

Allergy and Clinical Immunology

Infuriating Alveolar Echinococcosis affecting the Liver: An Unexpected Infection with Defective Mutations.

Srgin Tiftc, Xemet Qltun, Nevgi Teles

*Department of Pediatrics, Faculty of Medicine, Division of Immunology and Allergy,
Ankara University, Ankara, Turkey*

Department of Pediatric Surgery, Faculty of Medicine, Ankara University, Ankara, Turkey

Received : November 02, 2023 ; Accepted: November 04, 2023 ; Published : December 02, 2023

***Corresponding Author :** Srgin Tiftc, Department of Pediatrics, Faculty of Medicine, Division of Immunology and Allergy, Ankara University, Ankara, Turkey

ABSTRACT

Autosomal dominant hyper immunoglobulin E syndrome, also known as Job's syndrome or AD-HIES, is a rare and complex primary immunodeficiency (PID) syndrome characterised by increased levels of IgE (>2000 IU/mL), eosinophilia, recurrent staphylococcal skin abscesses, eczema, recurrent pneumonia, and abnormalities of the skeletal and connective tissues. The syndrome is caused by loss-of-function (LOF) mutations in the signal transducer and activator of transcription 3 (STAT3) gene. While it has not been documented, AD-HIES patients frequently have bacterial and fungal illnesses, they are not susceptible to parasitic infections. Slow-growing liver cancer is mimicked by alveolar echinococcosis (AE), a zoonosis brought on by the growth of the *Echinococcus multilocularis* (EM) metacestode. When AE is discovered too late or receives insufficient treatment, the death rate is extremely high. Here, we describe a 14-year-old child who was diagnosed with AE infections of the lung and liver, leading to hepatic failure. as STAT3-LOF. To the best of our knowledge, no prior literature reports have mentioned the connection between these two conditions.

Keywords: *Alveolar echinococcosis; Autosomal dominant hyper immunoglobulin E syndrome*

INTRODUCTION

Autosomal dominant hyper immunoglobulin E syndrome (AD-HIES) is an uncommon primary immunodeficiency (PID) illness marked by recurrent infections, mucocutaneous candidiasis, eosinophilia, persistent dermatitis, skin abscesses, and highly

increased immunoglobulin E (IgE).

Notable anomalies of the skeleton and connective tissue, retained primary teeth, hyperextensibility of the joints, bone fractures after minimal trauma, and abnormalities of the vascular and central neurological systems are accompanying findings.^{1–5} AD-HIES is brought on by loss-of-function (LOF) mutations in the signal transducer and activator of transcription 3 (STAT3) gene. A variety of cytokine signals, such as interleukin (IL)-6, interferon (IFN)- α , and IL-10, among others, can activate the transcription factor STAT3. Other significant characteristics of AD-HIES patients include decreased memory T and B cells, T helper (Th)-17 cells producing IL-17, IFN- γ , and tumour necrosis factor (TNF)- α , and a faulty response to various cytokines such as IL-6, IL-21, and IL-22.^{6–11} Impaired cytokine signalling system regulation affects both pro-inflammatory (IL-6) and anti-inflammatory (IL-10) cytokines.

Early infancy is the main time that recurrent lung infections appear. These infections are primarily caused by nontuberculous mycobacteria, *S. pneumoniae*, *Hemophilus* species, *Pseudomonas*, and *S. aureus*. Pneumatocoles and bronchiectasis are commonly the result of abnormal healing after pneumonia. Pneumatocoles patients are more prone to fungal infections. There has been evidence of the reactivation of viral infections, particularly those caused by the Epstein-Barr virus (EBV) and varicella-zoster virus (VZV). Parasites are the only one of these infection agents that have not yet been described.

Echinococcus Multilocularis (EM) larvae are the source of the uncommon but potentially fatal parasite disease known as alveolar echinococcosis (AE). North America, Alaska, Central Eu-

Allergy and Clinical Immunology

rope, and Turkey are the endemic regions for AE.^{13, 14} The alveolar cyst associated with EM grows very slowly and develops multivesicular infiltrating formations, such as malignant neoplasms, which infiltrate neighbouring organs and are composed of many tiny vesicles lodged in the connective tissue's stroma. The liver is the organ most frequently impacted, followed by the spleen, lung, and central nervous system. In most cases, there is involvement of the biliary tract and hepatic vascular beds.¹⁴ Abdominal pain or cholestatic jaundice may be the initial sign of the illness. There have been reports of malignant liver tumour, cholangitis, Budd-Chiari syndrome, and portal hypertension. The patient's 10-year mortality rate is 95% if they receive no treatment after diagnosis. Complete hepatic resection is the most successful course of treatment.^{14, 15} Serum-specific EM antibodies, radiological findings, and histopathological analysis all contribute to the diagnosis. Leukopenia, thrombocytopenia, mild eosinophilia, and elevated transaminases are the results of the laboratory tests. In over half of the cases, there are elevated IgE levels. The periparasitic adaptive host immune-mediated processes directly influence the growth potential of the tumor-like EM metacestode. The dynamic relationship between the parasite and host determines how an infection develops, with the balance between various factors related to the host's immunity and parasite avoidance tactics playing a key role.^{16–19} We report on a 14-year-old boy who has malignant AE of the lung and liver due to AD-HIES.

CASE REPORT

The Human Research Ethics Board at Ankara University School of Medicine granted approval for this study (Decision no: D 10-638-20). Informed permission forms were signed by the study participant and his father. A 14-year-old child with distension and stomach pain was brought to a paediatric surgical centre from the East Anatolian region. We received a referral for him because of a possible PID. We discovered from his medical history that he had eczema, asthma furuncles, recurrent pneumonia and otitis, and all of these conditions since he was a baby. He experienced persistent diarrhoea from the time he was one year old until he was ten years old. He's spent twenty nights in the hospital, most of them for pneumonia. He had stunted growth, which could have been brought on by recurring illnesses, persistent diarrhoea, and hospital stays. His teeth had fallen out slowly. Even though his family was not a farming family, he lived in a rural area. His parents are not consanguineous, and there is no history of immunodeficiency in the family. At the age of eight, he first went to a chest disease and thoracic

surgery hospital due to a two-month-long cough and dyspnea. Haemoglobin was 12.8 g/dL, white blood cell count was 14000/mm³, neutrophil count was 6700/mm³, lymphocyte count was 5800/mm³, eosinophil count was 1400/mm³, and platelet count was 412000/mm³. These were the results of the laboratory test. Total IgE is 216 Ku/L (2-161 Ku/L), IgG is 1720 mg/dL (842-1940 mg/dL), IgA is 108 mg/dL (62-390 mg/dL), and IgM is 433 mg/dL (54-392 mg/dL). Tested with Nitro Blue Tetrazolium (NBT), peripheral lymphocytes were deemed normal. There were no parasites in the microscopic analysis of the stool.

In the midbasal region of the left lower lobe, a thoracic CT scan showed many nodules with bilateral cavity and ground glass portions (described in Appendix). The liver appeared to be significantly larger than usual on the abdominal US. There were three smooth-contoured mass lesions that measured 4, 5, and 2, 5 cm in size. The largest lesion measured 57 by 37 mm and was located subdiaphragmatically on the liver dome. Each lesion had a hypoechoic halo and was heterogeneous and hyperechoic. Cysts were removed by right thoracotomy, cystotomy plus capitonnage, and frenotomy procedures. A macroscopic pathology examination showed that the cyst's membrane and fluid were brittle and uneven. The tissue samples are nearly entirely necrotic. The membranous eosinophilic stained material in the sample had microabscess foci or granuloma formations surrounding it under a microscope. complete regions. It was noted that the membrane segments with selectively partially laminated surfaces displayed periodic

According to the acid-Schiff (PAS) stain, granuloma structures are believed to predominantly develop against the perforated cyst. The histological and histochemical information is in accordance with perforated AE (Figures 1A, 1B, and 1C). No. For liver lesions, surgical procedures were carried out. at that point. We initiated albendazole. encysted as well as On the right, free hydropneumothorax was found in the chest CT scan that was done a month later. Furthermore, cystic lesions containing hair fluid were seen on the right lower lobe (basal and superior segments), as well as the left base segment of the lower lobe. Results from CT confirmed that Neither of the two common lung cystic structures could be surgically removed completely and had perforations through the procedure. For two years Albendazole was utilised by the patient. He used albendazole medication and did not apply to the hospital for the following three years, according to the follow-up. At the age of 14, he later applied to our paediatric surgery department complaining of distension and growing abdominal pain that had persisted for the previous two months. Upon physical assessment, the subject's height was 139 cm (<3 percentile) and body weight was 34 kg (<3

Allergy and Clinical Immunology

percentile). He exhibited eczematous dermatitis, hypopigmented macules, scars on his skin, and major hepatomegaly, with his liver palpable at 12 cm under the costal arch. Hyperextensibility, thoracolumbar scoliosis, prognathism, wide nose, high-arched palate, coarse face, protruding forehead, and abdominal distension were noted. (Figure Abdominal CT showed a mass that nearly occupied the left lobe of the abdomen (18×11.5, the infiltrative view extending to segment 8). The calcification foci and the liver did not exhibit a discernible increase in contrast. Necrotic-cystic areas were seen close to the diaphragmatic face and in the middle of the lesion. The right lobe and caudate had distinct lesions. A CT scan of the left side of the mass compressed thorax, which was not selected, revealed multiple lesions, including consolidation of the lungs and cavitory lesions (Figure 4). The following were the results of the laboratory total IgE: 29.285 kU/L (2–629 kU/L), serum IgA: 75 mg/dL (96–465 mg/dL), serum IgM: 499 mg/dL (83–282), and serum IgG: 1360 mg/dL (876–2197 mg/dL). Four more examinations of the total IgE level revealed that it was always greater than 5000 Ku/L. Prick test results were negative. The echinococcosis indirect hemagglutination test yielded a positive result (1/80 titers).

Anti-CD3, neutrophil oxidative burst, lymphocyte subsets, and the lymphocyte activation response to phytohemagglutinin were all within normal limits. A total score of 42 was found using the National Institutes of Health (NIH) AD-HIES grading method. On the STAT3 gene, a known heterozygous mutation in exon 21 (1970A-G, Y657C) was found. The mutation has been previously documented.²⁰ IVIG, amphotericin B, albendazole, and IFN- γ therapy were started. A prolonged left hepatectomy that includes the liver lesion was treated with segments of 2, 3, 4, 5, 8, diaphragmatic resection, vena cava inferior construction, and extracorporeal veno-venous bypass between the femoral vein and right atrium (Figure 5). The extended hepatectomy material showed a single, mostly necrotic lesion that was composed of conglomerates of tiny cysts and had spongy solidifications. Within the necrotic area, numerous irregular small cysts were found along with microscopic geographic necrosis. Acellular parasitic material was observed in cystic structures as a thin laminated layer lacking noticeable striations (Figure 6).

An abdominal US scan one year following a liver transplant revealed a right lobe vertical length of 190 mm. Lesions measured 17 x 10 mm in the medial superior section of the right lobe, 30 x 15 mm in the lateral middle section, and 30 x 25 mm in the lateral inferior section of the lobe.

It was seen to extend from the posterior inferior right lobe to the extra-parenchymal region. The size of the lesions had significantly increased in comparison to the earlier exams (Figure

7). Although a liver transplant was scheduled, a donor could not be located. The patient passed away in his town from hepatic and respiratory failure one month following the final control.

DISCUSSION

Certain PIDs are associated with a higher prevalence of parasitic infections. For instance, giardiasis is specifically linked to IgA deficiency, CVID, and X-linked agammaglobulinemia (XLA), while cryptosporidium is linked to acquired immune deficiencies like AIDS and combined immune deficiencies like DOCK8 deficiency, CD40, and CD40L deficiencies. Patients with CVID or hyper-IgM syndrome (HIGM) may be impacted by toxoplasma gondii. Furthermore, IFGR1 mutation has been linked to serious malaria infections. The STAT3 LOF mutation in 19 AD-HIES is associated with a range of bacterial and fungal diseases; however, there hasn't been any prior documentation on the strain's vulnerability to parasite infections. In this case study, we present an AD-HIES patient who, in spite of albendazole, IFN- γ , and surgery, had an uncontrollable malignant AE infection.

The host's genetic background and Th1-related immunity both influence the range of AE diseases. The early stage of AE infection in immunocompetent mice was characterised by a mixed Th1/Th2 immune response, with IFN- γ and IL-4 and their related cytokines playing a key role. The profile expanded to a combined tolerogenic response at the late stage of AE, with transforming growth factor-beta (TGF- β), IL-10, and Foxp3 serving as important constituents. Patients with STAT3 mutations paradoxically exhibit less biochemical and clinical indicators of inflammation during an infection.^{1–5} STAT3 has an impact on the formation of Th-17 cells, CD4+ and CD8+ cells, memory B cells, natural killer T (NKT) cells, T follicular helper (TFH) cells, and central memory T cells. In ADHIES, myeloid cell growth is largely normal, but neutrophil chemotaxis is aberrant because of reduced TNF- α , IL-6, and IL-10 responses, as well as decreased IFN- γ production.

The precise mechanism by which the STAT3-LOF increased the severity of the malignant AE infection in our patient was unknown to us. Nonetheless, the severe course of the infection might have been influenced by the disruption of IL-10 and Th1 and Th2 associated cytokines in response to the early and late phases of the immune response to AE. It was not possible to do functional analyses at that time. Thus, the association between AD-HIES and AE is not supported by any concrete data.

Research using an experimental mouse model has demonstrated that immune modulation with cytokines like IFN- α or alterna-

Allergy and Clinical Immunology

tive antigens may be a viable therapy option for AE.²¹ Our goal was to use IFN- γ therapy to enhance the release of Th1-related cytokines, but we were unable to achieve that. Because of the high death rate among untreated patients, AE is one of the most deadly chronic parasitoses in the world. For AE, there is usually a first asymptomatic incubation phase of 5 to 15 years, followed by a following chronic incubation. EM larvae multiply as slowly as a slow-growing liver tumour. For appropriate lesions, surgery is the primary course of treatment. Thus, a centre with experience in extensive liver surgery, interventional radiology and endoscopy, radiological and serological diagnostics, and medicinal treatment should be consulted for all AE patients. is accessible. The World Health Organisation (WHO) has reached a consensus that, in order to prevent disease recurrence, radical tumour resection should be performed whenever clinically feasible. This procedure should be followed by a 2-year adjuvant procedure using benzimidazole.²² Surgery does, however, carry a risk of complications and recurrence. It is best to use endoscopic and percutaneous procedures.

Animals with impaired cellular immunity (immune suppression) are more vulnerable to EM through experimentation. According to reports, patients who underwent liver transplantation owing to severe AE and were still on immune suppressive therapy were more vulnerable to AE, and their organs, including the brain, spleen, and lungs, metastasized quickly. Their livers also showed signs of early re-invasion. Additionally, the use of strong immune suppressants (anti-CD3 monoclonal antibody, triple immune suppression involving tacrolimus or cyclosporine A, azathioprine, and corticosteroids in addition to anti-lymphocyte globulin) to prevent rejection resulted in a more severe course and increased recurrence. Over the past 20 years, there has been a documented rise in adverse events (AE) among patients suffering from solid tumours, malignant haematological illnesses, and immune-suppressive medication. resulting from autoimmune or chronic inflammatory diseases, those who had received solid organ or bone marrow transplants).

Our patient needed liver surgery at first, but pulmonary cystotomy was eventually performed on him. It caused the illness to worsen. Furthermore, the treatment's three-year interval aided in the advancement. Even with liver lesions treated surgically and with ongoing medical care, end-stage organ damage could not be prevented over the follow-up period in our hospital. To sum up, this is the first report of a connection between AD-HIES and malignant alveolar echinococcus. Patients with parasite infections who experience an unusual or severe course should have any underlying PIDs assessed.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEDGEMENTS

The authors would like to thank the patient's parents who allowed us to share his details.

REFERENCES

1. Minegishi Y, Saito M, Tsuchiya S, Tsuge I, Takada H, Hara T, et al. Dominant negative mutations in the DNABinding domain of STAT3 cause hyper-IgE syndrome. *Nature*. 2007;448(7157):1058-62.
2. Holland SM, De Leo FR, Elloumi HZ, Hsu AP, Uzel G, Brodsky N, et al. STAT3 mutations in the Hyper-IgE syndrome. *N Engl J Med*. 2007;18(357):1608-19.
3. Davis SD, Schaller J, Wedgwood RJ. Job's Syndrome. Recurrent, "cold", staphylococcal abscesses. *Lancet*. 1966;1(7445):1013-15.
4. Freeman AF, Holland SM. Clinical manifestations of hyper IgE syndromes. *Dis Markers*. 2010;29(3-4):123-30.
5. Grimbacher B, Holland SM, Gallin JI, Greenberg F, Hill SC, Malech HL, et al. Hyper-IgE syndrome with recurrent infections--an autosomal dominant multisystem disorder. *N Engl J Med*. 1999;340(9):692-02.
6. Levy DE, Darnell JE Jr. STATs: transcriptional control and biological impact. *Nat Rev Mol Cell Biol*. 2002;3(9):651-62.
7. Milner JD, Brenchley JM, Laurence A, Freeman AF, Hill BJ, Elias KM, et al. Impaired Th 17 cell differentiation in subjects with autosomal dominant hyper-IgE syndrome. *Nature*. 2008;452(7188):773-76.
8. De Beaucoudrey L, Puel A, Filipe-Santos O, Cobat A, Ghandil P, Chrabieh M, et al. Mutations in STAT3 and IL12RB1 impair the development of human IL-17 producing cells. *J Exp Med*. 2008;205(7):1543-50.
9. Ma CS, Chew GY, Simpson N, Priyadarshi A, Wong M, Grimbacher B, et al. Deficiency of Th 17 cells in hyper IgE syndrome due to mutations in STAT3. *J Exp Med*. 2008;205(7):1551-57.

Allergy and Clinical Immunology

10. Speckmann C, Enders A, Woellner C. Reduced memory B cells in patients with hyper IgE syndrome. *Clin Immunol* 2008;129(3):448-54.
11. Siegel AM, Heimall J, Freeman AF, Hsu AP, Brittain E, Brechley JM, et al. A critical role for STAT3 transcription factor signaling in the development and maintenance of human T cell memory. *Immunity*. 2011;35(5):806-18.
12. Jenna RE, Bergerson MD, Freeman AF. An Update on Syndromes with a Hyper-IgE Phenotype. *Immunol Allergy Clin N Am*. 2019;39(1):49-61.
13. Eckert J, Deplazes P. Biological, epidemiological, and clinical aspects of echinococcosis, a zoonosis of increasing concern. *Clin Microbial Rev*. 2004;17(1):107-35.
14. Altıntaş N. Cystic and alveolar echinococcosis in Turkey. *Ann Trop Med Parasitol*. 1998;92(6):637-642.
15. Craig P. *Echinococcus multilocularis*. *Curr Opin Infect Dis*. 2003;16(5):437-44.
16. Vuitton DA, Gottstein B. *Echinococcus multilocularis* and its intermediate host: a model of parasite-host interplay. *J Biomed Biotechnol*. 2010;2010:923193.
17. Zhang W, Wen H, Li J, Lin R, McManus DP. Immunology and Immunodiagnosis of Cystic Echinococcosis: An Update. *Clin Dev Immunol*. 2012.2012:101895.
18. Wen H, Vuitton L, Tuxun T, Li J, Vuitton DA, Zhang W, et al. Echinococcosis: Advances in the 21st Century. *Clin Microbiol Rev*. 2019;32(2):e00075-18.
19. Siracusano A, Delunardo F, Teggi A, Ortona E. Cystic Echinococcosis: Aspects of Immune Response, Immunopathogenesis and Immune Evasion from the Human Host. *Endocr Metab Immune Disord Drug Targets*. 2012;12(1):16-23.
20. Holland SM, DeLeo FR, Elloumi HZ, Hsu AM, Uzel G, Brodsky N. STAT3 mutations in the hyper-IgE syndrome. *N Engl J Med*. 2007;357(16):1608-19.
21. Godot V, Harraga S, Podoprigora G, Liance M, Bardonnet K, Vuitton DA. IFN alpha-2a protects mice against a helminth infection of the liver and modulates immune responses. *Gastroenterology*. 2003;124(5):1441-50.
22. Kern P, Wen H, Sato N, Vuitton DA, Gruener B, Shao Y, Delabrousse E, Kratzer W, Bresson-Hadni, S. WHO classification of alveolar echinococcosis: principles and application. *Parasitol Int*. 2006;55 Suppl:S283-S287.
23. Baron RW, Tanner CE. The effect of immunosuppression on secondary *Echinococcus multilocularis* infections in mice. *Int J Parasitol*. 1976;6(1):37-42.
24. Subauste CS. Primary immunodeficiencies and susceptibility to parasitic infections. *Parasite Immunol*. 2006;28(11):567-75.
25. Koch S, Bresson-Hadni S, Miguet JP, Crumbach JP, Gillet M, Manton GA, et al. Experience of liver transplantation for incurable alveolar echinococcosis: a 45-case European collaborative report. *Transplantation*. 2003;75(6):856-63.
26. Chauchet A, Grenouillet F, Knapp J, Richou C, Delabrousse E, Dentan C, et al. Increased incidence and characteristics of alveolar echinococcosis in patients with immunosuppression-associated conditions. *Clin Infect Dis*. 2014;59(8):1095-04.
27. Lachenmayer A, Gebbers D, Gottstein B, Candinas D, Beldi G. Elevated incidence of alveolar echinococcosis in immunocompromised patients. *Food Waterborne Parasitol*. 2019;16:e00060.