

Case Report of Hemophagocytic Syndrome with Severe Pneumonia Amidst the Covid-19 Pandemic

Jun Zi¹, Xialing Huang² and Quan Zhou^{3*}

¹Department of pediatrics, Leiyang People's Hospital, Leiyang, Hunan, 421800, China.

²Department of Infectious Diseases, Leiyang People's Hospital, Leiyang, Hunan, 421800, China.

³Department of Infectious Diseases, the First Hospital of Changsha, Changsha, Hunan, 410000, China

***Corresponding author:** Quan Zhou, Department of Infectious Diseases, the First Hospital of Changsha, Changsha, Hunan, 410000, People's Republic of China, Tel: +8618508405005, E-mail address: hnnhzq@163.com

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Abstract

A 25-year-old woman developed respiratory failure due to severe pneumonia during the 2019 coronavirus disease (COVID-19) pandemic. However, repeated nasopharynx swabs and bronchoalveolar lavage fluid (BALF) tests ruled out the cause of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and eventually diagnosed as Haemophilus syndrome with severe pneumonia. After comprehensive treatment of anti infection and HLH-1994 regimen, the clinical and CT results were improved. In view of the great difference in the detection rate of COVID-19 nucleic acid in respiratory specimens, there is overlap between the diagnostic criteria of severe COVID-19 and hemophagocytic syndrome, which is challenging for the diagnosis of severe COVID-19. Therefore, doctors should be alert to the possibility of Haemophilus syndrome when receiving patients with suspected severe COVID-19.

Keywords: Covid-19; Cytokine Storm Syndrome; Haemophagocytic Syndrome; Coronavirus; Differential Diagnosis

Abbreviations

ALT=alanine aminotransferase, AST=aspartate transaminase, BALF= bronchoalveolar lavage fluid, CK-MB=creatin kinase-MB, COVID-19=coronavirus disease 2019, CRP=C-reactive protein, HPS=Hemophagocytic syndrome, HLH=hemophagocytic lymphohistiocytosis, LDH=lactate dehydrogenase, RT-PCR=reverse transcription polymerase chain reaction, SARS-CoV-2=severe acute respiratory syndrome coronavirus 2, RNA=ribonucleic acid, IgM=the immunoglobulin M, IgG=the immunoglobulin G, WBC=white blood cell

Introduction

Hemophagocytic syndrome (HPS) or hemophagocytic lymphohistiocytosis (HLH) is an acute and rapidly progressive systemic inflammatory disorder characterized by cytopenia, excessive cytokine production, and hyperferritinemia [1]. HPS has primary and acquired (secondary, reactive) forms. Secondary HLH may be caused in the presence of an underlying disorder, that is, secondary to a malignant, infectious, or autoimmune/auto inflammatory stimulus. It has been found in patients with autosomal recessive diseases, various persistent infections, immunosuppression, and malignant tumors [2]. Due to the changes in the ecological environment, the increase in urban population, the convenience of transportation and other factors, COVID-19 has been epidemic worldwide, causing great harm to people's health [3]. A subset of coronavirus disease 2019 (COVID-19) patients exhibit clinical features of cytokine storm [4]. The clinical and laboratory features of severe COVID-19 infection overlap with those of HLH, a hyper inflammatory disorder often associated with several viral infections. [5] Infection-related hem phagocytic syndrome, with related infection, is very similar to severe COVID-19 infection in clinical manifestations, so the differential diagnosis is difficult. This article reported on the diagnosis and treatment of a suspected severe COVID-19 person who was later diagnosed with severe pneumonia with hematopoietic syndrome, so as to provide a reference for the clinical differential diagnosis of COVID-19.

Case Presentation

The patient, a 25-year-old, was living in Changsha, Hunan, China, before the onset of illness. After the outbreak, there were many confirmed patients with COVID-19 in Changsha. She took an online ride-hailing car from Changsha to home on January 22, 2020. None of the people in this car were reported to have COVID-19. Onset on January 25, 2020, presenting as fever with cough and sputum. To confirm whether it was COVID-19 infection, she was admitted to the isolation ward on January 31, 2020. This case had no obvious past history. Breath sounds in both lungs were coarse, and a few wet rales were heard. No obvious abnormalities were seen in examination of heart, abdomen and limbs. On January 31, 2020, the blood routine examination showed that the white blood cell decreased to $1.77 \times 10^9/L$. The immunoglobulin M (IgM) tests of influenza A, influenza B, seven respiratory viruses and mycoplasma were negative. Pulmonary high resolution computed tomography (HRCT) was performed on the patient (Figure1 1a, 1b). Multiple nodules and patchy high density shadows with unclear boundaries in both lungs, most common in the upper lobe of both lungs and the middle lobe of the right lung.

On February 04, 2020, she still had fever and increased shortness of breath, with the SpO₂ maintained at about 90%. After high-flow oxygen inhalation (3.5L/min) and non-invasive ventilator assisted ventilation, dyspnea was not relieved. So she was transferred to the Department of Infectious Diseases, another hospital, on February 5, 2020.

After the transferring, blood routine test on February 5, 2020 showed that the number of white blood cells is getting lower and lower. Lung CT showed multiple infectious lesions in both lungs slightly more than the image on January 31, 2020. The result of the third throat swab nucleic acid test was also negative. The fact that the results of 3 nucleic acid tests were all negative, she was no longer isolated. She was transferred to intensive care unit and intubated due to respiratory fatigue. To further confirm the diagnosis, bronchoscopy and alveolar lavage were conducted, and the alveolar lavage fluid was sent for nucleic acid test, and the result was still negative. On February 14, 2020, bone marrow cytology examination showed decreased hyperplasia of the bone marrow and occasionally seen hemophagocytes, which was in line with hematopoietic syndrome.

Finally, according to the "Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia" (7th Trial Version) [6], after consultation with the expert group of COVID-19, the experts believed that the patient was suspected of COVID-19 in the early stage. Finally, after a variety of examinations and treatment, according to the HLH-2004 criteria [7], and H-score > 169[8], the patient could be diagnosed with hemophagocytic syndrome (Table 1). On February 14, 2020, the HLH-1994 program was used to control the development of the disease with dexamethasone + etoposide (0.1g).

After nearly 40 days of chemotherapy, the patient basically recovered completely. On April 2, 2010, the blood routine and chest CT were all normal. The blood routine was normal in the following six months.

Discussion

Infection-related HPS caused by viruses, bacteria or other pathogens is more common [9]. Secondary HLH syndrome observed in adults is most often caused by infection (usually viruses, such as Epstein Barr virus (EBV), cytomegalovirus (CMV), or human immunodeficiency virus (HIV)); Malignant tumor (lymphoma), primary rheumatism or drugs (Immune checkpoint inhibitors, lamotrigine). Clinical and laboratory features include fevers (that they may exceed 40 °C), cytopenias, organomegaly, coagulopathy, and profound hyperferritinemia often >10,000 µg/L; which often rapidly worsen despite initial empiric anti-microbial therapy resulting in eventual multisystem organ failure [10]. Early-stage patients usually do not show all the characteristics, which makes early diagnosis difficult. To diagnose HPS, hemophagocytes will be found in bone marrow cytology examination [11]. Besides, laboratory tests will show pancytopenia, especially thrombocytopenia. Infection-related hemophagocytic syndrome, with related infection, is very similar to severe COVID-19 infection in clinical manifestations, so the differential diagnosis is difficult.

The clinical manifestations of COVID-19 patients may include fever, cough, chest tightness, diarrhea, fatigue, poor appetite, etc., but fever, dry cough, and fatigue were the most common, which progressed to severe shortness of breath and decreased oxygenation [12]. Lung lesions progressed to multiple ground-glass opacities and infiltrative shadows in both lungs. Critically ill patients needed invasive assisted ventilation, some even died due to severe acute respiratory syndrome (ARDS) or multiple organ failure. The severity of coronavirus disease of 2019 (COVID-19) ranges from asymptomatic infection to critical illness, with up to one third of hospitalized patients requiring mechanical ventilation in an intensive care unit [13]. In a subset of patients with severe COVID-19, rapid progression of pulmonary infiltrates and multi-organ failure coincides with dramatic increases in inflammatory cytokines and other biochemical markers of inflammation, consistent with a COVID-19 associated cytokine storm syndrome (COVID-CSS) Cron [14].

CSS is an excessive immune response that is caused not by a single disease, but by different etiologies, that results in hyper inflammation. CSS includes formerly used terms such as hemophagocytic lymphohistiocytosis (HLH), macrophage activation syndrome (MAS), infection-associated hemophagocytic syndrome (IAHS), cytokine release syndrome (CRS), and cytokine storm (CS). CSS is common not only in microbial and viral infections but also in autoimmune diseases, hematological malignancies, and after some biological treatments. To date, there is no consensus definition of COVID-CSS [15]. It should be emphasized that different from previous understanding of other diseases-associated CSS, COVID-19-associated CSS has not only unique epidemiological, virological, and clinical characteristics, but also laboratory parameters, and pathophysiology. In particular, accumulating data have indicated that internationally recognized diagnostic criteria such the HLH-2004, HLH-2009, and the HScore method did not effectively identify COVID-19-associated CSS [16]. We briefly compared the HLH-2004 standard with the early prediction standard of covid-19 related CSS special diagnosis designed by the COVID-19 research group of Temple University [17] (Table 2).

The patient had been in contact with the epidemic area, and the early clinical manifestations were consistent with the typical manifestations of COVID-19. Chest CT examination was also consistent with the findings of patients with COVID-19 Radiology [18], which usually showed bilateral and multilobed distribution, mainly involving sub pleural / peripheral and posterior lung parenchyma, especially in the lower lobe. In the course of treatment, the condition worsened, and many indicators were in line with the early warning indicators for severe/critical cases proposed in the “Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7)” [6]. Changes in the level of immunologic injury and inflammation and early cellular damages were obvious in both severe and critically ill COVID-19 patients. According to the research findings, including lymphocyte (lym), lactate dehydrogenase (LDH), serum amyloid A (SAA), C-reactive protein (CRP) initial value and change trend, lactic acid (LAC) change trend and other clinical indicators, can be used as early warning indicators for critically ill patients [19]. One week after the onset of the disease, the patient's condition deteriorated rapidly and developed respiratory failure. Pulmonary CT showed that the infectious lesions of both lungs were aggravated, the three systems of blood routine were reduced, and the inflammatory indexes were continuously increased. Patients with severe pneumonia performance, but many times nucleic acid test negative, to our differential diagnosis and treatment

has brought challenges. The patient's persistent leukopenia and severe pulmonary infection caused our attention, so we gave her a bone marrow biopsy. Fortunately, haemophagocytosis demonstrated in a bone marrow aspirate. Emerging studies in patients with COVID-19 are suggesting a key role of monocytes/macrophages in the pathogenesis of this viral infection, and there is a significant overlap between several features reported in severe COVID-19 and the features included in the haemophagocytic lymphohistiocytosis (HLH) diagnostic criteria. Therefore, SARS-Cov-2, as other respiratory viruses, may also be considered a potential etiological trigger of haemophagocytic lymphohistiocytosis (HLH) [20]. A recent study found that the immune response associated with severe COVID-19 infection is similar to that of HLH, but with some differences [21]. Three patients with severe COVID-19 confirmed by RT-PCR also had haemophagocytosis demonstrated in a bone marrow aspirate performed for cytopenia [22]. At present, hemophagocytosis on bone marrow aspirate of severe COVID-19 patients is an occasional case. There is limited evidence with presence of hemophagocytosis in bone marrow in patients with COVID-19. Not all patients with severe COVID-19 infection met the HLH 2004 criteria or H-score > 169. The researchers suggest that HLH should be suspected in patients with severe or worsening COVID-19 infection. Bone marrow tests should be done where the diagnosis is in doubt so that appropriate therapy may be initiated as early as possible.

Conclusion

In view of the current differences in the detection rate of viral nucleic acids, doctors should be alert to the possibility of hemophagocytic syndrome when treating suspected severe COVID-19 patients. They should explore the cause of hemocytopenia and attach importance to the differential diagnosis of severe pneumonia.

Acknowledgments

The study was approved by the ethical committee of Leiyang People's Hospital according to the Helsinki principle. An informed consent was taken from the included patients in the study.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Additional information

Author Contributions

Xialing Huang and Jun Zi drafted the article; Jun Zi collected and analyzed the data; Quan Zhou designed the study, and revised the manuscript for important intellectual content; All authors read and approved the final version of the manuscript.

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