

First Case of *Ascaris lumbricoides* Infestation Complicated with Hemophagocytic Lymphohistiocytosis

Hemofagositik Lenfositoz ile Komplike Olmuş *Ascaris lumbricoides* Enfestasyonu: Bildirilen İlk Olgu

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ABSTRACT

Ascariasis is a common soil-transmitted helminth infestation worldwide. *Ascaris lumbricoides* infestation is generally asymptomatic or cause nonspecific signs and symptoms. We report a 5-year-old male with hemophagocytic lymphohistiocytosis associated with *A. lumbricoides* infestation. The presented patient recovered completely after defecating an *A. lumbricoides* following intravenous immunoglobulin (IVIG) and mebendazole treatment. We wanted to emphasize that because helminth infestation is easily overlooked, the diagnosis of ascariasis should be considered in patients who live in endemic areas and treated timely to prevent severe complications. (*Türkiye Parazitol Derg* 2015; 39: 164-6)

Keywords: *Ascaris lumbricoides*, hemophagocytic lymphohistiocytosis, child

Received: 16.03.2014

Accepted: 19.01.2015

ÖZET

Askariasis tüm dünyada sık görülen bir helmintik enfestasyondur. *Ascaris lumbricoides* enfestasyonu genellikle asemptomatiktir ya da spesifik olmayan semptom ve bulgular ile seyreder. Biz burada *Ascaris lumbricoides* ilişkili hemofagositik lenfohistiyositoz gelişmiş olan 5 yaşında bir erkek olguyu sunduk. Hastanın semptom ve bulguları intravenöz immunoglobulin (IVIG) ve mebendazol tedavilerini takiben *A. lumbricoides* helmintini defekte ettikten sonra hızla düzeldi. Sonuç olarak helmint enfestasyonları kolaylıkla gözden kaçtığı için, askariasis, endemic olduğu bölgelerde her zaman akılda bulundurulmalı ve ciddi komplikasyonların gelişiminin önüne geçmek için vaktinde tedavi edilmelidir. (*Türkiye Parazitol Derg* 2015; 39: 164-6)

Anahtar Sözcükler: *Ascaris lumbricoides*, hemofagositik lenfohistiyositoz, çocuk

Geliş Tarihi: 16.03.2014

Kabul Tarihi: 19.01.2015

INTRODUCTION

Ascariasis is a highly common infestation estimated to infect 1,221 billion people worldwide. Infestation is caused by the ingestion of *Ascaris lumbricoides* eggs via contaminated

soil or food (1). Hemophagocytic lymphohistiocytosis (HLH) is a severe disease resulting from uncontrolled hyperinflammatory reactivation of lymphocytes that in most cases is triggered by an infectious agent. Herein, we report a case of ascariasis that presented with HLH.

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DOI: 10.5152/tpd.2015.3617

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CASE REPORT

A 5-year-old male belonging to the Kastamonu Province presented with a 13-day history of swelling in the neck and behind the left ear. One week ago, he had been hospitalized at another hospital and treated with intravenous antibiotic for lymphadenitis for five days. As the patient's complaints did not resolve, he was referred to our hospital. Upon physical examination, his general condition was good, and his vital signs were normal. A hard, painful mass on the left side of the neck was palpated. The mass was 5x5x6 cm in diameter and extended from the superior part of the sternocleidomastoid muscle to the posterior cervical triangle. Other physical examination findings were normal.

Initial laboratory findings were as follows: white blood cell count (WBC), 8.700/ μ L; hemoglobin, 10.2 g/dL; platelet count, 616.000 μ L; erythrocyte sedimentation rate (ESR), 115 mm/h (normal: <30 mm/h); C-reactive protein (CRP), 21.3 mg/L (normal: <8 mg/L); antistreptolysin O (ASO) titer, 7.680 IU/mL; serum total protein, 9.4 g/dL (normal: 6–8 g/dL); albumin, 2.6 g/dL (normal: 3.1–4.8 g/dL). Serum electrolytes and renal and hepatic function test results were normal. Cervical ultrasonography (USG) showed multiple lymphadenopathies in the left submandibular region and left jugular chain and conglomeration in some of the lymphadenopathies. The two largest lymph nodes measured 26x16 mm and 26x14 mm. Thickness and echogenicity of surrounding fatty tissue increased. He was hospitalized, and empirical intravenous sulbactam-ampicillin was commenced for the nonspecific treatment of lymphadenitis. On day 3 of sulbactam-ampicillin treatment, there was no regression in the diameter of lymphadenitis; therefore, clindamycin was added to the treatment regimen. Serological examinations for Epstein–Barr virus, cytomegalovirus, *Brucella*, *Bartonella*, *Francisella tularensis*, and human immunodeficiency virus were negative. Routine blood and urine culture results were negative. On day 10 of hospitalization, the patient's condition deteriorated; his body temperature increased to 39°C, and widespread maculopapular rash and splenomegaly developed. On the fifth day of fever, laboratory findings were as follows: hemoglobin, 8.5 g/dL; WBC, 2.900/mm³; platelet count, 102.000/mm³. CRP and ESR increased to 89.5 mg/L and 62 mm/h, respectively. The serum IgG level was 2.110 mg/dL (normal: 635–1.880 mg/dL), total IgE was 107 IU/mL (normal: <60 IU/mL), and serum IgM and IgA were normal. Due to the patient's persistent fever and new onset splenomegaly and pancytopenia, laboratory investigations were made for HLH. The patient's fasting serum triglyceride level was 258 mg/dL (normal: 30–100 mg/dL), ferritin level was 8686 ng/mL (normal: 6–24 mg/dL), and fibrinogen level was 241 mg/dL (normal: 146–380 mg/dL). Serological studies for parvovirus B19, measles, toxoplasma, and *Leishmania* were negative. The C3 and C4 levels were normal. Antinuclear antibody, anti-dsDNA, and rheumatoid factor were negative. On day 6 of fever, the patient underwent bone marrow aspiration; histopathological analysis of the sample showed macrophage activation and hemophagocytosis. Abdominal USG showed multiple, long, linear, echogenic tubular structures in the ileal segment that were consistent with *A. lumbricoides* infestation (Figure 1). Stool testing showed a large number of *A. lumbricoides* eggs. The presence of fever, splenomegaly, hyperferritinemia, and hemophagocytosis in bone marrow suggested the diagnosis of HLH pancytopenia. The patient was given intrave-



Figure 1. Abdominal USG showed multiple, long, linear, echogenic tubular structures in the ileal segment that were consistent with *A. lumbricoides* infestation

nous immunoglobulin (IVIg) (400 mg/kg/day for 2 days) and mebendazole on day 6 of fever. Twenty-four hours after the completion of 2 days of IVIg therapy, the patient's fever persisted. On the following day, the patient completed mebendazole (100 mg/day for 3 days) treatment and defecated a 20-cm long adult *A. lumbricoides*. Complete apyrexia occurred on the same day, and his general condition improved. The rash began to fade, and 2 days later, laboratory parameters returned to normal. Cervical lymphadenitis resolved rapidly within 3 days. The patient completely recovered and was discharged 4 days after his fever subsided.

DISCUSSION

Ascariasis is one of the most common soil-transmitted helminthes infestations. A study from Turkey examined 28.911 random stool samples and reported that there were intestinal parasites in 24.1% of the samples. In that study, *A. lumbricoides* was reported to be one of the common parasites in parasite-positive specimens, with a prevalence of 0.12% (2). *A. lumbricoides* infestation can be asymptomatic or cause nonspecific signs and symptoms such as abdominal pain, loss of appetite, episodic diarrhea, anemia, urticaria, fatigue, and nausea. Chronic infestation can result in physical and intellectual growth. Intestinal obstruction, intussusception, volvulus, invagination, and perforation can develop in patients with a high parasite load. Intestinal worms entering the appendix can cause acute appendicitis. *A. lumbricoides* can also cause biliary and pancreatic disease. Acute intestinal nephritis and encephalopathy associated with ascariasis have rarely been reported (3). The presented patient's infestation included a 20-cm long adult worm and its eggs, which was considered as heavy infestation.

HLH is caused by excessive immune activation due to the impairment or lack of function of NK cells and cytotoxic T-cells. Such dysregulation leads to cellular damage, multi-organ dysfunction, and proliferation and activation of benign macrophages with hemophagocytosis (4). HLH can be inherited or can occur as a result of infectious, rheumatologic disorders or malignancy (5). Infections associated with secondary HLH include herpes virus, human immunodeficiency virus (HIV), hepatitis A, B, C viruses,

adenovirus, parvovirus, and influenza virus infections and bacterial infections such as tuberculosis, brucellosis, salmonellosis, and rickettsiosis as well as fungal and parasitic diseases (4, 6). Protozoal agents associated with HLH include *Leishmania donovani*, *Plasmodium falciparum*, *Plasmodium vivax*, *Toxoplasma gondii*, and *Babesia microti*. Strongyloidiasis, which is caused by *Strongyloides stercoralis*, is the only reported intestinal nematode infestation reported to be associated with HLH (4, 7).

HLH is diagnosed based on a molecular diagnosis consistent with HLH or on the fulfillment of five of the following eight criteria: 1–3. Fever, splenomegaly, and cytopenias (affecting ≥ 2 lineages, hemoglobin < 9 g/dL, platelet count $< 100,000/\mu\text{L}$, neutrophil count $< 1000/\mu\text{L}$); 4. hypertriglyceridemia (fasting blood sugar ≥ 265 mg/dL) and/or hypofibrinogenemia (150 mg/dL); 5. hemophagocytosis in the bone marrow, spleen, or lymph nodes; 6. low or absent NK cell activity; 7. ferritin level of ≥ 500 $\mu\text{g/L}$; 8. elevated soluble CD25. Other abnormal clinical findings that can occur during the course of HLH are neurological symptoms, lymph node enlargement, jaundice, edema, and skin rash (5, 6). The presented patient was referred to our clinic due to lymphadenitis that did not respond to antibiotic treatment. At initial presentation, he clinical symptoms or signs of HLH. During follow-up, the patient became febrile and met four of the eight criteria for secondary HLH, including fever, splenomegaly, hemophagocytosis in the bone marrow, and hyperferritinemia. He also had anemia, leucopenia, and thrombocytopenia nearly but not exactly to the described levels. Similarly, The patient's serum triglyceride level was high, but not to the diagnostic level. He also had skin rash and lymphadenitis unresponsive to antibiotic treatment, which supported the diagnosis of HLH. We could not investigate soluble CD25 activity or NK cell activity. It was reported that that all diagnostic criteria do not need to be fulfilled before the initiation of life-saving treatment because many patients fail to meet all diagnostic criteria until late during the course of the disease (8). As timely treatment of HLH can prevent irreversible end-organ damage, HLH was diagnosed in the presented case based on strong clinical suspicion. The challenges were to identify the trigger for the patient's abnormal hyperfunction of macrophages. Other infectious etiologies, underlying rheumatologic disorders, and malignancy were not noted in the presented case. There are no reports in the literature of an association between *A. lumbricoides* and reactive hemophagocytosis. In the presented case, the clinical signs of HLH, including cervical lymphadenopathies, rapidly resolved following the defecation of parasites from the body. Thus, the most likely cause of HLH in the presented patient is thought to be *A. lumbricoides* infestation.

The most important steps in the treatment of HLH are timely diagnosis and immune suppression in order to reduce the cytokine storm that is triggered in this condition. Because the treatment of HLH is also dictated by its etiology, it is also critically important to investigate and treat the underlying causes of HLH. Treatment options for HLH are numerous, and they are based on the combination of immune suppression and chemotherapy. IVIG may also be beneficial in patients with HLH due to infections and autoimmune diseases (6, 9). The presented patient recovered completely after defecating an *A. lumbricoides* following IVIG treatment and mebendazole, which stopped the hyperinflammation cascade.

CONCLUSION

It has been reported that while adult ascaris worms occupying the small intestine are usually asymptomatic, ascaris infestation similar to our patient and larval or adult worm migration can give rise to unpleasant symptoms (10). We wanted to emphasize that because the helminth infestation is easily overlooked, the diagnosis of ascariasis should be considered in patients who live in endemic areas and treated timely to prevent severe complications.

Informed Consent: Written informed consent was obtained from the patient's parents.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - F.Ç., G.T.; Design - G.T., G.I.B.; Supervision - G.T.; Funding - G.I.B.; Materials - A.T.O., G.C.; Data Collection and/or Processing - G.I.B., F.Ç.; Analysis and/or Interpretation - A.T.O., G.C.; Literature Review - A.T.O., G.C.; Writer - G.I.B.; Critical Review - G.I.B.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

Hasta Onamı: Yazılı hasta onamı bu çalışmaya katılan hastanın ailesinden alınmıştır.

Hakem Değerlendirmesi: Dış Bağımsız.

Yazar Katkıları: Fikir - F.Ç., G.T.; Tasarım - G.T., G.I.B.; Denetleme - G.T.; Kaynaklar - G.I.B.; Malzemeler - A.T.O., G.C.; Veri Toplanması ve/veya İşlemesi - G.I.B., F.Ç.; Analiz ve/veya Yorum - A.T.O., G.C.; Literatür taraması - A.T.O., G.C.; Yazıyı Yazan - G.I.B.; Eleştirel İnceleme - G.I.B.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

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