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CASE REPORT

A COVID-19 mystery: multisystem inflammatory syndrome in adults (MIS-A) associated with splenic rupture

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SUMMARY

Severe inflammation and one or more extrapulmonary organ dysfunctions have been observed in those who had recently developed COVID-19, except for a macrophage activation syndrome-like picture. A 50-year-old female patient was admitted to the emergency department with fever and a history of COVID-19 infection. More than one area of hemophagocytosis was found in the bone marrow aspiration. The HLH-2004 protocol was started with neurological involvement and she underwent splenectomy due to massive intra-abdominal bleeding secondary to splenic laceration on the 3rd day. Multiple microthrombosis and infarcts were observed in the splenectomy specimen. At the 4th week of the treatment, she was discharged with oral agents. Splenic microthrombosis and splenic rupture due to "multisystem inflammatory syndrome in adults" are the most important findings of this report.

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INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is an acute and rapidly progressive systemic inflammatory disease characterized by cytopenia, excessive cytokine production and hyperferritinemia (Soy *et al.*, 2021). Common clinical manifestations of HLH are acute-continuous fever, lymphadenopathy, hepatosplenomegaly, and multiple organ failure. There are primary and acquired (secondary, reactive) forms of HLH. The primary form is seen mostly in childhood and is caused by various inherited mutations, and is therefore called familial HLH (Soy *et al.*, 2021). Secondary, reactive, or acquired HLH (sHLH) can be triggered by malignancy, infection, and autoimmunity, and occurs in children, adolescents, and adults (Carter *et al.*, 2019). When sHLH occurs in the context of autoimmunity, it is referred to as macrophage activation syndrome (MAS). The clinical syndrome was first described in the 1980s in children, complicating severe cases of systemic-onset juvenile idiopathic arthritis (sJIA) (Silverman *et al.*, 1983; Hadchouel *et al.*, 1985).

In patients with severe COVID-19 pneumonia, high serum ferritin, CRP, and D-Dimer levels, as well as hypercytokinemia similar to that in MAS, suggest the development of severe MAS-like inflammation in COVID-19 pneumonia (Tay *et al.*, 2020); however, the high ferritin levels during COVID-19 are not as high as might be expected in MAS (Mehta *et al.*, 2020). In addition, hepatosplenomegaly, thrombocytopenia, hypofibrinogenemia during MAS are not common in COVID-19-associated MAS-like conditions (McGonagle *et al.*, 2020; McGonagle *et al.*, 2021). For these reasons, the MAS-like clinical picture during COVID-19 does not fully meet the classic MAS-HLH criteria. Severe inflammation (elevated CRP, ferritin, D-Dimer, cardiac and liver enzymes) and one or more extrapulmonary organ dysfunctions have been observed in those who had recently developed Sars-Cov2, except for a MAS-like picture. This clinical picture is defined as "multisystem inflammatory syndrome in adults" (MIS-A) (Morris *et al.*, 2020).

The MIS-A case definition used in this study included the following six criteria (Morris *et al.*, 2020):

1. A severe illness requiring hospitalization in an individual aged ≥21 years;

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2. Current or past infection with SARS-CoV-2;
3. Severe dysfunction in one or more extrapulmonary organ systems;
4. Laboratory evidence of elevated inflammatory markers (e.g., CRP, ferritin, D-dimer, interleukin [IL]-6);
5. Absence of severe respiratory illness;
6. Absence of an alternative unifying diagnosis

In this report, we present a patient with a diagnosis of COVID-19-associated MIS-A and followed-up. Informed consent was obtained from our patient to publish the presentation.

CASE REPORT

A 50-year-old female patient with hypertension and hypothyroidism was admitted to the emergency department with complaints of fever, nausea, and cough. On physical examination in the emergency room, fever was 38.9 °C and the left upper quadrant of the abdomen was painful with palpation. There was 5 cm palpable splenomegaly below the costal margin. In the laboratory examination: Leukocyte was 2650/mm^3, Hb.: 8.8 gr/dL, platelet: 76000/mm^3, neutrophil: 1750 /mm^3, lymphocyte: 540 /mm^3, D-Dimer: 16.81 mcg/ml, ferritin 3690.7 mcg/L, creatinine 1 mg/dl, AST: 74.4 IU/ml, ALT: 41.2 IU/L, and CRP was 172.4 mg/L. Viral serology was unremarkable (Hepatitis B, C, Epstein-Barr, Parvovirus B-19, Varicella zoster, herpes simplex type1-2, cytomegalovirus and rubella). She was hospitalized for further investigation of pancytopenia and splenomegaly. It was learned that she had been through a COVID-19 infection a month prior to admission.

In the portal vein, doppler ultrasonography of the patient (whose peripheral smear did not show atypical cells), liver size was 175 and spleen size was 190 mm in the long axis. The splenic and hepatic vein were observed naturally, and there was no thrombus. Two nasopharyngeal COVID-19 PCR samples repeated 48 hours apart were negative. There was no pathological imaging finding in thorax tomography. Autoimmunity panel was unremarkable (Anti-nuclear antibody, anti-ds DNA, rheumatoid factor, anti CCP, p-ANCA, c-ANCA, lupus anticoagulant, anti-phospholipid-panel, C3, C4). Blood cultures were negative.

On the 3rd day of the patient's follow-up, upon the increase in abdominal pain, a grade 3 laceration was observed in the spleen in the contrast-enhanced upper abdominal magnetic resonance imaging (MRI). With persistent fever, her cooperation and orientation were limited. In the neurological examination of the patient, she had left lateral gaze limitation. Diffuse T2W signal increases were observed in the deep white matter in the cranial MRI imaging. In the laboratory examination on the 3rd day, leukocyte was 4250 /mm^3, Hb.: 7.8 gr/dl, platelet: 41000 /mm^3, neutrophil 3120 /mm^3, lymphocyte 750 /mm3, creatinine: 0.7 mg/dl, AST.: 113 IU/L, ALT: 20.2 IU/L, LDH: 986 IU/L, ferritin 1023 mcg/L, CRP: 180.8 mg/L and INR: 2. More than one area of hemophagocytosis was found in the bone marrow aspiration of the patient with the preliminary diagnosis of MAS. The patient was diagnosed with COVID-19-associated MIS-A.

The HLH-2004 protocol was started for the patient with a concomitant neurological involvement. In the first 2 weeks: etoposide 2x150 mg/m2/week, dexamethasone 10 mg/m2/day and cyclosporine 2x 3 mg/kg/day intravenous. The patient's cerebrospinal fluid sampling was unremarkable. There was no growth in

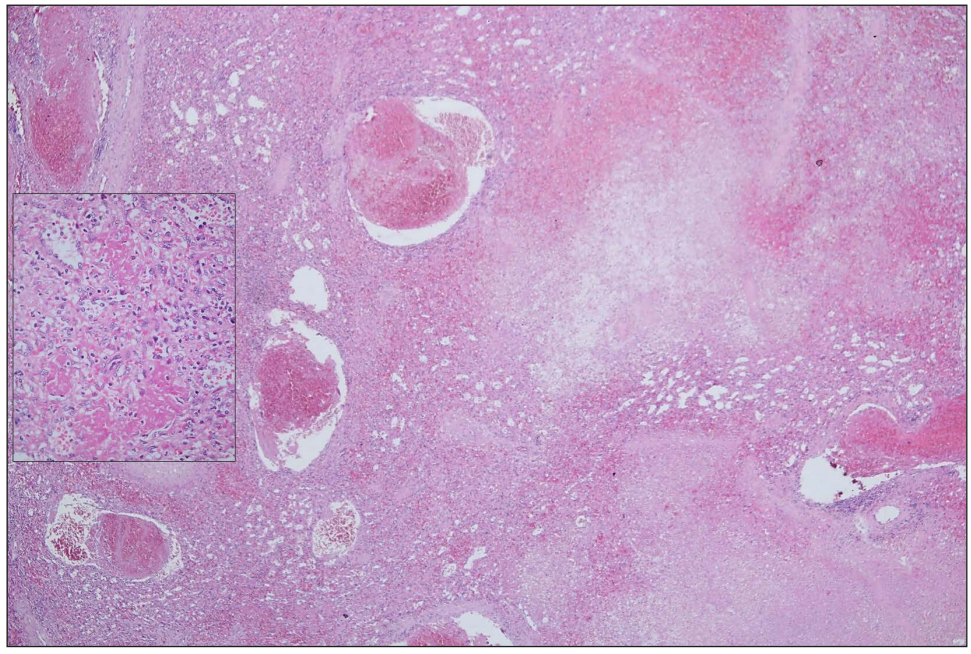

Figure 1 - *Histological sections of the spleen show fresh and early organized thrombi in many vessels (left), fibrin thrombi in the parenchyma (inset), large areas of infarction and necrosis (right) (Hematoxylin & Eosin).*

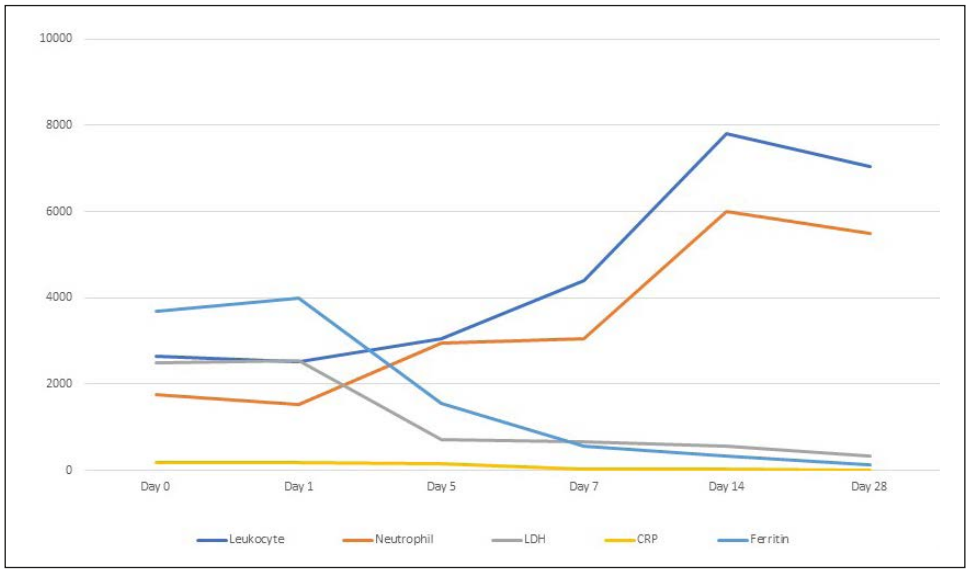

Figure 2 - *Laboratory parameters of patient: Beginning of the HLH-2004 protocol (D0) and follow-up to Day 28 (Leukocyte/mm³, neutrophil/mm³, lactate dehydrogenase IU/L, C-reactive protein (CRP) mg/dl, ferritin mcg/L).*

CSF culture, tuberculosis PCR was negative and viral panel was unremarkable. The patient underwent splenectomy due to massive intra-abdominal bleeding secondary to splenic laceration on the 3rd day after the start of treatment. Sections of the spleen showed thrombi in many vessels, fibrin thrombi in the parenchyma, large areas of infarction and necrosis (*Figure 1*).

The treatment was continued post-operatively. In the first week: Leukocyte was 1910/mm³, Hb.: 8.3 gr/dl, platelet 36000/mm³, neutrophil 1730/mm³, lymphocyte 180/mm³, LDH: 488.9 IU/L, AST : 20.4 IU/L, ALT: 17.3 IU/L, creatinine 0.7, INR.: 1.3 and ferritin was 416 mcg/L.

In the second week of the follow-up, the patient's systemic immunosuppressive treatment was continued, and intrathecal 12.5 mg methotrexate was also administered. In the 3rd week of treatment and follow-up, leukocyte was 3170/mm³, Hb.: 9.1 gr/dl, platelet 363000/mm³, neutrophil 1580/mm³, lymphocyte 1060/mm³, INR.: 1, LDH.: 276 IU/L, AST .: 15.8 IU/L, ALT.: 30.2 IU/L, CRP.: 31.8 mg/L, ferritin: 216 mcg/L and procalcitonin was 0.085 ng/ml. All lesions had regressed in the patient's cranial MRI. At the 4th week of treatment, she was discharged with oral etoposide 150 mg/m²/week, cyclosporine at the same dose, and dexamethasone 5 mg/m²/day. The last cyclosporine level was measured between 200-400 mcg/L. *Figure 2*. shows the change in the patient's laboratory parameters.

DISCUSSION

Atraumatic splenic rupture is mostly attributed to a previously identified factor (Renzulli *et al.*, 2009). Epstein-Barr and malaria are the most common infectious causes (Won *et al.*, 2009). Although cases of splenic rupture or splenic infarct associated with COVID-19 were reported (*Table 1*), there were important clinical and pathological differences between our case and these.

Mobayen *et al.* (Mobayen *et al.*, 2020) mentioned a patient who presented at the clinic with abdominal pain. The simultaneous COVID-19 PCR test of the patient, who was operated for acute abdomen and hemoperitoneum, was positive. In another case report (Shaukat *et al.*, 2021), splenic rupture and hemoperitoneum developed during the course of COVID-19 infection. There are also similar clinical pictures in other literature data (Agus *et al.*, 2021; Crowly *et al.*, 2021; Szantajnbak *et al.*, 2021; Karki *et al.*, 2020; Knefati M *et al.*, 2021; Trabulsi NH *et al.*, 2022).

In the pathological examination of our case, microthrombosis and infarcts were present. While most of the cases from the literature were with splenic rupture secondary to splenomegaly, in an important case report, splenic infarction and splenic rupture secondary to the visceral thrombus were revealed (Karki *et al.*, 2020). In a postmortem study of splenic lesions, a total of 10 patients were examined, and small artery thrombosis and spleen infarction were detected only in 1 case (Xu *et al.*, 2009). COVID-19-related visceral organ thromboembolism is an important cause of morbidity. Hypercoagulability in the follow-up of COVID-19 and the coexistence of spontaneous organ infarctions represent an important topic of discussion.

It is possible to say that there are studies in which many new criteria have been developed and examined, since the clinical picture revealed during COVID-19 does not comply with the previously reported MAS / HLH criteria. For this purpose, COVID-19-associated cytokine storm or MIS-A can be considered among the "cytokine storm syndromes" (CSS) (Ombrello et al, 2021). These syndromes consist of different clinical pictures in which more than one

Table 1 - *Similar splenic rupture or splenic infarct cases associated with COVID-19 in the literature.*

Author	*Year*	*Clinic*	*Imaging*	*COVID-19 History*	*Pathology*	*Treatment*	*Result*
Serin et al.	2022	Fever, nausea, cough	Splenomegaly grade 3 laceration in the spleen	PCR positivity 2 months ago	Multipl microthrombosis, infarct	HLH-2004 protocol Intrathecal methotrexate Splenectomy	She was discharged with oral etoposide, cyclosporine and dexamethasone at the 4th week of treatment.
Mobayen et al.	2020	Abdominal pain, fever, nausea	An extensive fluid collection around the spleen	Synchronous PCR positivity	Focally hemorrhagic area	Treatment for COVID-19 and splenectomy	The patient was discharged in good general condition after two weeks of hospitalisation
I. Shaukat, R. Khan, L. Diwakar et al.	2020	Cough, diarrhoea, abdominal pain, dispnea, syncop	Hemoperitoneum, Splenic extracapsular rupture	Synchronous PCR positivity	None	Splenic artery embolisation, intensive care support	Full recovery and discharged 3 weeks after the admission
Agus et al.	2021	Complaining of syncopal episodes, tachycardia, hypotension, diarrhea, abdominal pain, diffuse arthromyalgia, fever	Splenic subcapsular hematoma, abundant hemoperitoneum	Synchronous PCR positivity	The white pulp showed normal compartmentalization of B and T lymphocytes, demonstrated also by immunohistochemistry (CD3 and CD20), and the red pulp showed sinuses normal in size but increased in number, with a slight decrease in chordal tissue and capillaries	Treatment for COVID-19 and splenectomy	The postoperative course was complicated by a wound infection, and the patient was discharged on day 20 after therapy
Crowley AC et al.	2021	Diarrhea, dyspnea, abdominal pain	Large amount of heterogenous material surrounding the spleen with small to moderate amount of free fluid around the spleen, compatible with acute splenic hemorrhage,	Synchronous PCR positivity	None	Treatment for COVID-19	Before emergency splenectomy could be performed, the patient became hypotensive, developed cardiac arrest, and was died
Sztajnbok et al.	2020	Fever, vomiting, abdominal discomfort, mental confusion	Splenomegaly, splenic infarction.	Synchronous PCR positivity	None	Treatment for COVID-19, anticoagulant therapy	She was discharged on day 26 after ICU admission, without a prescription for oxygen therapy, although she was advised to continue the warfarin
S. Karki et al.	2020	Fever, abdominal pain	Splenomegaly, intraperitoneal collection, infarct and laceration	Synchronous PCR positivity	None	Treatment for COVID-19	Clinically stable during ICU admission and the hemoperitoneum resolved spontaneously
Knefaty et al.	2021	Severe left-sided abdominal pain	Subcapsular fluid collection, subcapsular hematoma	Synchronous PCR positivity	An area of capsular rupture, subcapsular hemorrhage	Treatment for COVID-19	Recovered without serious complications under ICU care
Trebulsi et al.	2022	Abdominal pain and vomiting	Heterogenous spleen with hyperechoic lesions largest measuring 3.8×3 cm likely representing infarcts	Synchronous PCR positivity	Extensive necrosis and areas of hemorrhage with blood clots	Treatment for COVID-19	Discharged with a residual neurological deficit

etiology may play a role in the clinic. Our case met all of the MIS-A criteria defined in the literature. In addition, developing microthrombosis and splenic infarction have also formed the association of very rare clinical pictures. It is known that procoagulant substances, which are acute phase reactants such as factor VIII, von Willebrand Factor, and fibrinogen, increase in COVID-19 and all related inflammatory conditions (Gomez-Mesa *et al.*, 2021). In severe stages of the disease, such as in MIS-A, there is also an increase in inflammatory cytokines (tumor necrosis factor and interleukins, including interleukin 1 and interleukin 6 and CCS featuring high concentrations of proinflammatory cytokines and chemokines may be found) (Levi et al, 2020; Marietta *et al.*, 2020; Serin *et al.*, 2022).

In conclusion, in light of all this data, the presence of splenic microthrombosis and secondary rupture to splenic infarction during the clinical course of COVID-19-associated MIS-A was described for the first time in the literature.

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Conflict of interests

The authors declare that they have no competing interests.

Authors' contributions:

All authors contributed to the editing of the manuscript. IS prepared the accompanying figure.

Consent for publication:

Written informed consent was obtained from the patient for publication of this report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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