

CLINICAL PROBLEM-SOLVING

Caren G. Solomon, M.D., M.P.H., *Editor*

Calm before the Storm

Manuel B. Braga Neto, M.D., Ph.D., Andrew D. Badley, M.D.,
Sameer A. Parikh, M.B., B.S., Rondell P. Graham, M.B., B.S.,
and Patrick S. Kamath, M.D.

In this Journal feature, information about a real patient is presented in stages (boldface type) to an expert clinician, who responds to the information by sharing relevant background and reasoning with the reader (regular type). The authors' commentary follows.

A 61-year-old man was evaluated in West Africa for a 1-week history of jaundice, light-colored stools, dark urine, pruritus, fatigue, and fever, with temperatures up to 38.5°C, without chills. He had dull pain in the right upper quadrant of the abdomen and had nausea but no vomiting.

Jaundice results from overproduction of bilirubin, impairment of bilirubin uptake or conjugation in the liver, hepatocellular inflammation, or biliary obstruction. History taking that obtains information about transfusions, travel, and the use of alcohol, medication, herbal supplements, and illicit drugs may provide clues to the cause of jaundice. In West Africa, viral hepatitis A, B, and E and the use of herbal drugs are common causes of jaundice. Drug-induced liver injury is always a consideration in patients with elevated liver-enzyme levels, and it is important to know whether this patient is taking medications, but other causes of liver injury must be ruled out.

The presence of dark urine, light-colored stools, and pruritus suggests cholestasis, which can be intrahepatic (owing to impaired canalicular excretion of bilirubin) or extrahepatic (owing to obstruction of the extrahepatic bile ducts). Cholelithiasis, the most common cause of extrahepatic cholestasis with fever, is unlikely to be the cause in the absence of biliary colic but cannot be ruled out. Pancreatic cancer or other malignant conditions that cause biliary obstruction can manifest with abdominal pain or painless jaundice and should be considered, particularly in older persons.

Intrahepatic cholestasis with fever is usually attributed to viral or alcohol-related hepatitis or to sepsis. Drug-induced liver injury is a common cause of cholestasis. Less common causes include autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis, lymphoma, and granulomatous infiltration of the liver by sarcoidosis or tuberculosis. Fever may also suggest a malignant cause.

The patient had a history of hypertension and hyperlipidemia. He did not smoke or consume alcohol. There was no family or personal history of liver disease or inflammatory bowel disease. The patient's medications included amlodipine and carvedilol for hypertension and esomeprazole for gastroesophageal reflux. Six weeks before jaundice developed, the patient was hospitalized with coronavirus disease 2019 (Covid-19). He received intravenous glucocorticoids (remdesivir was not available in his country), and broad-spectrum antibiotics (meropenem, ceftriaxone, and doxycycline) were administered for a presumed secondary bacterial pulmonary infection. The antibiotics were discontinued 1 month before the current presentation. The patient's

From the Division of Gastroenterology and Hepatology (M.B.B.N., P.S.K.), the Division of Infectious Diseases (A.D.B.), and the Division of Hematology (S.A.P.), Department of Medicine, and the Department of Laboratory Medicine and Pathology (R.P.G.), Mayo Clinic, Rochester, MN. Dr. Kamath can be contacted at kamath.patrick@mayo.edu or at the Division of Gastroenterology and Hepatology, Mayo Clinic College of Medicine and Science, 200 First St. SW, Rochester, MN 55905.

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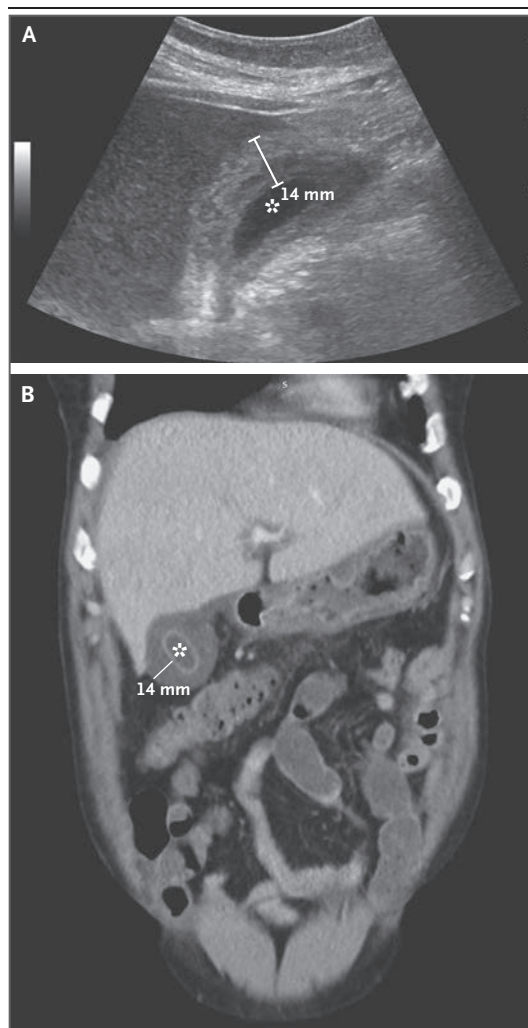


Figure 1. Imaging of the Gallbladder and Abdomen.

An ultrasound image of the gallbladder (Panel A) and a coronal view of the abdomen on computed tomography (Panel B) show a markedly thickened gallbladder wall measuring 14 mm (normal, ≤ 3 mm) without associated biliary duct dilatation. The gallbladder lumen is highlighted (asterisk).

aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were transiently elevated during his hospitalization for Covid-19 but were normal at the time of discharge.

Amlodipine, carvedilol, and esomeprazole are not typically associated with drug-induced liver injury. Antibiotics are a common cause of liver injury, but fever is uncommon and jaundice typically appears while the patient is receiving antibiotics, or days after the patient completes the antibiotic regimen, and then resolves in the following weeks. Although the onset of jaundice

has been recognized to occur 1 to 2 weeks after the end of treatment with ceftriaxone, the onset 4 weeks after discontinuation of antibiotics, as in this case, is probably not related to drugs and suggests an alternative cause for the liver disease — either viral or autoimmune hepatitis or a malignant condition. Primary sclerosing cholangitis is a less likely cause in the absence of inflammatory bowel disease.

On examination at presentation in Africa, the patient was noted to be jaundiced, with no hepatosplenomegaly or ascites. The gallbladder was not palpable.

The total bilirubin level was 3.5 mg per deciliter ($59.8 \mu\text{mol}$ per liter; normal range, 0.2 to 1.2 per deciliter [3.4 to $20.5 \mu\text{mol}$ per liter]) with a direct fraction of 2.9 mg per deciliter; ALT 495 U per liter (normal range at that hospital, 0 to 41), AST 127 U per liter (normal range at that hospital, 0 to 40), and alkaline phosphatase 251 U per liter (normal range at that hospital, 40 to 130). Results of serologic testing for hepatitis A, B, C, and E, human immunodeficiency virus (HIV) type 1 and 2 antigens and antibodies, antimitochondrial antibodies, anti-smooth-muscle antibodies, and antinuclear antibodies were negative. A complete blood count was within normal limits. Ultrasonography (Fig. 1A) and computed tomography (Fig. 1B) showed marked thickening of the gallbladder wall without evidence of a tumor, hepatosplenomegaly, or lymphadenopathy. Tenderness was not elicited by the pressure of the ultrasound probe when it was applied over the gallbladder.

Hyperbilirubinemia in this patient would be classified as conjugated (with a direct fraction of $>20\%$ of the total bilirubin) and may be due to hepatocellular injury or cholestasis. Differentiation of hepatocellular injury from cholestasis requires measurement of AST, ALT, and alkaline phosphatase levels, since the two conditions cannot be differentiated purely by the degree of elevation of the serum bilirubin level.

The R value, a ratio calculated by the formula $[(\text{ALT level} \div \text{ALT ULN}) \div (\text{alkaline phosphatase level} \div \text{alkaline phosphatase ULN})]$, with ULN denoting the upper limit of the normal range, is used to help differentiate hepatocellular injury from cholestasis. An R value greater than 5 suggests hepatocellular injury but should not be interpreted in isolation; in combination with pruritus and an elevated alkaline phosphatase

level, it suggests a mixed picture of hepatocellular injury and cholestasis. The absence of biliary dilatation on abdominal imaging indicates intrahepatic cholestasis; a cholangiogram is therefore not required. The patient reports no history of alcohol use, and the ratio of ALT to AST of more than 1 also argues against alcohol-associated hepatitis. With drug-induced liver injury, primary biliary cholangitis, autoimmune hepatitis, or viral hepatitis A, B, C, or E unlikely to be the cause, other viral causes (e.g., cytomegalovirus [CMV], Epstein–Barr virus [EBV], and herpes simplex virus [HSV]), rickettsia, and even fungal infections that cause cholestasis must be considered, especially given that patients with Covid-19 are at risk for aspergillus and *Candida auris* infections. Hepatic involvement in Covid-19, which ranges from asymptomatic liver-test abnormalities to liver failure, is also a diagnostic consideration.

Acalculous cholecystitis, gallbladder inflammation that may occur in patients who are critically ill, causes gallbladder wall thickening. However, the absence of pericholecystic fluid collections or tenderness over the gallbladder on ultrasound examination is inconsistent with this diagnosis.

Bacterial cultures and serologic testing for CMV, EBV, HSV, rickettsia, and fungi were negative. Because the symptoms continued for 3 weeks after his presentation in Africa, the patient was referred to our center and traveled here by commercial airline. On presentation to our center, he reported deepening jaundice, fatigue, fever (with temperatures up to 39°C), and a 1-week history of facial and lip swelling. On examination, he was afebrile. He had swelling of the lips, face, and eyelids and had conjunctival icterus but no conjunctivitis, rash, or spider nevi. He had an enlarged, tender liver without splenomegaly. There was no muscle wasting. The hemoglobin level was 12.9 g per deciliter (8.0 mmol per liter), platelet count 261 per microliter, and white-cell count 4.6 per microliter, with an absolute neutrophil count of 260 per microliter (normal range, 1500 to 6400). The serum creatinine level was 1.3 mg per deciliter (114.9 μ mol per liter) with normal electrolytes. The total bilirubin level was 14.3 mg per deciliter (244.5 μ mol per liter), direct bilirubin 13.2 mg per deciliter (225.7 μ mol per liter; normal range, 0 to 0.3 mg per deciliter [5.1 μ mol per liter]), ALT 305 U per liter (normal range, 7 to 55), AST 156 U per liter (normal range, 8 to 48), alka-

line phosphatase 241 U per liter (normal range, 40 to 129), and albumin 3.0 g per deciliter (normal range, 3.5 to 5.0), and the international normalized ratio (INR) was 2.0. A polymerase-chain-reaction test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was negative; tests for SARS-CoV-2 nucleocapsid and spike antibodies were positive. An ultrasound examination confirmed hepatomegaly, normal spleen size, and gallbladder wall thickening, without tenderness or biliary dilatation.

Laboratory investigation now shows a mixed pattern of cholestasis and hepatocellular injury (with an R value between 2 and 5). The prolonged INR and presence of hypoalbuminemia and hyperbilirubinemia suggest severe liver injury, but the absence of hepatic encephalopathy rules out acute liver failure. Hypoalbuminemia and prolonged INR in the absence of hyperbilirubinemia may reflect poor oral intake and vitamin K deficiency that may occur with antibiotic treatment. The facial and gallbladder swelling accompanied by liver-test abnormalities raises the question of a systemic inflammatory process. Hemophagocytic lymphohistiocytosis (HLH) should be considered in all patients with undiagnosed jaundice, fever, and systemic inflammatory features.

The serum ferritin level was 2292 ng per milliliter (normal range, 24 to 336), C-reactive protein (CRP) 58.7 mg per liter (normal range, $\leq$ 8), and D-dimer 970 ng per milliliter (normal range, $\leq$ 500).

The elevated levels of CRP, D-dimer, ferritin, and neutropenia are consistent with a severe systemic inflammatory response. This degree of elevation in the serum ferritin level is usually limited to hemochromatosis, hematologic cancer, adult-onset Still's disease, and HLH. Viral hepatitis is associated with an elevation in the serum ferritin level that parallels the ALT elevation, and may even be high enough to arouse suspicion for HLH syndrome, but viral hepatitis has been ruled out by serologic testing.

The rapid worsening of the liver disease with systemic inflammation argues against hemochromatosis. Hematologic cancer is an unlikely diagnosis, given the normal hemoglobin level and platelet and total white-cell counts and the absence of lymphadenopathy and splenomegaly. Adult-onset Still's disease is a diagnosis of exclu-

sion, and typical features are absent (e.g. high, spiking quotidian fever [temperature $\geq 39^{\circ}\text{C}$] that occurs in the evening with return of normal temperature in the morning, rash typical of adult-onset Still's disease, sore throat, and arthralgia).

The most likely diagnoses to explain the systemic inflammation and liver disease are post-Covid-19 multisystem inflammatory syndrome in adults (MIS-A) or HLH, both uncommon complications of Covid-19 infection. The diagnosis of MIS-A requires meeting three criteria: at least one of the two primary criteria — severe cardiac illness, or rash and nonpurulent conjunctivitis — plus the presence of neurologic signs and symptoms, hypotension, gastrointestinal symptoms, or thrombocytopenia, as well as laboratory evidence of inflammation and SARS-CoV-2 infection. Facial swelling and gallbladder thickening have been described in post-Covid-19 multisystem inflammatory syndrome in children (MIS-C).

HLH can be primary (owing to genetic defects involving cytotoxic T cells and natural killer [NK] cells) or secondary (induced by viral infections and autoimmune or malignant disorders and usually associated with liver injury). The diagnosis of HLH requires the presence of five of the following eight criteria: fever (temperature $\geq 38.5^{\circ}\text{C}$); splenomegaly; peripheral blood cytopenia (with at least two of the following laboratory values: hemoglobin level <9 g per deciliter [<5.6 mmol per liter], a platelet count $<100,000$ per microliter, or an absolute neutrophil count <1000 per microliter); hypertriglyceridemia (fasting triglycerides level >265 mg per deciliter) or hypofibrinogenemia (fibrinogen level ≤ 150 mg per deciliter) or both; hemophagocytosis in the bone marrow, spleen, lymph nodes, or liver; low or absent NK-cell activity; a ferritin level ≥ 500 μg per liter; and an elevated level of soluble interleukin-2 receptor α . Additional inflammatory markers, echocardiography, a liver biopsy, and bone marrow biopsy are warranted to narrow the diagnosis.

The patient became more tired the next day and was hospitalized. He was afebrile and normotensive; oriented to time, place, and person; and had no overt hepatic encephalopathy. Cardiovascular examination and echocardiography were normal. Three sets of blood cultures were obtained, after which treatment with cefepime and metronidazole was started, since high-dose glucocorticoids

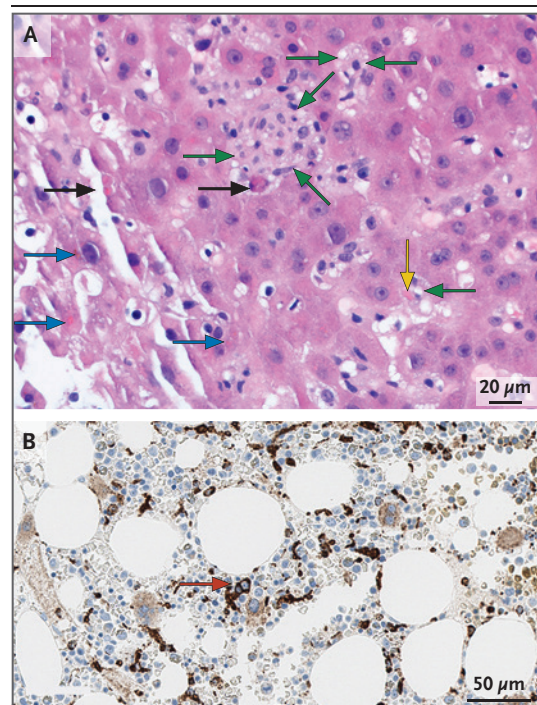


Figure 2. Findings on Biopsy of Liver and Bone Marrow.

Panel A shows hemophagocytosis, with the macrophages (green arrows) engulfing red cells (yellow arrow). Cholestatic hepatitis evidenced by hepatocytes with cholestasis (bile pigment, blue arrows) and dying hepatocytes (apoptosis, black arrows) is noted. Hemophagocytosis on bone marrow biopsy is shown in Panel B (red arrow).

were being considered and sepsis as a cause of jaundice and fever was not completely ruled out.

Prednisone administered orally at a dose of 60 mg daily was started after a transjugular liver biopsy and blood test for inflammatory markers were performed. Blood-culture results were negative. Pathological evaluation of the liver specimen revealed moderately active hepatitis with cholestasis and sinusoidal histiocytosis with hemophagocytosis (Fig. 2A). Only occasional hemophagocytosis was seen on a bone marrow biopsy (Fig. 2B). The serum cytokine panel showed a TNF- α level of 56.4 pg per microliter (normal value, <10.0), an interleukin-6 level of 7.8 pg per microliter (normal value, <5.0), and an interleukin-2 receptor α level greater than 4000 pg per microliter (normal value, ≤ 959). NK-cell activity was normal. A fasting triglyceride level was 329 mg per deciliter (normal level, <150), and the fibrinogen level was 353 mg per deciliter (normal range, 200 to 500). The H score, which estimates the risk of secondary HLH on the basis of clinical and biologic

variables and hemophagocytosis on the basis of histologic characteristics, was calculated to be 189, which indicates a 79% probability of secondary HLH. (H scores range from 0 to 337, with higher scores associated with increased probability of disease.)

Five of eight criteria for HLH (fever, hypertriglyceridemia, hemophagocytosis shown on biopsy, a high ferritin level, and an elevated level of soluble interleukin-2 receptor α) were met, and the H score also supports the diagnosis of HLH. In the absence of severe cardiac illness, rash, and conjunctivitis, the findings are consistent with HLH as the post-Covid-19 hyperinflammatory syndrome.

The CRP level normalized 3 weeks after the patient started receiving glucocorticoid treatment, at which time a slow taper was begun. The serum ferritin and D-dimer levels normalized after 7 weeks of glucocorticoid therapy. After 9 weeks of treatment, with the patient receiving prednisone at a dose of 7.5 mg daily, the serum bilirubin and alkaline phosphatase levels had normalized. At 6-month follow-up, the patient had resumed normal activities, and the levels of AST and ALT were less than two times the ULN.

COMMENTARY

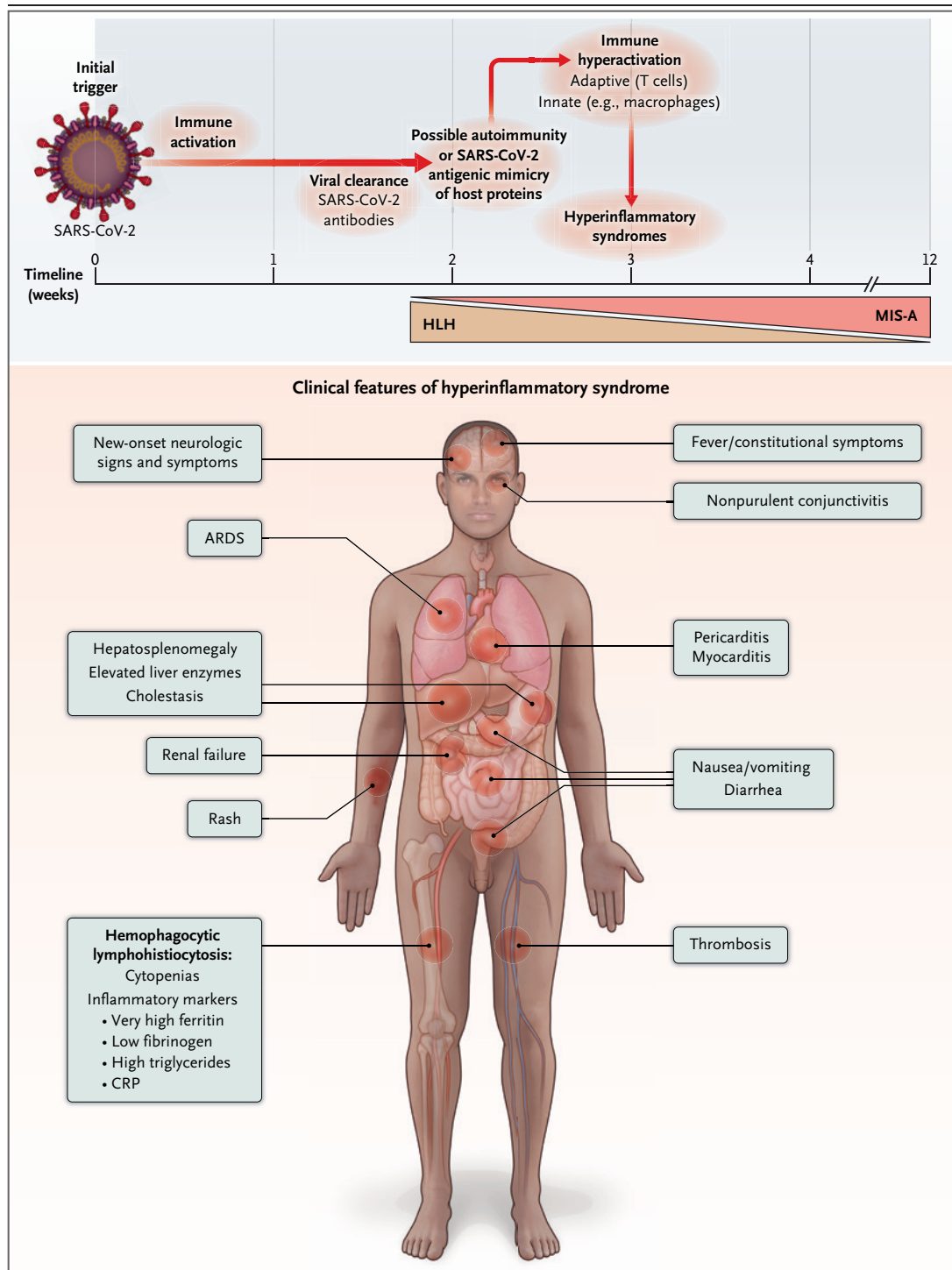
This previously healthy 61-year-old man presented with jaundice as well as features of both cholestasis and hepatocellular injury weeks after having Covid-19. Viral, autoimmune, and drug- or alcohol-associated hepatitis were ruled out. The unclear cause of jaundice in the presence of features of systemic inflammation aroused suspicion for HLH. The patient's symptoms met the diagnostic criteria for secondary HLH, and in the absence of other causes, post-Covid-19 HLH was diagnosed.

HLH is diagnosed when patients have at least five of eight diagnostic criteria that include physical examination findings, laboratory tests including elevated inflammatory markers, and histologic findings. Our patient's fever, hypertriglyceridemia, hemophagocytosis on a bone marrow biopsy, high level of ferritin, and elevated level of soluble interleukin-2 receptor α were consistent with the diagnosis of HLH, even in the absence of other criteria (splenomegaly, cytopenias, and low or absent NK-cell activity).¹ In

addition, this patient had an H score of 189, which was strongly suggestive of secondary HLH. In a retrospective study, the best cutoff value for diagnosis was an H score of 169, which had a sensitivity of 93% and specificity of 86% for HLH.² Details about H scores are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.

A hyperinflammatory syndrome may occur during severe Covid-19 illness or after Covid-19 has resolved.³⁻⁵ "Cytokine storm" is an umbrella term that encompasses the exaggerated activation of the immune system, systemic inflammation, and life-threatening multiorgan failure that may follow SARS-CoV-2 infection. Although there has been no broadly accepted definition of cytokine storm, three criteria have been proposed for the diagnosis: elevated circulating cytokine levels, acute systemic inflammatory symptoms, and cytokine-driven organ dysfunction.⁶ Profound leukopenia is common, and mononuclear cell infiltrates in the lungs, spleen, heart, and lymph nodes have been observed on postmortem analyses. The pattern of elevations in cytokine levels seen in severe Covid-19 most often includes elevations in interleukin-6, interleukin-7, TNF, interleukin-2 receptor α , and inflammatory cytokines such as CCL2, CCL3, and CXCL10 — all of which are products of hyperactivated monocytes and macrophages. Indeed, in single-cell analysis of bronchoalveolar lavage fluid samples, patients with severe Covid-19 have been found to have higher numbers of inflammatory macrophages than those with mild disease or healthy controls, an observation that supports a central role of macrophage activation in the pathogenesis of severe Covid-19 disease.⁷ HLH associated with viral infections or autoimmune disorders is similarly characterized by macrophage polarization toward a hyperinflammatory phenotype and thus has pathophysiological overlap with Covid-19 pathogenesis.

The clinical manifestations of Covid-19-associated cytokine storm include fever, fatigue, anorexia, acute respiratory distress syndrome, liver injury, and multiorgan failure (Fig. 3).⁶ These features are apparent in patients with severe Covid-19 pneumonia⁸ and overlap with clinical features associated with the two well-characterized, immune-mediated, severe systemic inflammatory syndromes that may follow Covid-19 illness. HLH usually occurs less than 14 days after the onset of infection,³ and MIS-C and MIS-A



typically occur several weeks after Covid-19. The delayed manifestation of HLH in our patient highlights the fact that immune-mediated complications probably represent a spectrum of disorders rather than distinct syndromes. The timeline, symptoms, and laboratory features of prolonged hyperinflammatory Covid-19 may also

overlap with those of HLH and MIS-A, sometimes making distinguishing the conditions difficult.⁸ Among reported patients with HLH associated with Covid-19, most were male, with a median age of 56 years; many cases occurred in the context of prolonged severe acute Covid-19. Most patients received care in an intensive care unit,

Figure 3 (facing page). Pathogenesis and Manifestations of Post-Covid-19 Hyperinflammatory Syndrome.

Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is followed a week or so later by activation of the immune system, which coincides with the development of other Covid-19 symptoms. When patients have a hyperinflammatory response and escalating oxygen requirements despite monoclonal antibodies or remdesivir with or without dexamethasone, either baricitinib or tocilizumab therapy is usually considered. Viral clearance is most often associated with resolution of symptoms. In a subgroup of patients, despite viral clearance and sometimes after an asymptomatic interval, hyperactivation of both innate and adaptive immune systems persists and there is an excessive release of proinflammatory cytokines leading to the hyperinflammatory syndrome. Hemophagocytic lymphohistiocytosis (HLH) and multisystem inflammatory syndrome in adults (MIS-A) are examples of the hyperinflammatory syndrome that induces fever and constitutional symptoms and are strongly considered when the patient's symptoms persist or worsen after viral clearance. HLH usually occurs within 14 days after onset of Covid-19 infection, whereas MIS-A usually occurs after 2 weeks and up to 12 weeks after infection. However, the hyperinflammatory syndrome is most often seen in patients with severe Covid-19, and when prolonged it may overlap with HLH. Some patients who receive a diagnosis of prolonged Covid-19 may in fact have HLH. Typical features of HLH include hepatosplenomegaly, cytopenias, coagulopathy, liver dysfunction, and hemophagocytosis in bone marrow or tissue (such as the liver). In MIS-A, cardiac dysfunction, rash with nonpurulent conjunctivitis, and gastrointestinal symptoms are more frequent,⁵ although cytopenias and liver dysfunction may also be present. Clinical features of HLH and MIS-A overlap, and the specific diagnosis is made on the basis of diagnostic criteria. ARDS denotes acute respiratory distress syndrome and CRP C-reactive protein.

and overall mortality was 46%, similar to that reported in severe Covid-19.⁹⁻¹² Hyperferritinemia, elevated AST levels, and fever were the main presenting features. Hemophagocytosis was present in 83% of cases in which a biopsy was performed. However, only eight patients met at least five of the eight criteria required to make a diagnosis of HLH; thus, treatment with glucocorticoids should be considered even if patients do not meet the required diagnostic criteria.

Prompt identification of cytokine storm is critical for management. Aside from supportive care, immunosuppressive therapy is necessary to contain the damage induced by the exaggerated immune response. Case series have shown that in patients with secondary HLH-associated cytokine storm, treatment with glucocorticoids, interleukin-1 β inhibitors, or Janus kinase (JAK) inhibitors JAK1 and JAK2 provides benefits.^{13,14} Although patients with HLH and hepatic involvement may have prompt overall improvement after glucocorticoid therapy, persistent AST and ALT elevation for more than 1 year after hospital discharge has been reported.¹⁵

Weeks after this patient had Covid-19, a severe hyperinflammatory syndrome consistent with HLH developed. The prompt alleviation of the constellation of symptoms and signs after immunosuppressive therapy was started underscores the importance of early recognition of this entity.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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