CASE REPORT / OLGU SUNUMU

DOI: 10.4274/mjima.galenos.2024.24187.8
Mediterr J Infect Microb Antimicrob 2024;13:24187.8
Erişim: http://dx.doi.org/10.4274/mjima.galenos.2024.24187.8

Guillain-Barre Syndrome and Hemophagocytic Lymphohistiocytosis Following COVID-19: A Case Report

COVID-19 Enfeksiyonu Sonrası Guillain-Barre Sendromu ve Hemofagositik Lenfohistiositoz: Olgu Sunumu

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Abstract

The Severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2) infection causes a wide range of neurologic and hematologic manifestations. Herein, we report the case of a 69-year-old Indian male with concurrent Guillain-Barre syndrome (GBS) and hemophagocytic lymphohistiocytosis (HLH) after a bout of COVID-19. He initially presented with acute ascending paraparesis and fever. Nerve conduction studies revealed axonal degeneration, affecting both motor and sensory nerves, and cerebrospinal fluid analysis revealed albuminocytologic dissociation. Thus, a diagnosis of GBS was made. Considering the fever, bicytopenia, elevated levels of triglycerides and ferritin, and bone marrow alterations, a diagnosis of HLH was made. Intravenous immunoglobulin therapy was administered, which produced a good clinical response.
Keywords: Guillain-Barre syndrome, hemophagocytic lymphohistiocytosis, SARS-CoV-2 infection, hyperinflammation, molecular mimicry

Öz

Şiddetli akut solunum sendromu-koronavirüs-2 (SARS-CoV-2) enfeksiyonu çok çeşitli nörolojik ve hematolojik belirtilere neden olur. Guillain-Barre sendromu (GBS) ile başvuran ve COVID-19 enfeksiyonu sonrası hemofagositik lenfohistiyositoz (HLH) gelişen 69 yaşında Hintli erkek hasta sunulmaktadır. Hasta akut asendan paraparezi ve ateş ile başvurdu. Sinir iletim çalışmaları beyin omurilik sıvısı analizinde albümino-sitolojik ayrışma ile birlikte hem motor hem de duyu sinirlerini etkileyen aksonal dejenerasyonu ortaya çıkardı. Hastada ateş, bisitopeni, trigliserit ve ferritin düzeylerinin yüksek olması ve kemik iliği biyopsisi bulguları nedeniyle HLH düşünüldü. Hasta intravenöz immünoglobulin tedavisine iyi bir klinik yanıt vermiştir.
Anahtar Kelimeler: Guillain-Barre sendromu, hemofagositik lenfohistiyositoz, SARS-CoV-2 enfeksiyonu, hiperenflamasyon, moleküler taklit

Introduction

The Severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2) is a positive-sense single-stranded RNA virus, belonging to the Betacoronavirus genus, that primarily affects the respiratory system. It can produce a myriad of symptoms that span from self-limiting mild upper respiratory tract infections to critical respiratory conditions such as acute respiratory distress syndrome and septic shock. Furthermore, it can cause widespread organ system engagement due to immune system disruption and multisystem inflammatory syndrome, which can lead to manifestations related to the central and peripheral nervous systems and the overall immunological milieu.

Herein, we present the case of a 69-year-old male with weakness and abnormal nerve conduction and cerebrospinal fluid (CSF) studies. He was diagnosed with Guillain-Barre syndrome (GBS) that was complicated by hemophagocytic

Cite this article as: Thomas A, Abraham AA, M. Abraham A. Guillain-Barre Syndrome and Hemophagocytic Lymphohistiocytosis Following COVID-19: A Case Report. Mediterr J Infect Microb Antimicrob. 2024;13:24187.8.

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Received/Geliş Tarihi: 30.04.2024 **Accepted/Kabul Tarihi:** 14.05.2024

Published: 24.05.2024

lymphohistiocytosis (HLH) owing to the presence of bicytopenia on hematological examination and bilineage dysplasia, with histiocytic prominence and phagocytosis of the red and white blood cells, on bone marrow biopsy.

Case Report

A 69-year-old male, hailing from Punjab, India, presented to the emergency department with paraparesis of the lower limbs for one week, fever for 3 days, and bicytopenia [hemoglobin (Hb): 8.7 g/dl; platelet count: 13,000/mm^3]. The weakness initially manifested as difficulty in gripping footwear, and it progressively worsened to hinder stair climbing and rising from a squatted position. Subsequently, the family members observed dragging of the foot, which culminated in the patient's inability to walk unassisted within 12 hours prior to admission. The patient denied experiencing double vision, swallowing difficulties, upper limb weakness, facial asymmetry, dysarthria, or dysphagia. He disclosed a recent moderate case COVID-19 one month prior to admission, which was confirmed via real-time reverse transcription-polymerase chain reaction (RT-PCR) assay. He had exhibited mild respiratory symptoms including dyspnea, sore throat, hyposmia, fever, and cough. He was hospitalized for 10 days for moderate COVID-19 pneumonia, and oxygen supplementation was necessary for 7 of these days. The respiratory symptoms resolved within 10 days, and a subsequent RT-PCR assay of the nasopharyngeal swab yielded a negative result for SARS-CoV-2.

At the time of the current admission, his respiratory rate was 35 breaths/min, pulse oximetry saturation was 95% on 2 L of oxygen, pulse rate was 130 beats/minute (sinus tachycardia), blood pressure was 110/80 mmHg, and temperature was 39.5 °C. The motor assessment revealed generalized muscle weakness, with a power of 4+ in the upper limbs and 1+ in the lower limbs, and hypotonia across all four limbs. The knee and ankle reflexes were absent, and the superficial sensations in the lower limb extremities were slightly impaired. There were no signs of meningeal irritation or cranial nerve function deficits. Considering the ascending paralysis and the absence of lower limb reflexes, a diagnosis of acute inflammatory demyelinating polyradiculopathy (AIDP) was considered.

Routine blood investigations were performed (Table 1), and blood and urine cultures did not yield any growth. Tests to rule out other infectious diseases, such as RT-PCR for COVID-19, tests for dengue nonstructural protein-1 antigen, dengue IgM, dengue IgG, scrub typhus serology, leptospiral antigen, leptospiral serology, and malarial antigen, peripheral smear for malarial parasite, Weil-Felix test, and Widal test also yielded negative results. Furthermore, culture and viral panel of the CSF yielded negative results.

A chest X-ray revealed infiltrations in the lower zones of both lungs. An HRCT of the chest revealed confluent areas of ground glass opacities, irregular densities, and reticular opacities with tractional bronchiectasis indicating fibrosis in bilateral lung fields, particularly involving the peripheries (Figure 1). These findings probably developed secondary to the prior COVID-19 infection (CORADS 6).

Nerve conduction studies (NCS) revealed significant axonal degeneration, affecting both motor and sensory nerves. Given the presence of ascending paralysis, absence of reflexes, severe axonal degeneration in NCS, and albuminocytologic dissociation in CSF analysis, a diagnosis of AIDP was established. Intravenous immunoglobulin (IVIG) therapy was initiated at a dose of 2 g/kg over a five-day period. Additionally, due to the presence of pancytopenia, a bone marrow biopsy was performed. Examination of the biopsy specimen revealed bilineage dysplasia that was characterized by histiocytic prominence and phagocytosis of both red and white blood cells. This led to a concurrent diagnosis of HLH, which was further supported by the elevated triglyceride (298 mg/dl; reference range 100-150 mg/dl) and ferritin (3294 ng/ml; reference range 12-300 ng/ml) levels. On the third post-

Table 1. Sequential blood investigation results of our patient

Day of admission	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10
Hemoglobin, g/dl	8.7	8.0	6.3	7.9	8.6	9.2	9.5	10	10.2	10.2
Leucocyte count, per mm^3	4,000	2500	2400	3200	4200	4900	5100	5200	5800	6100
Platelet count, per mm^3	45000	31000	28000	46000	54000	98000	112000	130000	154000	160000
CRP, mg/l	104									
Ferritin level, ng/dl	3294			2504			1913			984
Management		IvIg1	IvIg2 Intubation	IvIg3 6 units of RDP	IvIg4 3 units of PRBC	IvIg5	Extubation			

CRP: C-reative protein, IvIg: Intravenous immunoglobins, RDP: Random donor platelets, PRBC: Packed red blood cells

admission day, due to deteriorating consciousness, a decline in oxygen saturation, and respiratory distress, the patient was intubated. Subsequently, the patient developed bleeding via the endotracheal tube, a low platelet count (24,000/mm^3), and low Hb level (6.3 g/dl). Thus, six units of random donor platelets and three units of packed red blood cells were transfused. By day four of hospitalization, the power in both lower limbs had increased to +4, and the overall condition had improved. On day 6 of hospitalization, the patient was successfully extubated. Concurrently, the patient underwent intensive physiotherapy, which led to a gradual improvement of muscle strength within the next 2 days. Over the subsequent follow-up periods, his complete blood count returned to within the normal limits, he continued to regain muscle strength, and he was able to autonomously perform activities of daily living.

Discussion

Guillain-Barre syndrome is an immune-mediated disorder, which generally occurs after infection and affects the peripheral nerves and nerve roots. However, HLH is a disorder of excessive inflammation and tissue destruction caused by a hyperimmune state. In individuals previously infected with COVID-19, the concurrent emergence of HLH and GBS is infrequent, as they are distinct disease entities with disparate underlying pathophysiological mechanisms and clinical manifestations. Nonetheless, GBS and HLH can occur in patients with COVID-19 infection. To the best of our knowledge, ours is the first case of concurrent HLH and GBS in a patient with a recent history of COVID-19 infection. Although much about COVID-19 remains to be elucidated, it is most probably an affliction of the immune system, causing both hyper-inflammatory and autoimmune reactions.

The pathophysiology of HLH and GBS is reportedly impacted by the S or spike protein of SARS-CoV-2. This protein targets angiotensin-converting enzyme 2 (ACE2), which is predominantly expressed in extrapulmonary organs such as the heart, kidneys, blood vessels, and gastrointestinal system[1]. TMPRSS2 and the endosomal cysteine proteases cathepsin B and L (CatB/L) are responsible for the activation of the viral S proteins[2]. Subsequently, the virus absorbs the ACE2 receptor, which reduces its expression on the cell membrane[3]. ACE2 is an enzyme that catalyzes the cleavage of angiotensin (Ang) II into Ang (1-7) and Ang I into Ang (1-9) (Figure 2)[4].

Ang (1-7), the main product of ACE2 activity, binds to the Mas receptor and produces vasodilation, antioxidant effects, and antiproliferative effects, which attenuate the Ang II action[5]. Therefore, the ACE2/Ang (1-7)/Mas axis counterbalances the ACE/Ang II/AT1R axis and is an essential regulatory pathway of the renin-angiotensin-aldosterone system (RAAS). The virus-mediated negative regulation of ACE2 causes a burst of inflammatory cytokine release via the downregulation of the RAAS (ACE/Ang II/AT1R axis) and attenuation of the Mas receptor (ACE2/MasR axis)[6]. This process elevates the Ang II levels and triggers the release of TNF-α and soluble IL-6. Consequently, multiple cytokines, including vascular endothelial growth factor, monocyte chemoattractant protein-1, IL-8, and IL-6 are implicated. This IL-6 surge impairs innate and acquired immune responses[7], which leads to the attack of self-antigens by lymphocytes and widespread organ dysfunction in HLH[8].

Owing to molecular mimicry of gangliosides and spike glycoproteins or epitopes of SARS-CoV-2, antibodies produced

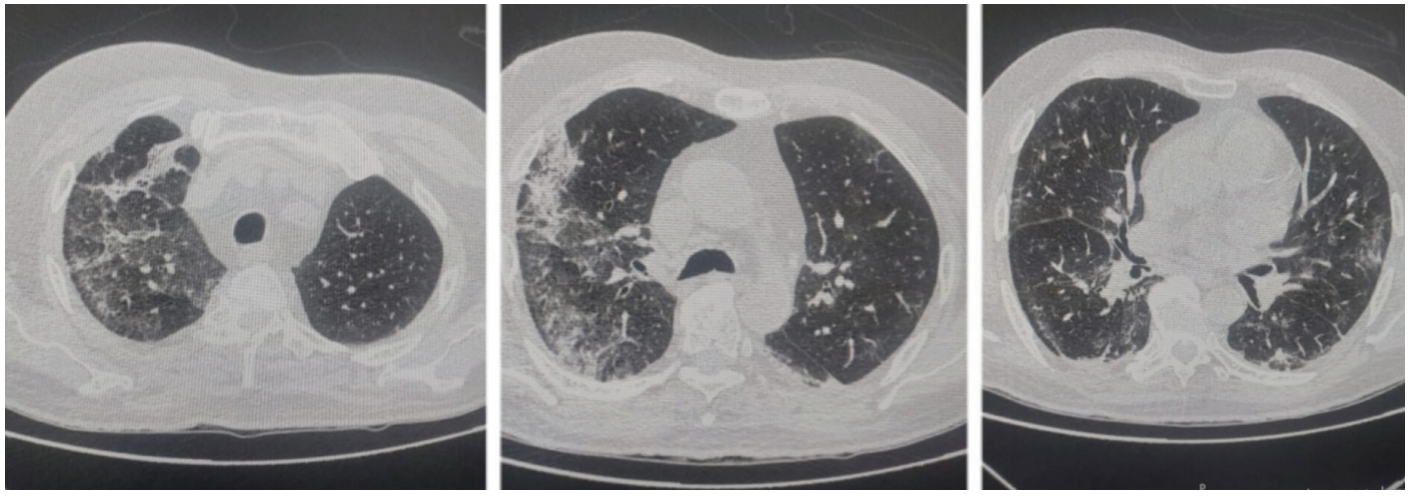

Figure 1. HRCT chest showing ground glass opacities irregular densities and reticular opacities with tractional bronchiectasis concerning fibrosis in bilateral lung fields to be correlated for sequelae to prior viral panel

HRCT: High-resolution computed tomography

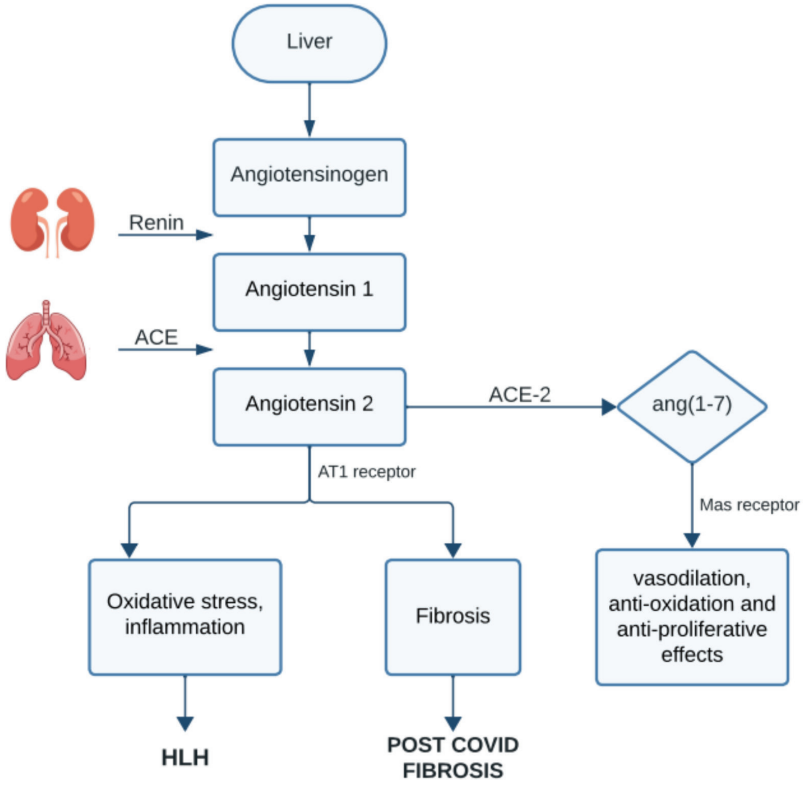

Figure 2. RAS cascade showing the angiotensin peptide metabolic pathway
HLH: Hemophagocytic lymphohistiocytosis

in response to the virus may bind to the gangliosides present on peripheral neurons via the interaction of T- and B-cells. These autoantibodies bind to the nodes of Ranvier, prompting local complement-mediated damage and formation of the membrane attack complex. This subsequently results in Wallerian degeneration (Figure 3)[9].

Given the patient's tropical origin and presence of fever, the initial investigations focused on prevalent infections in such regions. However, further investigations revealed no evidence of an infectious etiology. Considering the presence of fever, bicytopenia, elevated levels of triglycerides and ferritin, and bone marrow alterations, our patient met the criteria for HLH. According to the HLH 2004 study[10], a diagnosis of HLH can be made if there is molecular confirmation of pathologic mutations of PRF1, STX11, UNC13D, SH2d1A, Munc18-2, Rab27a, or BIRC4 or the presence of any five of the following eight criteria: fever >38.5 °C, splenomegaly, peripheral blood cytopenia (bicytopenia/pancytopenia), hypertriglyceridemia (>265 mg/dl) and/or hypofibrinogenemia (>150 mg/dl), low or absent natural killer cell activity, elevated ferritin level (>500 ng/ml), hemophagocytosis in the bone marrow, spleen, lymph node, or liver, and elevated soluble CD25 level of >2 standard deviations above the mean.

Furthermore, the acute onset of ascending weakness, absence of deep tendon reflexes, NCS findings, and presence of albuminocytologic dissociation in the CSF confirmed the diagnosis of GBS. NCS is the primary ancillary diagnostic test. Electrodiagnostic studies often reveal patchy demyelination, which presents as conduction block, reduced motor conduction velocities, prolonged latencies, and dispersed responses[11]. Analysis of the CSF typically demonstrates a classic pattern of albuminocytologic dissociation, indicating a normal white blood cell count and elevated protein level[12].

In our patient, IVIG therapy was administered. IVIG therapy has demonstrated efficacy in a subset of adult patients with secondary HLH, when initiated early in the macrophage activation process, particularly during the rise in ferritin levels[13].

Conclusion

The SARS-CoV-2 infection can cause both acute and long-term complications inherent to its multisystemic effects. Guillain-Barre syndrome and HLH are distinct disease entities that involve different organ systems with distinct pathophysiologies resulting from a prior infection.

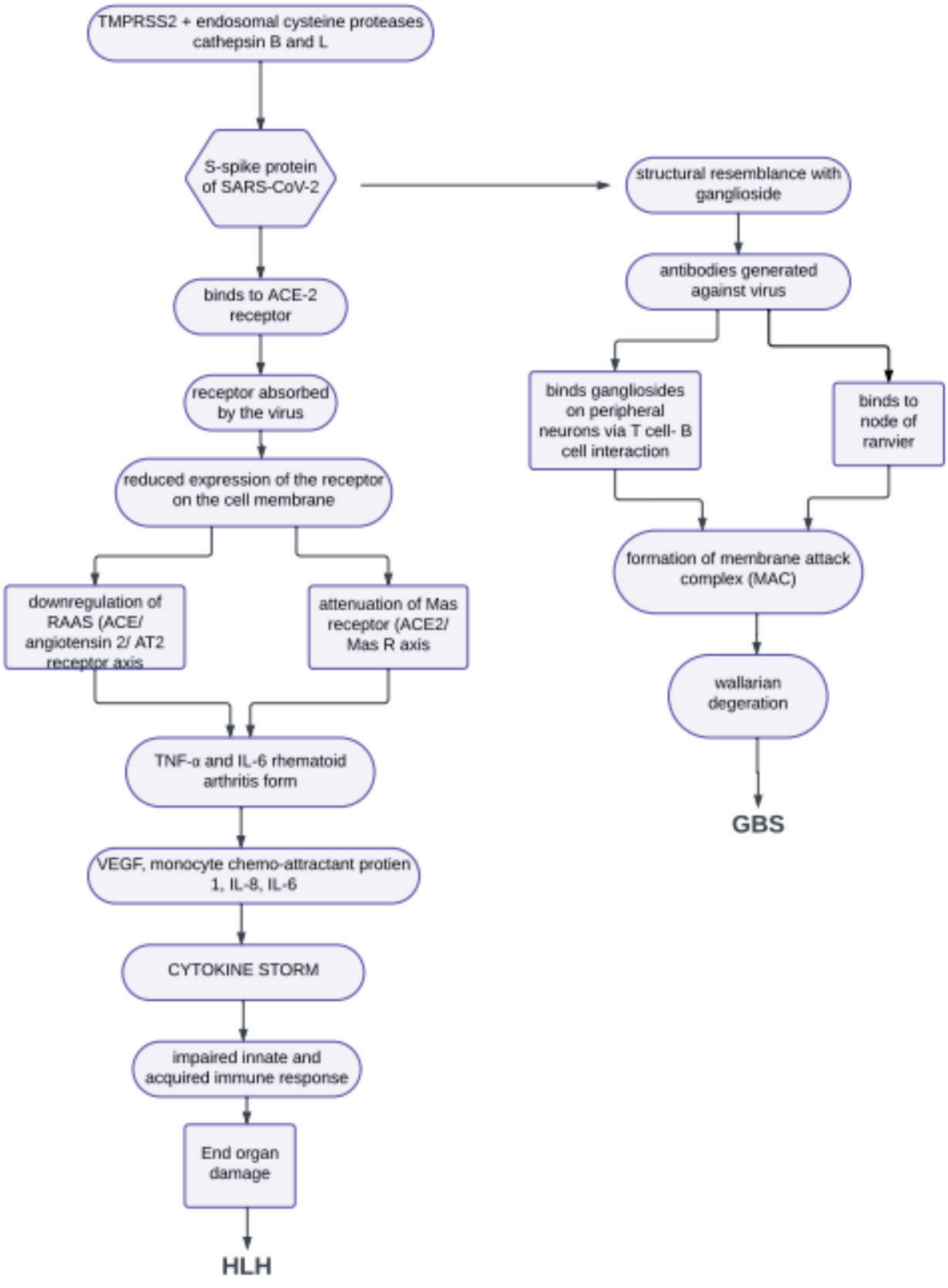

Figure 3. Flow chart 2

HLH: Hemophagocytic lymphohistiocytosis, GBS: Guillain-Barre syndrome

Ethics

Informed Consent: An informed consent was obtained from the patient for the publication of this case report and the use of their medical data.

Authorship Contributions

Surgical and Medical Practices - Concept - Design - Data Collection or Processing - Analysis or Interpretation - Literature Search - Writing: A.T., A.A.A., A.M.A.

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

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

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