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LETTER TO EDITOR

# Autoimmune Lymphoproliferative Syndrome with *Cryptococcus* Infection

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To the Editor:

Autoimmune lymphoproliferative syndrome (ALPS) is a childhood disorder characterized by chronic nonmalignant lymphoproliferation, autoimmune manifestations, and susceptibility to lymphoma [1]. ALPS patients have chronic persistent lymphadenopathy, hepatosplenomegaly, and hypergammaglobulinemia, with increased levels of circulating double-negative T cells (DNT cells; $CD3^+CD4^-CD8^-$ T cell receptor (TCR)-αβ+). Germline or somatic deleterious mutations in *FAS*, *FASL*, or *CASP10* are typically observed in these patients, and the somatic mutation in *FAS* is the most prominent. ALPS patients with hypereosinophilia have a significantly higher risk of death due to infectious complications [2]. Studies on ALPS with *Cryptococcus neoformans* infection are limited, and most of these ALPS patients have hypergammaglobulinemia. Here, we present a rare case of ALPS with hypereosinophilia, hypogammaglobulinemia, and *Cryptococcus neoformans* infection.

Informed consent for publication of this case report was obtained from the patient's parents. A 1-year-old boy presented to our institution due to persistent fever and hypereosinophilia for 2 weeks. His medical history revealed axillary lymph node tuberculosis from 2 months of age with a diagnosis of scrofulous lymphadenopathy, which was resolved in 6 months after antituberculosis therapy; his mother had chronic, nonmalignant, and noninfectious lymphadenopathy and was susceptible to infection (about once a month), and she had a history of pulmonary tuberculosis with ALPS-like symptoms.

In addition, the patient received antibiotic therapy during previous hospital admission, but no obvious improvement was found. Physical examination showed that Bacille Calmette-Guerin scar was negative, and he had bilateral cervical and axillary lymphadenopathy. His liver and spleen were not palpable below the costal margin. Laboratory investigations revealed hypereosinophilia (eosinophil count, $32.96 \times 10^9$/L) and neutropenia (neutrophil count, $0.96 \times 10^9$/L), with normal red blood cell and platelet counts. Serum immunoglobulin (Ig) tests showed hypogammaglobulinemia (serum IgA, 10 mg/dl; IgG, 162 mg/dl). Bone marrow biopsy indicated marked increases in eosinophil counts. Serologic analysis showed that his blood samples were negative for an Epstein-Barr virus, cytomegalovirus, parvovirus B19, human immunodeficiency virus, hepatitis B surface antigen, and anti-hepatitis C, as well as sepsis screening, antinuclear antibodies, and anti-double-stranded DNA antibodies. The results of liver and kidney function tests, coagulation profile, and chest X-ray were normal. Abdominal ultrasound examination showed no hepatosplenomegaly. Lymph node biopsy demonstrated reactive lymphoid hyperplasia. High-resolution computed tomography (CT) of the chest and abdomen was suggestive of multiple enlarged mesenteric and retroperitoneal lymph nodes. The patient was subsequently treated with intravenous methylprednisolone (2 mg/kg/day) for 1 week, followed by oral prednisolone (1 mg/kg/d) for 2 weeks. The eosinophil count subsequently decreased to the normal level. However, progressive hepatosplenomegaly was noted at follow-up examinations.

During the following 6 months, the patient had intermittent fever with neutrophil deficiency and reduced serum immunoglobulin levels; these symptoms usually improved after antimicrobial treatment and infusion with gamma-globulin, colony-stimulating factor, and methylprednisolone. However, intermittent fever and reduced serum Ig levels occurred repeatedly. Genetic testing was negative for X-linked agammaglobulinemia-related mutations, and lymphadenopathy and splenomegaly aggravated. Six months later after the first admission, the patient presented to our institution again with complaints of persistent fever, which aggravated over the

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previous 2 weeks. Physical examination showed that lymphadenopathy and splenomegaly extended to the umbilicus. Given persistent hypogammaglobulinemia and his family medical history, an immunodeficiency diagnosis was considered. Further genetic testing revealed heterozygous genetic mutations in *FAS* (chr10-90773886 c.687G>C; p.L229F) at exon 9 with maternal inheritance; whole-exome sequencing with parental verification confirmed the *FAS* mutation but did not find other highly suspicious mutations. The frequency of this mutation in the population is estimated to be 1/120,532 according to the exome aggregation consortium (ExAC). The prediction of combined annotation dependent depletion (CADD) news score is 3.236. It was not described previously. A definitive diagnosis of ALPS is based upon the presence of both required criteria and one primary accessory criterion. The required criteria: the patient showed chronic (> 6 months) nonmalignant, noninfectious lymphadenopathy, splenomegaly, and those with elevated levels of DNT cells (4.11% of total lymphocytes) in the peripheral blood. Primary and second accessory criteria are as follows: somatic pathogenic mutations in FAS and elevated plasma levels of vitamin B12 (2600 pg/mL). The patient in this study met all the criteria, and the diagnosis of ALPS was thus confirmed. The patient was also diagnosed with secondary hypereosinophilia, and he was thus treated with methylprednisolone, followed by oral prednisolone. He was subsequently prepared for bone marrow transplantation. Improved clinical and laboratory findings were observed after 1 month. He had regular follow-up examinations but did not want bone marrow transplantation any more.

Two months later, he had intermittent fever and chest and abdominal pain with progressive enlargement of the spleen and hypereosinophilia. Electrocardiography and gastroscopy showed no positive findings. However, CT scanning demonstrated increased splenic volume and multiple enlarged lymph nodes in the chest and abdomen. Abdominal ultrasound revealed mesenteric lymphadenitis (appendicitis and intussusception were excluded). Previous studies have indicated that ALPS patients with exon 7–9 mutations of the *FAS* gene are prone to lymphoma [3]. Therefore, lymph node biopsy was performed. Ten hours later after node biopsy, the patient had a convulsive episode lasting for about 1 min, which repeatedly occurred 5 times. Anesthesiologists and neurologists concluded that this convulsive episode was not related to anesthesia-related complications. Subsequently, brain CT revealed multiple abnormal densities in his brain, and pathological examinations suggested *C. neoformans* infection (Fig. 1), which was further confirmed by cerebrospinal fluid smear and blood culture. Amphotericin B liposome and symptomatic supportive treatment were then administered for 1 week. Subsequently, the parent stopped treatment, and he died of severe *C. neoformans* infection after 2 weeks.

ALPS is an inherited disease of abnormal lymphocyte survival due to the failure of induction of apoptosis [3]. ALPS is associated with specific gene mutations [4] and mostly manifests between the ages of 6 months and 18 years, and a significantly higher incidence of disease-related symptoms has been observed in male than in female patients [3]. The patients' mother had chronic, nonmalignant, and noninfectious lymphadenopathy and was susceptible to infection, and she had a history of pulmonary tuberculosis with ALPS-like symptoms. Combined with his symptoms and family medical history, diagnosis of ALPS was considered and confirmed. Most patients experience the following phases: early-onset, chronic (> 6 months), nonmalignant lymphoproliferation, autoimmune manifestations, hypergammaglobulinemia, and susceptibility to lymphoma; however, hypogammaglobulinemia is rare in these patients [5]. Increased count of circulating TCR$\alpha\beta^{+}$ DNT cells is a diagnostic hallmark in ALPS patients. Inherited mutations have been observed in many patients. It has been demonstrated that patients with *FAS* gene mutation affecting the intracellular portion of the FAS protein have an increased risk of B cell lymphoma, and the median age of onset is 18 years [3]. However, pathological results indicated that the present patient did not have lymphoma probably because of his young age.

Most ALPS patients have elevated IgG levels. The present patient had persistent hypogammaglobulinemia and was required with Ig transfusion, and the findings are in line with those in a previous study [5], which revealed that 5 out of 66 patients with ALPS had low IgG levels and were susceptible

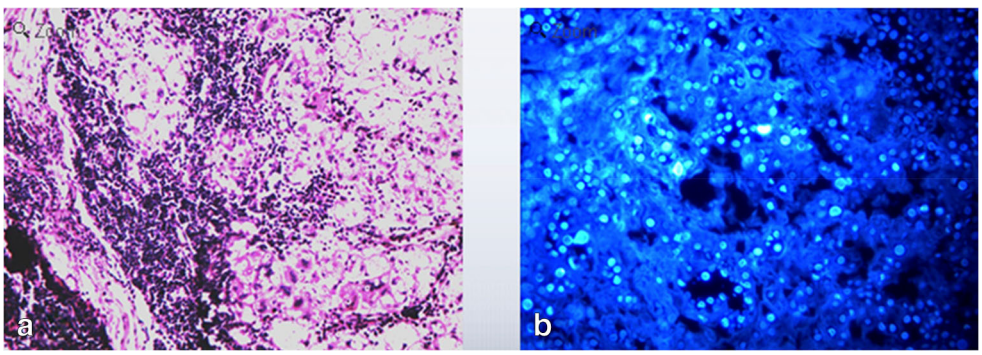


**Fig. 1** Pathological examinations indicate *C. neoformans* infection. **a** PAS (+); **b** Fungal immunofluorescence (+). Abbreviations: PAS, periodic acid Schiff

to infection. The present patient was diagnosed with hypereosinophilia secondary to ALPS. Kim [2] showed that ALPS patients with eosinophilia had a significantly higher risk of death due to infectious complications. In this case, pathological results and cerebrospinal fluid culture confirmed *C. neoformans* infection, which might have resulted from this immunodeficiency syndrome.

To our knowledge, no case of co-existence of ALPS and *neoformans* infection has been reported. ALPS should be considered a differential diagnosis in children with lymphadenopathy, splenomegaly, and unexplained cytopenia, particularly in those with immunodeficiency.

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## Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflict of interest.

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