The Turkish Journal of Pediatrics 2021; 63: 1103-1107
https://doi.org/10.24953/turkjped.2021.06.021

Case Report

Covid-19 in a patient with Familial Hemophagocytic Lymphohistiocytosis in children

V. Hülya Üzel[1], Kamil Yılmaz[2]

[1]*Division of Pediatric Hematology,* [2]*Department of Pediatrics, Dicle University Faculty of Medicine, Diyarbakır, Turkey.*

ABSTRACT

Background. Based on the information obtained so far, COVID- 19 is relatively mild in children. We will present a 6-month-old male patient infected with COVID -19 in April 2020, while receiving HLH 2004 chemotherapy protocol with the diagnosis of familial (Genetic / Primary) Hemophagocytic Lymphohistiocytosis (HLH).

Case. Herein we present a case accompanied by a defective perforin gene defect in the primary HLH pathogenesis, Covid-19 infection with the presence of fever and hyperferritinemia, which was evaluated in favor of reactivation and the patient was given both the HLH-2004 chemotherapy protocol treatment and COVID -19 therapy as recommended by the guidelines. Our patient improved clinically and in terms of laboratory test results at the end of the 15th day of hospitalization and was discharged.

Conclusions. It should be remembered that COVID-19 can be seen with different clinical manifestations in the pediatric age group, and COVID-19 tests should be recommended, especially in children with immunosuppression and fever.

Key words: COVID-19, hemophagocytic lymphohistiocytosis, perforin.

The coronavirus disease 2019 (COVID-19), was declared as a public health emergency of international concern on January 30, 2019 and as a pandemic on March 11, 2020 by the World Health Organization (WHO).[1] According to the data obtained to date, the disease is milder in children.[2] Patients undergoing cancer treatment and those who have had cancer constitute a risky group in the COVID-19 pandemic.[3-5]

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening clinical syndrome characterized by an uncontrolled and ineffective immune response triggered mostly by infectious agents. HLH is generally classified as familial HLH (FHL), which occurs due to an underlying genetic defect, and secondary HLH that can develop due to a variety of acquired causes.[6] Viruses are the most important infectious agents that trigger HLH, and herpesviruses, especially Epstein Bar Virus (EBV) and Cytomegalo Virus (CMV) are frequently detected. Herein we will present a 6-month-old male patient who was diagnosed with FHL, who was not fully compatible with stem cell donors and was infected with COVID -19 in April 2020, while receiving the HLH 2004 chemotherapy protocol.

Case Report

The patient applied to our hospital at the age of about 2 months, with the symptoms of fever, restlessness and paleness, splenomegaly on physical examination and bicytopenia on her blood count. The patient was diagnosed with HLH due to the clinical, laboratory and bone marrow aspiration smear findings. The HLH 2004 chemotherapy treatment protocol was started. Viral and bacterial examinations (serology, culture) were negative. The marriage between mother and father was a first-degree consanguineous marriage and the genetic

✉ V. Hülya Üzel
drhulya-uzel@hotmail.com

Received 3rd September 2020, revised 2nd December 2020, 4th January 2021, 27th February 2021, accepted 14th April 2021.

analysis of the patient revealed a PRF1 Exon 3 c.1122G> (p.Trp374Ter) rs104894176 mutation, which was found to be compatible with homozygous class 1 HLH.

The treatment of primary HLH was given to the patient. The patient, who did not have a fully compatible stem cell donor, recovered clinically and in terms of laboratory findings in the first month, applied with the complaint of fever and cough during the 12th week of the HLH protocol (17 April 2020). In his physical examination, his general condition was moderate, he was conscious, his body temperature was 38.5oC, respiratory rate was 48/min, pulse was 127/min, abdominal distension was present and rales were detected in the basal areas of the lungs. Other system examinations were found normal. Considering that hemophagocytic reactivation might occur, a laboratory examination was performed which showed the following: hemoglobin 10.5 g/dL, leukocyte count 15020/mm3, neutrophil: 6.5 uL, monocyte: 2.023 uL, lymphocyte: 6.06 uL, platelet count 440.6 / mm3, prothrombin time (PT) 16sec, partial thromboplastin time (aPTT) 31 sec, INR 1.34, serum triglyceride 519mg / dL, ferritin 795 ng / mL, fibrinogen 468mg / dL and lactic dehydrogenase (LDH): 357 U / L, C- reactive protein (CRP): 10.27 mg / L (0-0.5), Procalcitonin:> 100. Arterial blood gases, liver and kidney function tests, serum electrolytes, albumin, bilirubin and full urine examination were normal. Peripheral smear, showed 60% neutrophil, toxic granulation, 40% lymphocyte, platelets were sufficiently clustered and atypical cells were not observed.

Hyperferritinemia (795mg / dl), hypertriglyceridemia (519mg / dl) were detected in the patient. Bilateral perihilar infiltrations were seen on the chest x-ray of the patient, who had no contact history with a person diagnosed or suspected to have COVID-19 (Fig 1). Thorax CT revealed peripheral atelectasis and consolidation areas were observed in the posterior sections of the lower lobe of both lungs, and small peribronchial consolidation areas and nodular infiltrations were observed in the upper lobes in both lungs, and those findings were evaluated as possible COVID-19 (Fig. 2). HLH 2004 treatment protocol was continued considering the possible HLH reactivation in the patient with persistent fever and hyperferritinemia and hypertriglyceridemia. Cyclosporine, dexamethasone and intravenous immunoglobulin (IVIG) were given. An oro-nasopharyngeal swab sample was taken.

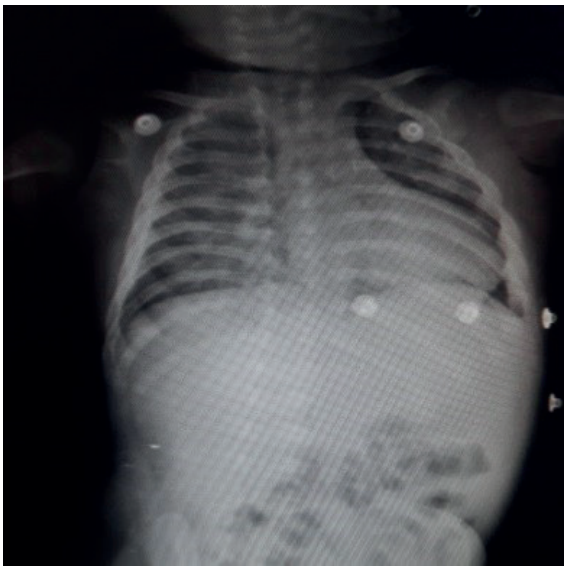

Fig. 1. Bilateral perihilar infiltrations were seen on the Chest x-ray.

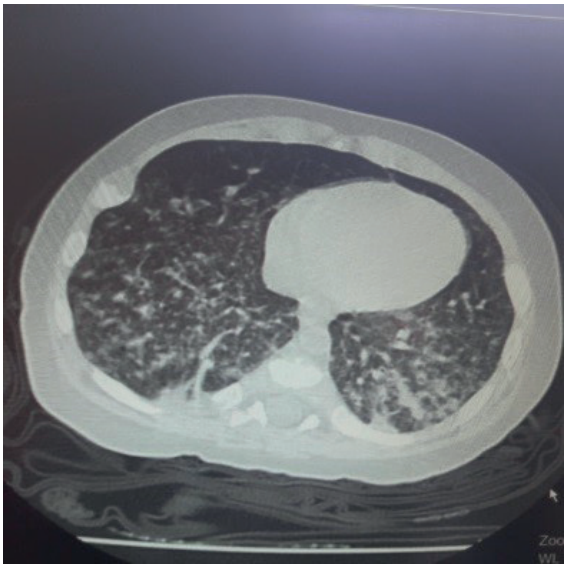

Fig. 2. Thorax CT revealed peripheral atelectasis and consolidation areas.

The patient who was positive for SARS CoV2 polymerase chain reaction (PCR) was hospitalized in the COVID-19 pediatrics clinic. The patient was treated according to the recommendation of guidelines for COVID-19 pneumonia and unclear coinfection.

Antimicrobial therapy, hydroxychloroquine, azithromycin, low molecular weight heparin (LMWH), HLH-2004 treatment protocol were administered. In blood gas analysis; PH: 7.47, PCO2: 29.3mmHg, 45.8mmHg, PO2, Lactate: 5.5mmol / L, cSO2: 83.2%. The patient was taken to the intensive care unit and oxygen support was given with a mask. When the patient's respiratory distress increased, the level of D-Dimer was studied and it was found that D-dimer level increased to 9.11, and a low-molecular-weight heparin (enoksoparin) single dose of 100 unit /kg /dose was started. Lopinavir / ritonavir combination (Kaledra tb) was given. On the fifth day of hospitalization, the patient with a hemoglobin level of 7.4 gr / dL was given cross-matched, irradiated erythrocyte support.

As the patient's symptoms regressed on the 7th day of hospitalization, he was transferred back to the pediatric ward. In addition to the HLH 2004 protocol, Azithromycin, hydroxychloroquine was given for five days, Meropenem, Amikacin and Lopinavir / ritonavir for ten days and low molecular weight heparin (LMWH) for fourteen days. No side effects were observed in the patient. On the 10th day, when the COVID -19 PCR test was negative, the patient was clinically and laboratory stable, and the HLH -2004 protocol was continued and he was discharged on the 15th day of his admission. Consent was received from the patient's family for this case report.

Discussion

Cancer patients who have been receiving active chemotherapy, any antibodies or targeted therapy or intensive radiotherapy in the past 6 months, are susceptible to infection due to immune system deficiency, and have a high risk of contact with infected or carrier individuals due to clinical controls, examinations and treatments.[1,3] Our patient was also a patient with familial HLH and was receiving chemotherapy treatment.

FHL is defined as a rare, autosomal recessively inherited immune regulation disorder characterized by uncontrolled T cell and macrophage activation and excessive cytokine release.[7] The first identified genetic defect is a mutation in the PRF1 gene (FHL-2).[8,9] The most common mutation is W374X, the exon three stop codon mutation. The genetic result of our patient was detected as PRF1 Exon 3 c.1122G> (p.Trp374Ter) rs104894176 homozygous class1 HLH (FHL-2). Today, the treatment that provides a cure in familial (primary) HLH is to perform hematopoietic stem cell transplantation (HSCT) after remission is achieved by chemotherapy.[9]

HLA appropriate donor was not found from our patient's family and relatives. The patient was in remission from the first month of treatment, clinically and in terms of laboratory findings. In the 12th week of his treatment, he was infected with COVID-19. In addition to the clinical deterioration in familial HLH, infections are known to lead to acquired HLH. The most important infectious agents leading to HLH are viruses. Especially herpesviruses, EBV, CMV are frequently detected.[4,8] In the course of sepsis developing due to infections, some patients may develop symptoms of macrophage activation syndrome (MAS) or, in other words, acquired (secondary) hemophagocytic lymphohistiocytosis (sHLH). It is thought that COVID-19 infection starts with type II pneumocyte damage and subsequently leads to the development of viral pneumonia and acute respiratory distress syndrome (ARDS), and these clinical manifestations may activate macrophage activation syndrome (MAS) and disseminated intravascular coagulation (DIC).[10-13]

It is extremely difficult to differentiate COVID-19 pneumonia and ARDS pathologically. On the

day of admission to the hospital, treatment was started for the coinfection of COVID-19 pneumonia / HLH reactivation based on the guidelines. High CRP and ferritin levels reported in many COVID-19 cases were also detected in our patient and were found to be compatible with the literature.[14] In the follow-up of our patient, the level of d-dimer gradually increased and he was taken to the intensive care unit because of respiratory distress. We added a single dose of LMWH to the treatment of the patient on the 3rd day of his hospitalization, considering that micro-thromboses may have started.

Although studies in children are very limited, recent studies have indicated the importance of viral load in COVID-19-pneumonia.[15-17] For this reason, it is very important to develop an effective antiviral which should be included in the treatment plan early. The necessity of applying the HLH 2004 protocol in the treatment of patients developing MAS or secondary HLH is especially important in intensive care patients.[15]

Both the HLH-2004 chemotherapy protocol treatment and COVID-19 treatment were administered to our patient as recommended by the guidelines. Our patient improved clinically and in terms of laboratory findings at the end of the 15-day hospitalization period and was discharged.

In conclusion, it should be remembered that COVID-19 can be seen with different clinical manifestations in the pediatric age group. We recommend performing COVID-19 testing especially in children who are under immunosuppressant treatment and have a fever. In this manuscript, we would like to state that the COVID-19 infection is among the factors that can cause HLH reactivation in familial HLH patients. In patients with high mortality, such as familial HLH, early detection and treatment of COVID -19 infection will increase chance of survival.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: VHÜ, KY; data collection: KY; analysis and interpretation of results: VHÜ, KY ; draft manuscript preparation: KY. All authors reviewed the results and approved the final version of the manuscript.

Conflicts of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

REFERENCES

1. World Health Organization. Coronavirus disease (COVID-19) pandemic. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019 (Accessed on May 2, 2020).
2. Tezer H, Bedir Demirdağ T. Novel coronavirus disease (COVID-19) in children. Turk J Med Sci 2020; 50(SI-1): 592-603. https://doi.org/10.3906/sag-2004-174
3. Sullivan M, Bouffet E, Rodriguez-Galindo C, et al. The COVID-19 pandemic: a rapid global response for children with cancer from SIOP, COG, SIOP-E, SIOP-PODC, IPSO, PROS, CCI, and St Jude Global. Pediatr Blood Cancer 2020; 67: e28409. https://doi.org/10.1002/pbc.28409
4. Janka GE. Familial and acquired hemophagocytic lymphohistiocytosis. Annu Rev Med 2012; 63: 233-246. https://doi.org/10.1146/annurev-med-041610-134208
5. Zhu N, Zhang D, Wang W, et al; China Novel Coronavirus Investigating and Research Team. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020; 382: 727-733. https://doi.org/10.1056/NEJMoa2001017
6. Tian S, Hu W, Niu L, Liu H, Xu H, Xiao SY. Pulmonary pathology of early-phase 2019 novel coronavirus (COVID-19) pneumonia in two patients with lung cancer. J Thorac Oncol 2020; 15: 700-704. https://doi.org/10.1016/j.jtho.2020.02.010
7. Ueda I, Morimoto A, Inaba T, et al. Characteristic perforin gene mutations of haemophagocytic lymphohistiocytosis patients in Japan. Br J Haematol 2003; 121: 503-510. https://doi.org/10.1046/j.1365-2141.2003.04298.x

8. Filipovich AH, Chandrakasan S. Pathogenesis of hemophagocytic lymphohistiocytosis. Hematol Oncol Clin North Am 2015; 29: 895-902. https://doi.org/10.1016/j.hoc.2015.06.007

9. Bode SF, Ammann S, Al-Herz W, et al; Inborn Errors Working Party of the EBMT. The syndrome of hemophagocytic lymphohistiocytosis in primary immunodeficiencies: implications for differential diagnosis and pathogenesis. Haematologica 2015; 100: 978-988. https://doi.org/10.3324/haematol.2014.121608

10. Fox SE, Akmatbekov A, Harbert JL, et al. Pulmonary and cardiac pathology in African American patients with COVID-19: an autopsy series from New Orleans. Lancet Respir Med 2020; 8: 681-686. https://doi.org/10.1016/S2213-2600(20)30243-5

11. Tian S, Hu W, Niu L, Liu H, Xu H, Xiao SY. Pulmonary pathology of early-phase 2019 novel coronavirus (COVID-19) pneumonia in two patients with lung cancer. J Thorac Oncol 2020; 15: 700-704. https://doi.org/10.1016/j.jtho.2020.02.010

12. McGonagle D, Sharif K, O'Regan A, Bridgewood C. The role of cytokines including interleukin-6 in COVID-19 induced pneumonia and macrophage activation syndrome-like disease. Autoimmun Rev 2020; 19: 102537. https://doi.org/10.1016/j.autrev.2020.102537

13. Chen ZM, Fu JF, Shu Q, et al. Diagnosis and treatment recommendations for pediatric respiratory infection caused by the 2019 novel coronavirus. World J Pediatr 2020; 16: 240-246. https://doi.org/10.1007/s12519-020-00345-5

14. Henry BM, Lippi G, Plebani M. Laboratory abnormalities in children with novel coronavirus disease 2019. Clin Chem Lab Med 2020; 58: 1135-1138. https://doi.org/10.1515/cclm-2020-0272

15. McGonagle D, Sharif K, O'Regan A, Bridgewood C. The role of cytokines including interleukin-6 in COVID-19 induced pneumonia and macrophage activation syndrome-like disease. Autoimmun Rev 2020; 19: 102537. https://doi.org/10.1016/j.autrev.2020.102537

16. World Health Organization. Clinical management of severe acute respiratory infection when novel coronavirus (2019-nCoV) infection is suspected: interim guidance. Available at: https://apps.who.int/iris/handle/10665/330893 (Accessed on January 28, 2020.)

17. T.C. Sağlık Bakanlığı Halk Sağlığı Genel Müdürlüğü. COVID-19 (SARS-CoV-2 Enfeksiyonu) Rehberi. Bilim Kurulu Çalışması. Ankara, 13 Nisan 2020. Available at: https://www.teb.org.tr/versions_latest/1240/13nisansbrehberi (Accessed on April 13, 2020).