

CASE REPORT

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An Unexpected Infection in Loss-of-Function Mutations in *STAT3*: Malignant Alveolar Echinococcosis in Liver

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ABSTRACT

Loss-of-function (LOF) mutations in signal transducer and activator of transcription 3 (*STAT3*) gene causes autosomal dominant hyper immunoglobulin E syndrome (AD-HIES or Job's Syndrome), a rare and complex primary immunodeficiency (PID) syndrome characterized by increased levels of IgE (>2000 IU/mL), eosinophilia, recurrent staphylococcal skin abscesses, eczema, recurrent pneumonia, skeletal and connective tissue abnormalities. Although bacterial and fungal infections are common in AD-HIES, susceptibility to parasitic infections has not been reported. *Alveolar echinococcosis* (AE), a zoonosis caused by the growth of the *Echinococcus multilocularis* (EM) metacestode, mimics slow-growing liver cancer. The mortality rate of AE is very high when it is diagnosed late or under-treated. Here, we report a 14-year-old boy with AE infections of the liver and the lung resulting in liver failure and diagnosed as *STAT3*-LOF. To our knowledge, the association between these two conditions has not been reported in the literature before.

Keywords: Alveolar echinococcosis; Autosomal dominant hyper immunoglobulin E syndrome

INTRODUCTION

Autosomal dominant hyper immunoglobulin E syndrome (AD-HIES) is a rare primary immunodeficiency (PID) disorder characterized by significantly elevated immunoglobulin E (IgE),

eosinophilia, chronic eczema, skin abscesses, recurrent infections, and mucocutaneous candidiasis. Accompanying findings are notable abnormalities of the connective tissue and the skeleton, retained primary teeth, joint hyperextensibility, bone fractures following minimal trauma as well as vascular and central nervous system abnormalities.¹⁻⁵ Loss-of-function (LOF) mutations in signal transducer and activator of transcription 3 (*STAT3*) gene cause AD-HIES. *STAT3* is a transcription factor activated downstream of numerous cytokine signals including interleukin (IL)-6,

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interferon (IFN)- α , and IL-10, among others. Decreased memory T and B cells, T helper (Th)-17 cells with IL-17, IFN- γ , and tumor necrosis factor (TNF)- α production and defective response to multiple cytokines such as IL-6, IL-21, and IL-22 are other important features in AD-HIES patients.⁶⁻¹¹ Regulation of the pro-inflammatory (IL-6) and anti-inflammatory (IL-10) cytokine signaling system is impaired.²

Recurrent pulmonary infections manifest in early childhood and are predominantly due to infections with *S.aureus*, *S. pneumoniae*, *Hemophilus species*, *Pseudomonas*, and *nontuberculous mycobacteria*. Aberrant healing following pneumonia frequently leads to bronchiectasis and pneumatoceles. Patients with pneumatoceles are more susceptible to fungal infections.¹²

Reactivation of viral infections, especially of varicella-zoster virus (VZV) and Epstein-Barr virus (EBV) infections, has been observed. Among all these infection agents, parasites have not been described yet.¹²

Alveolar echinococcosis (AE) is a rare but potentially life-threatening parasitic disease caused by the larval stages of the *Echinococcus Multilocularis* (EM). AE is endemic to North America, Alaska, Central Europe, and Turkey.^{13,14} The alveolar cyst of EM grows very slowly and develops multivesicular infiltrating structures like malignant neoplasm consisting of numerous small vesicles embedded in the stroma of the connective tissue and it infiltrates neighboring organs. The most commonly affected organ is the liver, followed by the lung, spleen, and central nervous system. Vascular beds of the liver and the biliary tract are involved in the majority of the cases.¹⁴ The first symptom of the disease may be abdominal pain or cholestatic jaundice. Cholangitis, portal hypertension, Budd-Chiari syndrome, and malignant liver tumor have been reported.¹³ If the patients are untreated after the diagnosis, the 10-year mortality rate is 95%. The most effective treatment is radical hepatic resection.^{14,15} The diagnosis is based on radiologic findings, serum specific EM antibodies, and histopathological examination. Laboratory findings are leukopenia, thrombocytopenia, mild eosinophilia, and elevated transaminases. Elevated IgE levels are present in more than 50 percent of the cases.¹³

The growth potential of the tumor-like EM metacestode is directly dependent upon the nature of the periparasitic adaptive host immune-mediated

processes. The relationship between the host and the parasite is interactive and the outcome of infection depends on the balance achieved by the combination of different variables associated with the host immunity and the parasite avoidance strategies.¹⁶⁻¹⁹

In this report, we present a 14-year-old boy with AD-HIES with malignant AE of the liver and the lung.

CASE REPORT

Approval of the Ankara University School of Medicine Human Research Ethics Board was obtained for this study (Decision no: İ 10-638-20). The patient and his father in the study signed informed consent forms. A 14-year-old boy from the East Anatolian region was admitted to a pediatric surgery clinic with abdominal pain and distension. He was referred to our department for a suspected PID. In his medical history, we learned that he had recurrent pneumonia and otitis, asthma furuncles, and eczema, since the age of 1 year. He had chronic diarrhea that started at the age of 1 and continued until the age of 10. He has been hospitalized 20 times, mostly due to pneumonia. He had growth retardation, possibly due to chronic diarrhea, recurrent infections, and hospitalizations. His deciduous teeth had fallen late. He lived in a rural area, but the family members were not farmers. There is no consanguinity between his parents and no family history of immunodeficiency. He initially applied to a chest disease and thoracic surgery hospital for cough and dyspnea lasting for 2 months at the age of 8 years. Laboratory results showed hemoglobin of 12.8 g/dL, white blood cell count of 14000/mm³, neutrophil count of 6700/mm³, lymphocyte count of 5800/mm³, eosinophil count of 1400/mm³, and platelet count of 412000/mm³. IgG: 1720 mg/dL (842-1940 mg/dL), IgA: 108 mg/dL (62-390 mg/dL), IgM:433 mg/dL (54-392 mg/dL), total IgE: 216 Ku/L (2-161 Ku/L). Nitro blue tetrazolium (NBT) test, peripheral lymphocyte was considered as normal. No parasite was found in the microscopic stool examination.

Thorax CT revealed multiple nodules with cavitation bilaterally and ground glass areas in the mediobasal part of the left lower lobe (detailed in Appendix). The abdominal US showed that the liver slightly larger than normal. Three smooth-contoured mass lesions were observed, the largest of which was 57×37 mm on liver dome localized sub-diaphragmatically, the others were 4, 5, and 2, 5 cm in

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size. They all were heterogeneous and hyperechoic lesions with a hypoechoic halo. Right thoracotomy, cystotomy plus capitonnage, and frenotomy operations were performed to remove cysts. Macroscopic pathology examination revealed that the cyst content and membrane were irregular and fragile. Almost all of the tissue samples are necrotic. Microscopically, micro abscess foci or granuloma structures were surrounding the membranous eosinophilic stained material in intact areas. It was observed that the membrane pieces with partly selected laminations were stained with periodic acid-Schiff (PAS) stain, granuloma structures are thought to develop primarily against the perforated cyst. Histopathological and histochemical data are supported by perforated AE (Figure 1A, 1B, 1C). No surgical interventions were performed for liver lesions

at that time. Albendazole was started. Encysted and free hydropneumothorax was detected on the right in the thoracic CT performed 1 month later. Also, cystic lesions with hair-fluid levels were observed in the right lower lobe (superior and basal segments), and the left lower lobe basal segment. CT findings supported that both cystic structures common in the lungs couldn't be removed totally by surgery and were perforated via the operation. For 2 years, the patient used albendazole. On the follow-up, he did not apply to the hospital for the next 3 years and use albendazole treatment. Later, he applied to our pediatric surgery department with complaints of increasing abdominal pain and distension for the last 2 months at the age of 14. On physical examination body weight was 34 kg (<3 percentile), height was 139 cm (<3 percentile).

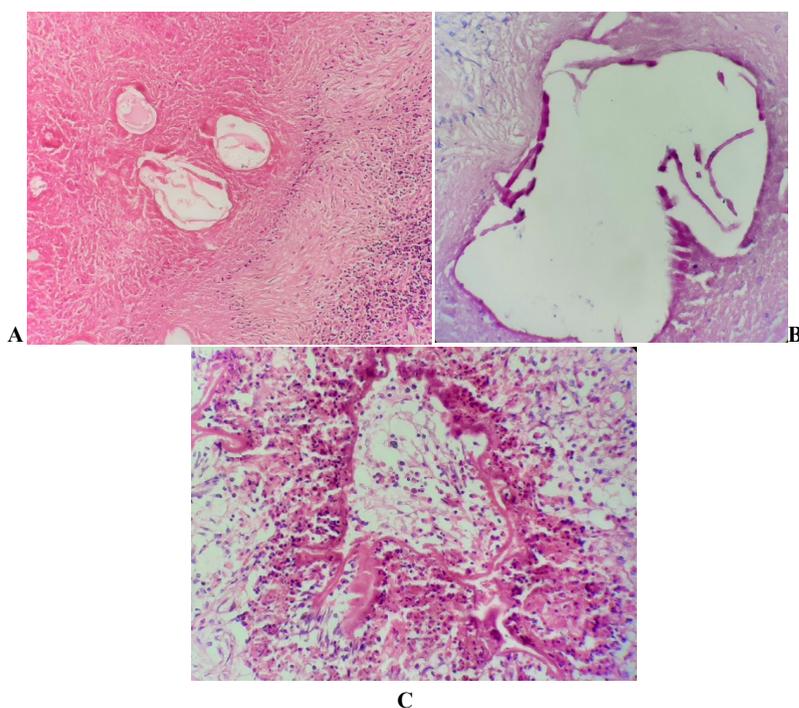


Figure 1. Microscopic pathological examination of the lung lesion caused by alveolar echinococcosis (AE). A. Histological examination of pulmonary cystic lesions shows the cuticle membrane in necrotic material hematoxylin-eosin (HE×200), B. Periodic Acid-Schiff (PAS)-positive-cuticle membrane (PAS×400), C. Cuticle membrane is surrounded by foreign body giant cells (HE×400). The macroscopic pathologic examination revealed that the cyst content was irregular and fragile in the consistency of 2×1×0.8 cm. The cyst wall thickness is 0.4cm. The cyst membrane part is 2.5×2×1 cm, fragile, and irregular consistency. Almost all of the tissue samples are necrotic. Microscopically, microabscess foci or granuloma structures are surrounding the membranous eosinophilic stained material in intact areas. It was observed that the membrane pieces with partly selected laminations were stained with PAS staining, Bacillus was not seen in the Erlich-Ziehl-Neelsen (EZN) staining. Granuloma structures are thought to develop primarily against the perforated cyst. Histopathological and histochemical data were evaluated as compatible with perforated AE.



Figure 2. The patient's general appearance. **A.** Coarse face, protruding forehead, hypertelorism, prognathism, wide nose, rhagades in mouth, **B.** Abdominal distension

He had massive hepatomegaly (liver palpable as 12cm under the costal arch), eczematous dermatitis, hypopigmented macules, and scars on his skin. Coarse face, protruding forehead, hypertelorism, prognathism, wide nose, high-arched palate (Figure 1A), joint hyperextensibility, thoracolumbar scoliosis, and abdominal distension were detected. (Figure 2A, 2B).

Abdominal CT revealed a mass (18×11.5×11 cm) in the infiltrative view extending to segment 8, which almost completely covered the left lobe of the liver, and

the calcification foci did not show significant contrast enhancement. Necrotic-cystic areas were observed in the central section of the lesion and near the diaphragmatic face. There was a separated lesion in the caudate and right lobe. The left side of the portal vein is not selected due to the mass compression (Figure 3). A thorax CT scan showed multiple lesions; the majority of these were cavitory and with consolidation in both lungs (Figure 4).

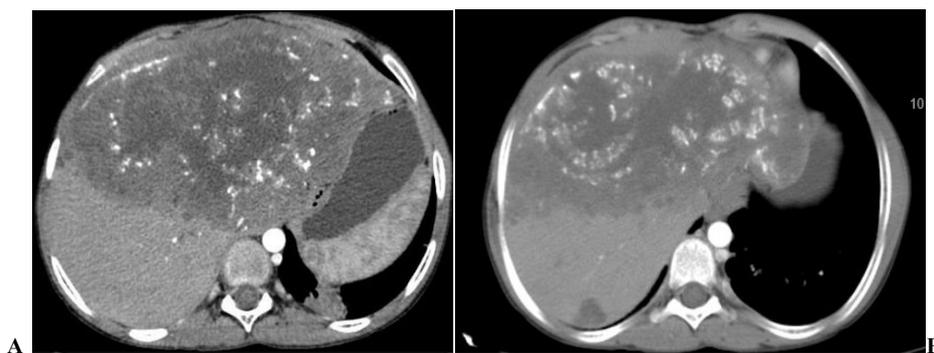


Figure 3. Abdominal CT signs of liver alveolar echinococcosis (AE) at first administration to our hospital. **A.** A mass lesion (18×11.5×11 cm) was observed in the infiltrative view extending to segment 8, which almost completely covers the left lobe of the liver and the calcification foci did not show significant contrast enhancement. Necrotic-cystic areas were observed in the central section of the lesion and near the diaphragmatic face. The caudate lobe is also involved. **B.** Separate lesions, some of which are multi-cystic, reaching 1.7 cm, were observed in the right lobe. The left side of the portal vein is not selected separately within the mass. The left hepatic artery is thin within the lesion. Portal vein right branch, main portal vein, splenic vein, and superior mesenteric vein are open. Splenomegaly was observed.

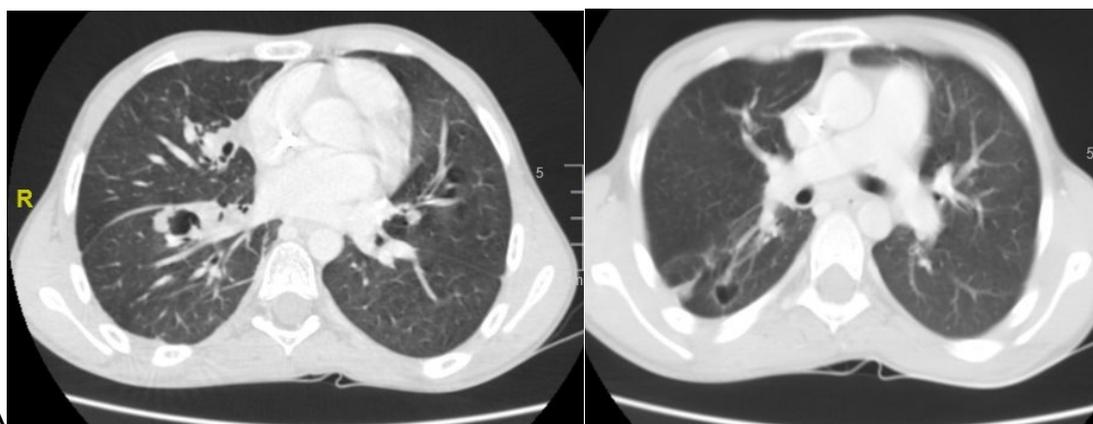


Figure 4. Thorax CT signs of alveolar echinococcosis (AE). **A.** Multiple nodules with cavitations in both lungs bilaterally, 27 mm in diameter, **B.** In the lower lobe of the upper, and right lung, ground-glass areas in the lower lobe of the mediobasal part of and left lower lobe focal areas of the left lung.

Laboratory findings were as follows: eosinophil count of $1800/\text{mm}^3$, serum IgG: 1360 mg/dL (876-2197 mg/dL), serum IgA: 75 mg/Dl (96-465 mg/dL), serum IgM: 499 mg/Dl (83-282), total IgE: 29.285 kU/L (2-629 kU/L). Total IgE level was examined 4 more times, and all of them were found to be over 5000 Ku/L. The prick test was negative. The indirect hemagglutination test for *echinococcosis* was positive (1/80 titers). Lymphocyte subsets, lymphocyte activation response to phytohemagglutinin, and anti-CD3 and neutrophil oxidative burst tests were normal.

The National Institutes of Health (NIH) scoring system for AD-HIES was used and revealed a total score of 42. A known heterozygous mutation at exon 21 (1970A→G, Y657C.) was detected on the *STAT3* gene. The mutation has been reported previously.²⁰

Albendazole, amphotericin B, IFN- γ , and IVIG therapy were initiated. Extended left hepatectomy, including segments of 2, 3, 4, 5, 8, diaphragmatic resection, vena cava inferior construction with extracorporeal veno-venous bypass between femoral vein and right atrium was performed for the lesion in the liver (Figure 5). Extended hepatectomy material revealed a solitary, mostly necrotic lesion in $13 \times 7 \times 4$ cm dimensions with spongy solidifications and comprising conglomerates of tiny cysts. Microscopically geographic necrosis and numerous irregular small cysts within the necrotic area were detected. Cystic structures showed acellular parasitic material as a thin laminated layer without prominent striation (Figure 6).

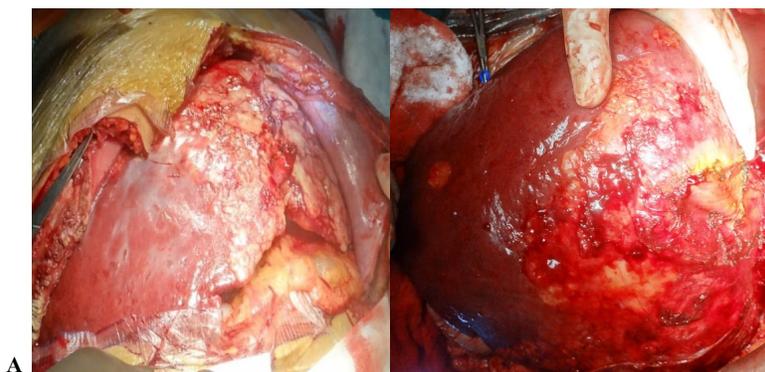


Figure 5 A. Macroscopic image of the liver. **B.** Extended left hepatectomy, including segments of 2, 3, 4, 5, 8, diaphragmatic resection, vena cava inferior reconstruction with extracorporeal veno-venous bypass between femoral vein and right atrium was performed for the lesion in the liver

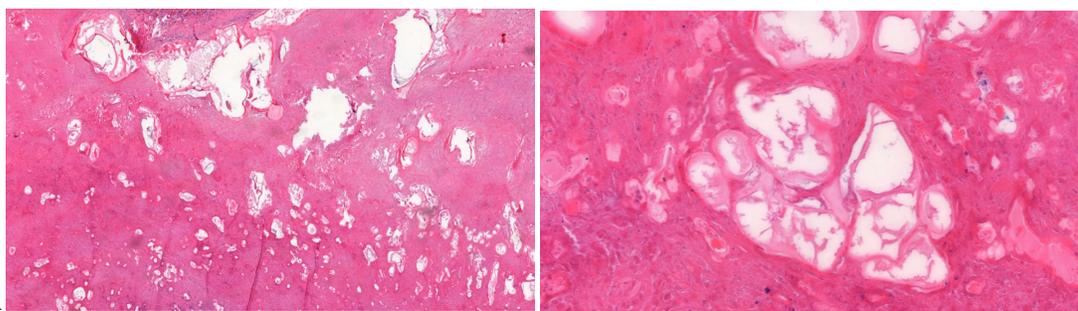


Figure 6. Microscopic pathological examination of the liver lesion caused by alveolar echinococcosis (AE). **A.** Multicystic lesion in the liver with lots of small, polymorphous, and partly conglomerated cysts within the necrotic and fibrotic stroma (H&E, $\times 4.3$). **B.** Cysts having a thin laminated layer of the parasitic material (H&E, $\times 40.3$)

One-year after liver operation abdominal US showed the right lobe vertical length was measured as 190 mm. The lesions were 17×10 mm in the right lobe medial superior section, 30×15 mm in the lateral middle section, 30×25 mm in the lateral inferior

section, including cystic areas and calcifications.

In addition, three anechoic cystic formations of 12 mm, 8 mm, and 4 mm diameters attracted attention. Intrahepatic and extrahepatic bile ducts are of normal width. He continued to albendazole, IFN- γ , and IVIG.

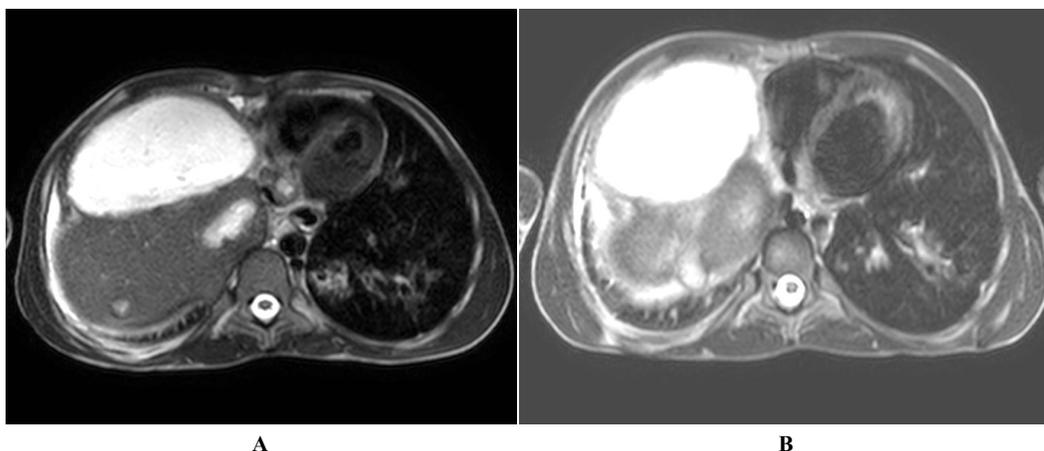


Figure 7. Abdominal MR scan signs 2 years after the liver operation. **A.** Numerous intraparenchymal cystic lesions were observed in the right lobe of the liver. Of these, segment 6 localized lesion is observed hypointense in T2 (It is not possible to specifically differentiate calcification or fibrosis). A cystic lesion measuring $11.2 \times 9.6 \times 9$ cm in size extending from the liver dome level into the thorax and pressing the right atrium was observed. The cyst is near the portal vein in the posterior and it is indented. **B.** In addition, a cystic lesion measuring $13 \times 10 \times 9.5$ cm in size with a lobule contour extending from the right lobe posterior inferior to the extra-parenchymal area was observed. Comparing to the previous examination of the patient a significant increase in lesion size was noticed. The spleen size was measured 14.5 cm and increased

He had abdominal pain and cough in the following two years and, icterus was detected in the last control. An abdominal MR scan documented numerous intraparenchymal cystic lesions in the right lobe of the liver. Lesion on segment 6 was hypointense in the T2

sequence (It is not possible to specifically differentiate calcification or fibrosis). A cystic lesion in $110 \times 90 \times 90$ mm size extending from the liver dome into thorax compressed the right atrium and portal vein. In addition, a cystic lesion in $13 \times 10 \times 9.5$ cm size

extending from the right lobe posterior inferior to the extra-parenchymal area was observed. Comparing to the previous examinations, there were significant increases in lesions' sizes (Figure 7). Liver transplantation was planned, but a donor could not be found. One month after the last control, the patient died due to the liver and respiratory failure in his town.

DISCUSSION

Some parasitic infections are more common in some PIDs; for example, giardiasis is specifically observed in IgA deficiency, common variable immunodeficiency (CVID), and X-linked agammaglobulinemia (XLA) while cryptosporidium is observed in combined immune deficiencies such as DOCK8 deficiency, CD40, and CD40L deficiencies, and acquired immune deficiencies such as acquired immunodeficiency syndrome (AIDS). *Toxoplasma gondii*, can affect a patient with hyper-IgM syndrome (HIGM) syndrome or CVID. Also, it is reported that IFGR1 mutation causes severe malaria infections.¹⁹

AD-HIES (STAT3 LOF mutation) is characterized by various bacterial and fungal infections but susceptibility to parasitic infections has not been previously reported, to our knowledge. Herein, we report an AD-HIES patient with uncontrolled malignant AE infection despite surgery, IFN- γ , and albendazole treatment.

The AE disease spectrum is dependent on the genetic background of the host as well as on Th1-related immunity. In immunocompetent animals, the early stage of AE infection was marked by a mixed immune response of Th1/Th2, distinguished by the concomitant involvement of IFN- γ and IL-4 and their associated cytokines. At the late stage of AE, the profile extended to a combined tolerogenic response including Foxp3, IL-10, and transforming growth factor-beta (TGF- β) as key components.¹⁶⁻¹⁹

In the course of an infection, clinical and biological signs of inflammation are paradoxically weak in patients with *STAT3* mutation.¹⁻⁵ *STAT3* affects the development of CD4+ and CD8+, central memory T cell, Th-17 cells, T follicular helper (TFH) cells, natural killer T (NKT) cells, and memory B cells.^{5,7,13-17} Myeloid cell development is essentially normal in AD-HIES but neutrophil chemotaxis is abnormal due to decreased production of IFN- γ and decreased TNF- α , IL-6, and impaired IL-10 responses.⁶⁻¹¹

We did not know exactly how the STAT3-LOF aggravated the severity of malignant AE infection in our patient. However, the disruption of Th1 and Th2 related cytokines and IL-10 response to the early and late periods of the immune response against AE may have contributed to the severe course of the infection. Functional analyses could not be performing at that time. Thus, we have no conclusive evidence of the relationship between AD-HIES and AE.

The experimental mouse model studies revealed that immune modulation with cytokines, such as IFN- α , or with different antigens could be an option for treatment of AE.²¹ We intended to increase the release of Th1-related cytokines by IFN- γ treatment but we failed. AE is one of the most lethal chronic parasitosis in the world due to high death rates in untreated patients. The initial asymptomatic incubation period of 5 to 15 years and subsequent chronic incubation are typical for AE. The larvae of EM proliferate like a slow-growing liver tumor.¹³⁻¹⁵ The main treatment option is surgery for suitable lesions. Therefore, all AE patients should be referred to a center where expertise in extensive liver surgery, interventional radiology and endoscopy, radiological and serological diagnosis, and medical treatment is available. According to the latest consensus of the World Health Organization (WHO) a radical resection of tumors whenever clinically possible, accompanied by a 2-year adjuvant procedure with benzimidazole is recommended to prevent recurrence of diseases.²² However, surgery has complications and recurrence risk. Percutaneous and endoscopic intervention should be preferred.

Cellular immunity deficiency (immune suppression) is accompanied by an increase in the susceptibility to EM in animals by trial.²³ It has been reported that patients with liver transplantation due to severe AE and still receiving immune suppressive therapy had increased susceptibility to AE, rapid metastasis to organs such as lungs, brain, spleen, and even earlier re-invasion in the liver. Also, intensive immune-suppressive treatment use to protect against rejection (anti-CD3 monoclonal antibody, triple immune suppression including cyclosporine A or tacrolimus, azathioprine, and corticosteroids treatment plus anti-lymphocyte globulin) led to more recurrence and severe course.²⁴ During the last 20 years an increase in AE had been reported in patients with secondary immune deficiencies (malignant hematological diseases, solid tumors, patients receiving

immune-suppressive drugs due to chronic inflammatory/autoimmune diseases, those who had undergone bone marrow or solid organ transplantations).^{25,26, 27}

Pulmonary cystotomy was performed on our patient although liver surgery had to be performed initially. It led to disease progression. In addition, 3 years interval of the treatment also contributed to progression. During the follow-up in our hospital, even if surgery was performed for liver lesions and medical treatment continued, the development of end-stage organ damage could not be avoided.

In conclusion, the association of AD-HIES with malignant alveolar echinococcus is reported for the first time. In the case of atypical or severe course in patients with parasitic infections, they should be evaluated for underlying PIDs.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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