^9/L. Erythrocyte sedimentation rate was 110 mm/h. Liver function showed indirect and direct bilirubin levels of 62.9 mmol/L and 13.7 mmol/L, respectively. Bone marrow analysis revealed significantly increased proportion of erythrocytes, presence of polychromatic erythrocytes, increased number of platelets, and no abnormality in the morphology of erythrocytes, granulocytes, and lymphocytes. Direct Coombs test was positive (anti-IgG, 1:512; anti-IgM, 1:32; and anti-C3, 1:512). Cold agglutinin test was positive with a titer of 1:1024. Saline-suspended erythrocytes were directly agglutinated at low temperatures. Serologic examination for Mycoplasma pneumoniae (MP) was positive for IgG, but negative for IgM. The serum tested positive for Epstein-Barr virus (EBV)-DNA and EBV capsid antigen IgA. Ferritin was slightly above the upper limit (346.59 ng/ml), while all other tumor markers were within normal ranges. Antibodies to hepatitis B and C virus, human immunodeficiency virus, and syphilis were not found. Antinuclear antibodies were also all negative.

To treat his infection and relieve hemolysis, we administrated acyclovir (0.2 g, p.o., q. 4h.), long-acting interferon-α (180 μg, i.h., q.w.), thymopeptide enteric-coated tablets (20 mg, p.o., b.i.d.), and pidotimod dispersible tablets (0.4 g, p.o., b.i.d.) for 3 months. His general condition improved along with the recovery of the hemogram index (hemoglobin, 111 g/L; leukocyte, 5.6 × 10^9/L;
neutrophil, $3.7 \times 10^9/L$; lymphocyte, $1.3 \times 10^9/L$; platelets, $150 \times 10^9/L$; and reticulocytes, 2.5%). Erythrocyte sedimentation rate has decreased to 8 mm/h. EBV-DNA dropped below the detection threshold ($<1 \times 10^{-2}$ copies/ml) posttreatment. The cold agglutinin titer reduced to 1:256. Indirect and direct bilirubin levels were 13.8 mmol/L and 7.0 mmol/L, respectively.

CAD is a kind of cold autoimmune hemolytic anemia (AIHA) accounting for 10–20% of all AIHA cases. CAD may be idiopathic or secondary. Lymphocytic malignancies and infections (e.g., MP or infectious mononucleosis) are the most frequent underlying diseases for secondary CAD. Positive IgG for MP indicates past infection, whereas positive EBV-DNA and virus capsid antigen IgA reveals current infection. Moreover, the role of concomitant human papillomavirus infection in the development of CAD is unclear. Keeping warm is the main principle for the treatment of CAD. CAD in this patient is likely to have been secondary to his viral infection, which should be treated to relieve the hemolysis. Therefore, antiviral and immunostimulant therapies were administered. The viral infections were controlled, resulting in an improved general condition and proving the effectiveness of the treatment. Rituximab, alone or in combination with other drugs, was satisfactorily effective in the treatment of CAD in both retrospective and prospective studies. In addition, other novel therapies such as eculizumab and bortezomib are emerging.

The spleen is the largest accumulation of lymphoid tissue and exhibits important immunological functions. In infants and children, splenectomy is conducted mostly to treat splenic trauma, hereditary spherocytosis, and ITP. Splenectomized children are immunocompromised and are at high risk for bacterial infections. The case we reported indicated that viral infections and subsequent complications such as CAD should also be considered in children who have undergone splenectomy to treat ITP. Antiviral and immunostimulant treatments might be useful in such patients to treat viral infections.

**Declaration of patient consent**
The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patients’ guardians understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**
There are no conflicts of interest.

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