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Massive Splenic Infarction Following COVID-19 Infection, with Histopathological Observations, and Review of the Literature

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Abstract

We report a 63-year-old man who developed massive splenic infarction two months following COVID-19 infection. He presented with high grade fever, weakness, dysuria and chronic productive cough. He was found to have a large splenic infarction involving most of the spleen. We document the course and outcome of his illness, and the histopathological findings of the resected spleen. A discussion of COVID-19 associated hypercoagulability is presented, with a comprehensive review of the literature on splenic infarction associated with COVID-19 infection.

Keywords

COVID-19, Splenic Infarction, Hyper-Coagulability, Thrombosis

1. Introduction

An epidemic of viral pneumonia cases started in December, 2019 in Wuhan, Hubei, China, now known as Coronavirus Disease 2019 (COVID-19), had a huge global impact being a far reaching epidemic resulting in millions of fatalities in countries all over the world. Deep sequencing analysis from lower respiratory tract samples proved the etiologic viral agent to be a novel coronavirus, which was named 2019 novel coronavirus (2019-nCoV) [1]. Although the lungs of the affected patients carried the brunt of the disease, resulting in diffuse alveolar damage (DAD), many other organs, including the heart, the kidneys, the hepatobiliary system, the central nervous system, as well as the spleen and lymph nodes, had been affected as well [2].

Thrombotic complications had been one of the hallmarks of COVID-19 infection, which resulted in a hypercoagulable state [3] with subsequent venous and arterial embolic events, leading to infarctions in various organs including the spleen [4].

The contribution of the Arab Region to the huge body of literature related to COVID-19 amounted to 6131 papers out of 143,975 publications reflecting the global overall COVID-19 research output by 2021, representing 4.26% of the global research output. Saudi Arabia had the lead followed by Egypt. The main research lines identified in COVID-19 from the Arab world were related to public health and epidemiology; immunological and pharmaceutical research; signs, symptoms and clinical diagnosis; and virus detection [5]. Herein we report the first detailed case of splenic infarction following COVID-19 infection from Jordan, with emphasis on histopathological findings, and a comprehensive review of the literature.

2. Case Report

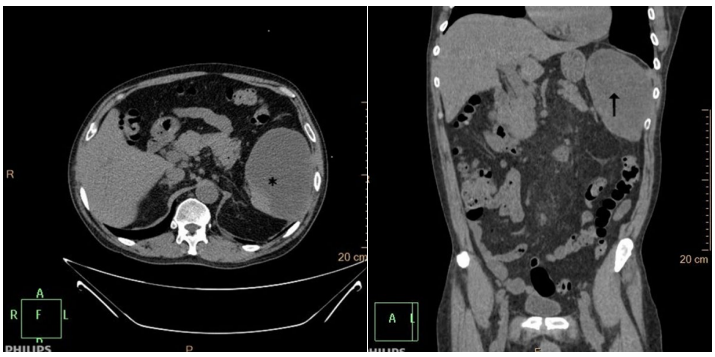
A 63-year-old male with known history of hypertension, presented in April 2021 with high grade fever (39 degrees C), chronic productive cough, dysuria, and generalized weakness. The patient had a history of COVID-19 infection two months earlier in February 2021.

Complete blood count at that time revealed a hemoglobin level of 7.2 g/dl (normal 12 - 16 g/dl), an elevated white blood cell count of 24,950/cubic mm (normal 4500 - 11,000/cubic mm), and elevated platelet count of 711,000/cubic mm (normal 150,000 - 450,000/cubic mm). Blood film showed normochromic normocytic anemia with leukocytosis, neutrophilia with toxic granulation of neutrophils, lymphocytosis with atypical reactive appearing lymphocytes and thrombocytosis. Creatinine, urea, and uric Acid levels were elevated. Sodium, potassium and chloride levels were within the normal range. The INR level was slightly elevated at 1.63 (normal 0.9 - 1.2). ESR and CRP levels were elevated at 130 mm/H (normal $\leq$15 mm/H) and 19 mg/dL (normal <0.3 mg/dL) respectively. The procalcitonin level was in the equivocal range. Amylase and Lipase were elevated at 174 U/L (normal 40 - 140 U/L) and 180 U/L (normal 10 - 140 U/L) respectively. Urine analysis revealed numerous erythrocytes.

Chest x-ray showed increased bronchovascular marking, with lung consolidation or pleural effusions. Abdominal ultrasound revealed increased bilateral kidney parenchyma echogenicity with a simple cortical left renal cyst. There was a large irregular hypoechoic thick content splenic lesion measuring 10 × 9 cm suggestive of splenic infarction or abscess. Abdomen/Pelvic CT scan showed the spleen to exhibit markedly hypoattenuated parenchyma measuring 12.5 × 9 × 13 cm suggestive of splenic abscess or infarction (**Figure 1(A)** and **Figure 1(B)**).

Two days following hospital admission, the patient underwent laparoscopic splenectomy. Initially, the white blood cell count dropped to 19,990/cubic mm, and CRP to 165.6 mg/L following surgery. On the second post-operative day, the patient was found to have an increase in his white blood cell count to 24,500/cubic

mm. Procalcitonin level was elevated to 4.3 ng/ml (normal < 0.05 ng/ml), which is a high risk of severe sepsis and/or septic shock. Abdominal ultrasound showed minimal free fluids in the left para-colic gutter. Blood and urine cultures obtained at the time of admission revealed no bacterial growth. Infectious Disease (ID) consultation was obtained on the case. Vancomycin, Mepra, Fluconazole and Teicoplanin were prescribed by the ID specialist during the patients stay to cover potential infectious agents.



(A) (B)

Figure 1. (A) CT scan showed the spleen to have an area of markedly hypoattenuated parenchyma measuring 12.5 × 13 × 9 cm corresponding to a large splenic infarction (asterisk). (B) Abdominal CT scan showed hypoattenuation of most of splenic parenchyma (arrow).

The patient was discharged six days later with procalcitonin level of 0.43 ng/ml (low risk of severe sepsis and/or septic shock). White blood cell count 18.3 × 10^3 cubic mm, platelet level of 432 × 10^3/cubic mm, hemoglobin level of 9.6 g/dL, and CRP level of 56.4 mg/L. Creatinine level was at 2.50 mg/dl, Urea at 44 mg/dl and Uric Acid at 7.4 mg/dl. Potassium, Sodium and Chloride were within normal limits before discharge. Abdominal ultrasound before discharge showed an irregular fluid multi-loculation at the splenic bed measuring approximately 75 cc in volume. The patient was placed at the time of discharge empirically on three antibiotics and an antifungal agent (Flagyl, Omnicef, Amoclan, and Fluconazole) and to have follow up at the outpatient clinic. On his last visit one month later, he was found to have full recovery.

3. Pathological Findings

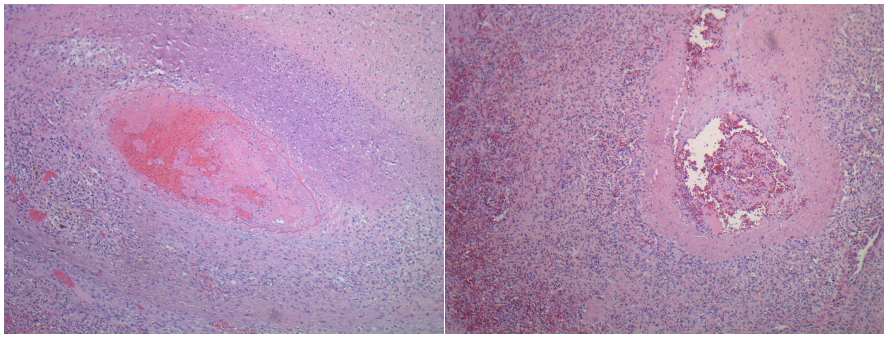
The spleen was submitted for pathological evaluation in irregular fragments of rubbery dark tan and brown tissue with few lobules of yellow fat, measuring 11 cm in aggregate diameter. Cut sections of the fragments showed areas of tan yellow coloration, as well as hemorrhagic areas.

Histopathological examination reveal several vascular structures including arteries, veins and capillaries to harbor thrombi within their lumina (**Figure 2(A)** and **Figure 2(B)**).

Areas of extensive infarction featuring coagulative necrosis of splenic lymphoid

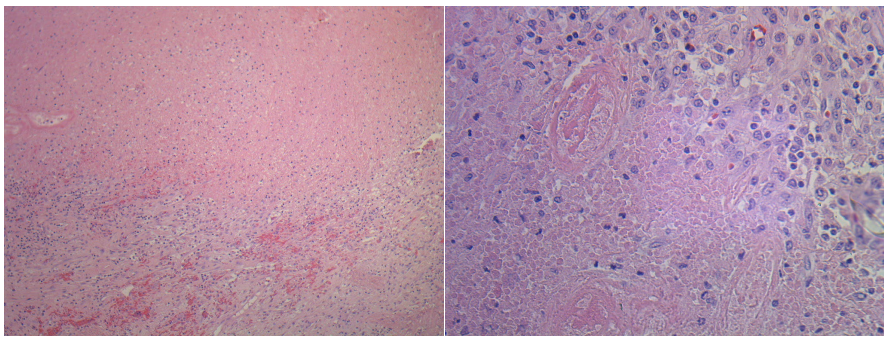
parenchyma (Figure 3(A)) with outline of capillaries filled with fibrin thrombi with infarcted parenchyma was noted (Figure 3(B)).

There were foci of necrosis surrounded by histiocytes and lymphocytes and multinucleated giant cells (Figure 4). Ziehl-Neelsen stain for acid fast bacilli, and Gomori methenamine silver (GMS) stain for fungus were both negative.



(A) (B)

Figure 2. (A) A branch of splenic artery with conspicuous internal elastic lamina featuring a thrombus filling its lumen, surrounded by infarcted necrotic splenic parenchyma. H&E × 10. (B) A vein filled with partially organized thrombus. H&E × 10.



(A) (B)

Figure 3. (A) An area of infarction of the splenic parenchyma featuring coagulative necrosis of splenic lymphoid tissue. H&E × 10. (B) An area of infarction featuring outline of capillaries filled with fibrin thrombi. H&E × 40.

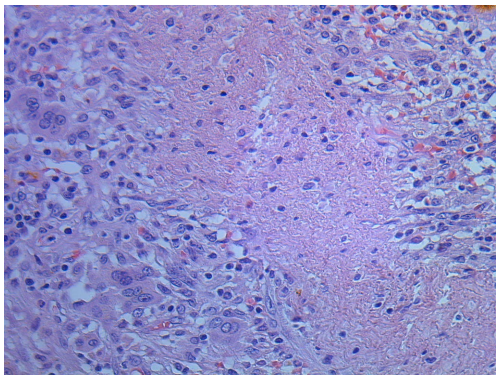


Figure 4. An area of necrotic parenchyma surrounded by histiocytes, lymphocytes and multinucleated giant cells. H&E × 40.

4. Discussion

COVID-19 had been postulated to predispose to both venous and arterial thromboembolism. Drastic inflammatory responses including, but not limited to, cytokine storm, vasculopathy, and neutrophil extracellular traps (NETosis) may contribute to an overwhelming activation of coagulation with subsequent disseminated intravascular coagulation (DIC) with a predominant phenotype of thrombotic/multiple organ failure. High D-dimer levels on admission as well as continuously increasing concentrations of D-dimer are associated with disease progression and poor overall survival [4].

In an overview of thrombotic pathways implicated in COVID-19, Hanff *et al.* observed that thrombus formation took place through several pathways including cytokine storm, macrophage activation syndrome, complement activation, platelet activation, and renin/angiotensin system dysregulation. Several of these pathways are interrelated and auto-amplifying [6].

A study of 138 patients with COVID-19 infection treated at an Intensive Care Unit (ICU) in the Netherlands, Klok *et al.* reported a 31% incidence of thrombotic complications, mainly in the form of pulmonary embolism. Arterial thrombotic events were less frequent seen in 3.7% of cases [7].

In a retrospective study of 400 hospital-admitted COVID-19 patients from Harvard Medical School hospitals, a comparison was made between patients with and without coagulation-associated complications. It was observed that elevated D-dimer at the initial presentation was predictive of coagulation-associated complications during hospitalization [8].

In a review of 64 articles published between December 2019 and June 2020, related to thromboembolic complications seen in COVID-19, Mondal *et al.* observed that the incidence of thromboembolic disease was high and was seen in a multitude of organ systems ranging from cutaneous thrombosis to pulmonary embolism, stroke or coronary thrombosis [9].

Splenic infarction in COVID-19 infection is uncommon. In a review of 46 postmortem studies with a total of 793 patients who died of complications related to COVID-19 infection, Menezes *et al.* reviewed the autopsy findings in various organs, including the spleen [10]. The spleen was reviewed in 82 patients observed in only 12 out of 46 studies in that review. Splenomegaly, chronic congestion, and non-specific splenitis were observed in 6% (5/82) of patients only. On histological examination, there was splenomegaly with expansion of red pulp by congestion and lymphoplasmacytic infiltrate. In 50% of patients (30/61), there was atrophy of the white pulp due to lymphocyte depletion with the absence of marginal zones. No splenic infarcts were found in these patients [10].

In another review, Caramaschi *et al.* summarized the histopathologic findings from autopsies and biopsies performed in patients with COVID-19 reported in a total of 58 studies that included a total of 662 patients. The lungs were the most significantly affected organs, with lung injury has been described in 263 cases from 28 studies [11].

In that review, the spleen had been examined in 161 patients in 13 studies. Postmortem histopathological findings included lymphocytes depletion, white pulp atrophy, parenchymal necrosis, and vascular involvement including congestion, hemorrhage, infarction, vasculitis and arterial thrombosis [11].

Satturwar *et al.* conducted a study of comparative meta-analysis of autopsy findings based on data from articles on Coronavirus Disease 2019 (COVID-19), (241 patients) and Severe Acute Respiratory Syndrome–associated Coronavirus 1 (SARS-CoV-1) deaths (91 patients) [12]. Diffuse alveolar damage (DAD) was the most common cause of mortality in both viral groups. Extrapulmonary postmortem findings associated with COVID-19 include thromboembolism, brain infarction, endotheliitis, acute renal tubular damage, white pulp depletion of the spleen, and cardiac myocyte necrosis.

There were differences in the frequency of white pulp depletion of the spleen in the two groups. It was noted in 18 out of 81 (22.2%) cases of COVID-19 examined compared to 23 out of 23 (100%) cases of SARS-Cov-1. Splenitis was observed in 15 out of 78 (19.2%) cases of COVID-19 examined but none in cases SARS-Cov-1. Necrosis of the spleen was detected in 5 out of 81 (6.2%) cases of COVID-19 compared to 6 out of 23 (26.1%) cases of SARS [12].

We reviewed all cases of splenic infarction related to COVID-19 infection reported in the literature since the start of this global epidemic. A total of 62 cases were documented in articles published since 2021 [13]-[64]. The details of these cases are summarized in **Table 1**. Not included in this table are cases mentioned in radiological or autopsy studies that reported splenic infarctions, but without individual demographic data or information related to the presentation, treatment and outcome of those patients [4] [11] [65]-[67].

There were 43 males and 19 females. The age of the patients ranged from 17 to 82 years, with mean age of 53.35 years, with 22 patients (35%) were above the age of 60 years. All patients tested positive for COVID-19 by PCR testing, and most had respiratory symptoms, except for a few who were asymptomatic with splenic infarction was an incidental finding or the initial presentation [25] [29] [34] [45]. Most patients complained of abdominal pain prior to the diagnosis of splenic infarction. There were 47 patients who had comorbidities listed in **Table 1**, including hypertension (22 patients); diabetes mellitus (13 patients); obesity (8 patients), myocardial infarction and cardiomyopathy (5 patients); asthma (4 patients); hypothyroidism (3 patients); hemoglobinopathies including sickle cell trait and hemoglobin S-C disease (3 patients); and several other conditions including one patient each affected by aortic dissection, atrial fibrillation, patent foramen ovale, viral hepatitis, and malaria. Several patients had more than one comorbidity. There were two patients, who were pregnant, had splenic infarction developing during their postpartum period following COVID-19 infection [22] [31].

As listed in detail in **Table 1**, thrombosis of major blood vessels including the various parts of the aorta (ascending, thoracic and abdominal) (11 patients) [26] [35] [40] [42] [47] [53] [57]-[59] [62] [64], as well as major abdominal blood

vessels including splenic artery (12 patients) [16] [20] [22] [27] [29] [37] [40] [42] [43] [51] [53] [55]; celiac trunk (5 patients) [37] [42] [43] [46] [56]; superior mesenteric artery (3 patients) [20] [28] [62]; portal vein (3 patients) [24] [28] [62]; renal arteries (one patients) [42]; and hepatic artery (one patient) [56] were reported. Some patients had more than one blood vessel getting thrombosed.

Splenic infarction had been associated with infarctions of other organs, as listed in **Table 1**, including kidneys, either unilateral or bilateral involvement (13 patients) [13] [14] [17] [33] [34] [39] [42] [47] [50] [54] [59] [64]; brain (6 patients) [15] [17] [18] [36] [42] [49]; lungs (3 patients) [15] [21] [42]; liver (2 patients) [42] [64]; heart (2 patients) [33] [48]; small bowel (one patient) [14]; and gallbladder (one patient) [20].

Some patients had three organs affected by infarction including the spleen in all of them as listed in **Table 1**: kidneys and brain (2 cases) [17] [50]; kidneys and liver (2 cases) [42] [64]; kidneys and heart (one case) [33]; kidney and lung (one case) [42]; kidneys and gallbladder (one case) [20]; and brain and lung (one case) [15]. There were two cases of abdominal rectus muscle hematomas associated with splenic infarction [30] [62].

Table 1. Reported cases of splenic infarction in patients with COVID-19 infection.

No	Author Year Country [Reference]	Age and Sex	Presentation	Co-morbidities	Imaging CT scan Studies	D-Dimer	Other infarcted organs or thrombosis.	Treatment	Outcome
1.	Ramanathan *et al.* 2020 USA [13]	54/M	Sudden abdominal pain with nausea and vomiting for 5 hours.	Obesity	Large areas of hypo-attenuation in the splenic parenchyma consistent with infarcts.	0.54 mcg/ml Up to 1.55 mcg/ml	Kidney	Apixaban 10mg PO BID seven days, then 5 mg PO daily for thirty days.	Discharged, 4 days later.
2.	Bessuti *et al.* 2020 Italy. Patient 2 [14]	53/M	Severe left flank pain.	Mitral valve replacement.	Large infarctions involving the spleen and the left kidney.	NA	Left kidney	LMWH (6000 UI 2×/day)	Discharged home after 7 day.
3.	Bessuti *et al.* 2020 Italy. Patient 3 [14]	72/M	Severe abdominal pain following admission to ICU.	Renal failure, hypertension, myocardial infarction, and type 2 diabetes.	Small bowel ischemia associated with massive splenic infarction.	(6910 ng/mL)	Small bowel	Resection of the ischemic bowel loop and splenectomy, with heparin infusion.	Improving but re-hospitalized five weeks later.
4.	Pessosa *et al.* 2020 Brazil. Patient 1 [15]	67/M	Weakness in the left upper limb and drooping of the mouth.	Hypertension	Ischemic brain stroke. Splenic Infarction. Pulmonary embolism.	NA	Brain and lungs.	NA	Not stated.
5.	Pessosa *et al.* 2020 Brazil. Patient 2 [15]	53/F	Dry cough, fever and anosmia, together with dyspnoea	Rheumatoid arthritis.	Areas suggestive of splenic infarction.	NA	None	NA	Not stated.

Continued

6.	Agha and Berryman 2020 USA [16]	60/M	Moderate, dull, and left-sided abdominal pain.	Asthma, Sleep apnea, morbid obesity, IgG deficiency, hypertension.	Splenic artery thrombosis and infarction of over 50% of the spleen.	259 ng/mL then up to 1088 ng/ml	None	Heparin drip for 24 hours and then to enoxaparin 1 mg/kg twice daily.	Discharged home on day 21 on oral rivaroxaban.
7.	Imoto *et al.* 2020 Japan [17]	64/M		Gastric and duodenal ulcers.	Multiple cerebral infarcts, bilateral renal and splenic infarcts.	471.3 ng/mL	Brain and kidneys	Favipiravir, meropenem, teicoplanin, and steroid for ARDS, and enoxaparin.	Patient died on day 26 of admission.
8.	Hossri *et al.* 2020 USA Patient 1 [18]	29/F	Abdominal pain and vomiting. Lethargy and fever.	Hemoglobin S-C disease.	Splenomegaly with a splenic infarct measuring 8.6 × 0.7 cm.	2822 ng/mL	Brain	Hydroxy-chloroquine. Continuous heparin infusion.	Intubated for acute hypoxemic respiratory failure on hospital day 3.
9.	Karki *et al.* 2020 Nepal [19]	32/M	Fever, abdominal pain, pancytopenia and fall in hemoglobin level.	Patient had generalized maculo-papular rash.	Hemo-peritoneum with splenic infarct.	NA	None.	Supportive care. Patient was transfused with three unit of packed RBC.	Hemo-peritoneum resolved spontaneously on 7th day of admission.
10	Redekar *et al.* 2020 India [20]	55/M	Diffuse dull continuous abdominal pain associated with of vomiting.	Ischemic heart disease, post PTCA status 5 years ago.	Multiple splenic, bilateral renal and gall bladder wall infarcts.	8 ng/mL	Superior mesenteric and splenic arteries thrombosis.	Started on heparin infusion 1000 units Switched to LMWH Dalteparin.	Discharged with oral Acenocoumarol 1 mg/day.
11.	Yildiz *et al.* 2021 Turkey [21]	68/M	Dyspnea and epigastric pain radiating to the left upper quadrant for 3 days.	Cerebro-vascular events, hypertension, and coronary bypass.	CT with intravenous (IV) contrast demonstrated splenic infarction.	1.72 µg/L	Pulmonary embolism.	Favipiravir, enoxaparin 60 mg SC BID, famotidine 40 mg PO BID, and ceftriaxone 2 g QD IV.	Discharged 6 days later with improving laboratory studies and clinical condition.
12.	Tranca *et al.* 2021 Romania [22]	31/F	Mild, dull abdominal pain with progressive thrombocytosis.	Pregnant, 26 weeks.	75% splenic infarction, with splenic artery thrombosis.	NA	None	Enoxaparin (1 mg/kg, twice a day) and Aspirin Remdesivir and Dexamethasone.	Intrauterine fetal death. Cesarean section was performed.
13.	Moradi *et al.* 2021 Iran [23]	59/F	Left upper quadrant and left flank pain. Discoloration of the heel of her left lower limb.	Diabetes mellitus, hypertension, dyslipidemia, hypothyroid-ism.	Multiple wedge shape hypodense areas in the splenic parenchyma.	NA	None	Heparin 1000 U/h infusion for 5 days followed by oral Rivaroxaban, aspirin, and Clopidogrel.	Asymptomatic on three months follow up.
14.	Rehman *et al.* 2021 USA [24]	33/F	Acute colicky right lower quadrant abdominal pain. No respiratory symptoms.	None	CT scan: Non-opacification of the right portal vein and wedge-shaped infarct in the spleen.	0.61 µg/mL	Portal vein thrombosis	Subcutaneous enoxaparin during hospital stay and was switched to warfarin upon discharge.	Abdominal pain resolved on day 8 of hospitalization.

Continued

15.	Ghalib *et al.* 2021 USA [25]	67/F	Progressive dyspnea and pain in her left calf.	Hypertension, diabetes mellitus, coronary artery disease, hypothyroid-ism, asthma.	CT angiogram of the chest showed a wedge-shaped area the medial aspect of the spleen.	1072 ng/mL	None	Therapeutic anticoagulation with continuous heparin infusion.	Discharged 7 days later on therapeutic anticoagulation with LMW heparin (enoxaparin)
16.	Sztajnbok *et al.* 2021 Brazil [26]	60/F	5-day history of fever, vomiting, abdominal discomfort, and mental confusion.	None	CT of abdomen showed splenomegaly with well-defined splenic infarcts.	3373 ng/mL then 853 ng/mL	Thrombus in the right wall of descending aorta	Enoxaparin (60 mg BID), followed by warfarin	Discharged on day 26 after ICU admission. Ad-vised to continue the warfarin.
17.	Norton and Sheikh 2021 United Kingdom [27]	30/M	Fever, nausea, vomiting, and abdominal pain.	Cardio-myopathy and asthma. Patent Foramen Ovale (PFO).	Occlusive thrombus in the splenic artery and splenic infarction.	1,198 ng/mL	PFO causing paradoxical emboli.	IV antibiotics (Tazocin) and LMWH (Tinzaparin 13,000 units SC Bid), then warfarin.	Outpatient cardiology review for consideration of referral for PFO closure was arranged.
18.	Dag˘istanli and Sönmez 2021 Turkey [28]	46/F	Abdominal pain of 3 days duration.	Diabetes mellitus type 2.	Splenomegaly and decreased densities in cystic manner (infarction) with secondary abscess.	11.73 mg/L	Portal vein, superior mesenteric and splenic veins thrombosis.	Percutaneous drainage was performed for fluid collection in the spleen followed by antibiotic therapy.	Discharged with healing on eighth day.
19.	Castro *et al.* 2021 Brazil [29]	67/M	Moderate, dull, left-sided abdominal pain of 12 days duration.	Hypertension.	Splenic infarction involving about 70 % of parenchyma.	1523 ng/mL	Distal thrombus in the splenic artery.	Abdominal pain decreased gradually after anticoagulation and simple analgesia.	Discharged home on fifth day on oral Rivaroxaban.
20.	Dennison *et al.* 2021 USA [30]	70/M	Acute onset of severe left lower quadrant abdominal pain.	Hypertension, prostatic hypertrophy, GERD, and depression.	4 cm area of infarction in the anterior superior part of the spleen.	14.41 mg/L	Large hematomas within both rectus muscles.	Remdesivir IV and dexamethasone. Enoxaparin discontinued due to active bleed.	Patient returned to normal activity 2 months following discharge.
21.	Mahmood *et al.* 2021 USA [31]	27/F	Pregnant. She had abdominal pain on day 21 postpartum.	None	Multiple new hypodense splenic infarcts.	>20 µg/mL	None	Therapeutic dose of LMWH.	Patient extubated on day 23.Placed on Apixaban.
22.	Alejandre-de-Ona *et al.* 2021 Spain [32]	19/M	Abdominal left flank pain that appeared after four episodes of generalized tonic-clonic seizures.	Sickle cell trait. Epilepsy since childhood treated with le-vetiracetam.	Massive splenic in-farction with 15-cm splenomegaly and patency of both splenic artery and vein.	1065 ng/mL	None	Empirical antibiotic therapy with piperacillin-tazobactam for one week and conventional analgesia.	Discharged, in excellent condition two months later. Vaccination against encapsulated bacteria.

Continued

23.	Jahromi *et al.* 2021 Iran [33]	76/M	Sudden, sharp abdominal pain with nausea and vomiting on eighth day of admission.	Asthma	Hypodensity of right kidney, and hypodense area in spleen (infarction).	0.40 µg/mL then 1.67 µg/mL	Right kidney. Myocardial infarction.	Remdesivir, dexamethasone, subcutaneous unfractionated heparin 5,000 U q 12 hours.	Discharged after 10 days on oral anticoagulants. Referred for coronary angiography.
24.	Al-Mashdali *et al.* 2021 Qatar [34]	43/M	Severe right-sided flank pain of sudden onset with nausea and vomiting. No dyspnea.	Type B aortic dissection diagnosed 4 months before this presentation.	Right kidney infarction and splenic infarction.	3.17 mg/L	Right kidney.	The patient was started on heparin infusion.	Discharged with a prescription of warfarin at the dose of 3.5 mg.
25.	Güven 2021 Turkey [35]	54/M	Mild nausea and abdominal pain in the second week of COVID-19 treatment.	Diabetes mellitus, uncontrolled.	Splenic parenchymal infarction.	9650 µg/L	Thrombus in 2-cm segment of abdominal aorta at supra-celiac level.	Enoxaparin was started at 8000 IU/12 hour.	Aortic thrombus completely disappeared without any additional complications one month later.
26.	Pistor *et al.* 2021 Switzerland [36]	17/M	Acute wake-up stroke. Same day, he had acute onset of left-sided abdominal pain.	Elevation of both von Willebrand factor and ADAMTS13 activity.	Partial splenic ischemia, supposedly due to ongoing embolization.	2465 mg/L	Brain	Anticoagulated first with unfractionated heparin, later switched to LMWH.	Recovered rapidly. No residual stroke effect. LMWH was switched to aspirin.
27.	Bandapaati *et al.* 2021 United Kingdom [37]	50/M	Sudden-onset left-sided abdominal pain of 6hours duration.	None. Patient received first dose of the Oxford vaccine 7days prior to his current presentation.	Non-occlusive thrombus (50%) in the coeliac trunk and splenic artery with splenic infarction.	3026 mcg/L	Thrombi in celiac trunk and splenic artery.	LMWH of 125mg. Patient was observed for 3days with no further evolution of symptoms.	Discharged with the continuation of LMWH. Following discharge, he was asymptomatic.
28.	Aarabi, and Karimialavijeh 2021 Iran [38]	58/F	Persistent left upper abdominal pain a week ago, with fever, nausea.	Hypertension and diabetes type 2.	Multiple hypodense areas in the spleen (infarcts).	NA	Thrombosis of splenic artery.	NA	NA
29.	Prentice *et al.* 2021 United Kingdom [39]	50/M	Acute exacerbation of epigastric pain 14 days from index symptoms.	None	Near complete splenic infarction.	85,216 ng/mL	Right kidney (renal cortical infarct).	Subcutaneous enoxaparin injections for 4weeks before switching to Apixaban.	Meningococcal and hemophilus influenza vaccines and penicillin lifelong therapy.
30.	Singh and Singh 2021 India [40]	40/M	Severe acute abdominal pain in the left hypochondrium on day 4 of admission.	None	Splenic artery thrombus with the associated partial splenic infarction.	1800 ng/ml	Thrombus in the upper abdominal aorta.	Tramadol and heparin IV, followed by LMWH 60 mg twice for 5 days.	Discharged on 11th day of admission, and clinically is asymptomatic.

Continued

31.	Mathew *et al.* 2021 India [41]	34/M	Dull aching epigastric abdominal pain and jaundice of 3 days duration.	Pancreatitis with common bile duct stone.	Splenomegaly (18 cm) and multiple splenic infarcts.	6160 ng/ml	None	Patient was initiated on steroids and Low Molecular Weight heparin.	Clinical improvement over the next 5 days.
32.	Gold *et al.* 2021 Israel Case 1 [42]	68/M	Weakness, fever, dyspnea, diffuse abdominal pain, constipation.	None	Large splenic, hepatic and renal infarcts. Occlusion of celiac artery.	109,189 ng/mL	Pulmonary embolism. Occlusion of both renal arteries.	Started on heparin.	Deceased after 2 days of admission.
33.	Gold *et al.* 2021 Israel Case 2 [42]	59/M	Fever, cough, dyspnea.	Hypertension, diabetes mellitus, and hyper-lipidemia.	Thrombosis of celiac trunk, splenic vessels; with spleen and right kidney infarction.	3270 ng/mL	Extensive thrombosis of thoracic, descending, abdominal aorta.	Started on heparin.	Deceased from sepsis 1 month after event.
34.	Gold *et al.* 2021 Israel Case 3 [42]	70/M	Fever, cough, loss of appetite.	None	Spleen and kidney infarctions.	50,074 ng/mL	Multiple cerebral infarctions.	Started on LMWH-therapeutic dose.	Deceased 2 weeks after event.
35.	Gold *et al.* 2021 Israel Case 4 [42]	78/M	Fever, cough, dyspnea.	Hypertension.	Spleen and bilateral kidney infarctions.	19041 ng/mL	Multiple pulmonary emboli with lung infarctions.	Started on LMWH-therapeutic dose.	Deceased 3 days after event.
36.	Javaid *et al.* 2022 USA [43]	44/M	Severe abdominal pain. Prior to coming to ER, he had a syncopal episode.	Hypertension, prior gastro-intestinal hemorrhage, and obesity.	Hypo-enhancement of the entire spleen (infarction), Hepatomegaly.	NA	Filling defect in celiac trunk extending into splenic artery.	Patient was treated supportively.	Discharged in good condition, after a total of 2 days in the hospital.
37.	Imam and Hammond 2022 Canada [44]	58/F	Generalized weakness and left sided abdominal pain Cultures grew Clostridium paraputrificum.	Diabetes mellitus type 2, hypertension, and reflux.	Infarction of the spleen with a fluid and gas collection that measured 11 × 8.5 × 14 cm.	NA	Throm-bosis of splenic artery and vein, and the portal system.	CT-guided drainage of the splenic abscess. Antibiotics: piperacillin-tazobactam and clindamycin.	Drainage failed. Splenectomy was done. Antibiotic treatment was switched to meropenem.
38.	Al Suwaidi *et al.* 2022 Dubai, United Arab Emirates [45]	23/F	Generalized abdominal pain, radiating to the back. Vomiting. No dyspnea.	None	Low attenuating area involving the lower half of the spleen.	1.54 µg/mL	None	Rivaroxaban (20 mg).	Patient kept on conservative management, her condition improved.
39.	Arslan 2022 Turkey [46]	42/F	Upper left quadrant abdominal pain.	None	Wedge-shaped hypo-enhancing region of the spleen (infarction).	NA	Thrombus in the trunk of the celiac artery.	Intravenous heparin therapy, enoxaparin SC twice daily and aspirin 100 mg PO once daily for 3 months.	No complications were observed in the patient during 3-month follow-up.

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40..	Mavraganis *et al.* 2022 Greece [47]	64/M	Abdominal pain, localized mostly on the left upper and lower quadrant.	None	Hypo-attenuation in the splenic parenchyma splenic infarct.	0.57 mg/L up to 3.7 mg/L	Left kidney. Thrombi in thoracic aorta.	Enoxaparin (8.000 IU bid) and aspirin 80 mg, replaced with fondaparinux 7.5 mg.SC.	Discharged on amoxicillin and aspirin, fondaparinux, and omeprazole.
41.	Atici and Akpinar 2022 Turkey [48]	45/M	Left upper quadrant and left flank pain that persisted for one day	None	An area 57 × 48 mm noncontrast hypodense area in the spleen consistent with splenic infarct.	310 µg/L Normal	Acute anterior MI detected on ECG.	Intravenous hydration, nonopioid analgesics and anticoagulant treatment (Enoxaparin).	Discharged with 100 mg acetylsalicylic acid and ticagrelor (90 mg).
42.	Trabulsi *et al.* 2022 Saudi Arabia [49]	57/M	Abdominal pain and vomiting.	Diabetes mellitus and hypertension.	US showed heterogeneous spleen with hyperechoic lesions largest 3.8 × 3 cm (infarcts).	NA	CT showed large splenic infarct with perisplenic hematoma, and hemoperitoneum. Brain infarction.	Splenectomy done. Multiple areas of splenic laceration and rupture. Histology showed extensive necrosis and hemorrhage.	Discharged in satisfactory condition on heparin. Follow up visit on wheelchair due to residual neurological deficit.
43.	Rigual *et al.* 2022 Spain [50]	53/M	Speech disturbances and left hemiplegia.	Type 2 diabetes mellitus.	Splenic infarct and hemorrhagic transformation and bilateral renal infarction.	3890 ng/dL down to 850 ng/dL	Brain scan: Occlusion of right middle cerebral artery.	LMWH 1 mg SC. Enoxaparin and acetyl salicylic acid 100 mg/24 h.	Discharged at day 30 to a rehabilitation facility.
44.	Fernandes *et al.* 2022 Brazil [51]	42/M	Dyspnea for five days, followed by sever pain in hypochondrium and flank.	Hypertension	Splenic arterial and venous thrombi, and splenic infarcts.	1,328 ng/mL.	None	Enoxaparin 1 mg/kg for 12/12 hours.	Patient had a good clinical evolution and was discharged after 5 days.
45.	Sarmadian *et al.* 2022 Iran [52]	82/F	Generalized abdominal pain.	Hypertension, chronic atrial fibrillation, ischemic heart disease, and chronic obstructive pulmonary disease.	Wedge-shaped hypodense region 90 × 46 mm in the inferior pole of the spleen (splenic infarct).	1940 ng/ml	None	Intravenous heparin. Also treated with Seroflo, Spiriva, dexamethasone, bromhexine, metronidazole, pantoprazole, and metoprolol.	Discharged on the eighth day. She was also recommended to continue Apixaban.
46.	Childers *et al.* 2022 USA [53]	66/M	Dyspnea, myalgia but no nausea, vomiting, diarrhea or abdominal pain.	Dyslipidemia.	CT angiogram of aorta show thrombi in aorta and splenic artery with splenic infarct.	1.65 to 3.51 mg/L then up to 6.92 mg/L	Thrombus in distal thoracic aorta.	Heparin drip. Discontinued two days later after decision for no surgical intervention. Started then on Enoxaparin.	Patient expired secondary to worsening hypoxemia but never developed any abdominal symptoms or limb ischemia.
47.	Belfiore *et al.* 2022 Italy Case 1 [54]	76/F	Syncope. No fever.	None	Hypodense flap of both kidneys and infarction of the spleen.	7051 µg/L	Renal cortical necrosis.	NA	NA

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48.	Dimitriou *et al.* 2022 Greece [55]	46/M	Mild epigastric pain on second day of admission which became worse.	Asthma, chronic viral hepatitis B (HBV).	Initial CT was negative. Second CT on day 14 showed a large splenic infract.	NA	Complete obstruction of the splenic artery.	Splenectomy was done. Later developed fluid collection in the left sub-diaphragmatic space.	Second operation done 24 days after splenectomy to evacuate a hematoma. Discharged on the 56th day.
49..	Batayneh *et al.* 2022 USA [56]	76/M	Sharp severe lower abdominal pain of sudden onset of two days duration.	Hypertension.	Thrombus in the distal celiac artery and multifocal ischemic splenic infarcts.	NA	Thrombus in celiac artery extending into the hepatic artery.	Intravenous heparin for therapeutic anticoagulation.	Discharged home on Apixaban.
50.	Hashim *et al.* 2022 India Case 1 [57]	49/M	Acute left-sided chest and left upper quadrant abdominal pain.	None	Aortic thrombus and splenic infarct.	6245 mcg/mL	Aortic thrombus.	Aspirin 75 mg once a day and injection enoxaparin 60 mg twice a day.	Discharged on rivaroxaban for 3 months. He is well on follow-up over 1 year.
51..	Malayala *et al.* 2022 USA [58]	47/F	Intractable epigastric pain of one day duration with nausea and vomiting.	Obesity. Obstructive sleep apnea.	Second CT done 2 days later showed a 2.4 cm splenic infarct.	193 ng/mL Normal	First CT showed aortic thrombus.	Anticoagulation with LMWH. Empirical antibiotics.	Follow up CT scan two weeks after discharge revealed decreased size of the thrombus in the aorta.
52.	Brem *et al.* 2022 Morocco [59]	59/M	Pain in the right lower limb.	Diabetes mellitus.	CT showed a thrombus in the descending thoracic aorta associated with renal and splenic infarct.	33，620 ng/mL	Left Kidney. Thrombus in isthmus of aorta and descending thoracic aorta.	Femoropopliteal embolectomy. LMWH 60 mg bid. Poor response requiring amputation of the right lower limb.	Patient's condition improved and was discharged 15 days later with anticoagulation treatment.
53.	Özden and Safa 2023 Turkey [60]	74/M	Abdominal pain in the left upper quadrant of one week duration.	None	CT showed a splenic infarct, located in the mid-lower pole of the spleen measuring 7 cm.	NA	None	Anticoagulant and antibiotic therapy. Laparoscopic splenectomy was performed.	Discharged in good condition.
54.	Isel *et al.* 2023 Turkey [61]	50/F	Abdominal left upper quadrant pain, with 5 cm palpable spleen below the costal margin.	Hypertension, hypothyroid-ism, COVID-19 related Multisystem inflammatory syndrome.	MRI showed grade 3 laceration in the spleen.	16.81 mcg/mL	Brain.	Splenectomy due to massive intra-abdominal bleeding, with large areas of infarction and necrosis.	Discharged on the fourth week on etoposide, cyclosporine, and dexamethasone.
55.	Pitliya *et al.* 2023 India Patient 1 [62]	35/M	Fever for 6 days, chills and rigor, abdominal pain, and skin rash.	Cocaine use.	Splenic laceration along with peritoneal collection.	WNR	None	3 Units of packed RBC, symptomatic management.	Hemoperito-neum resolved within a week.

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56.	Pitliya *et al.* 2023 India Patient 2 [62]	67/M	Moderate abdominal pain for 12 days, nausea, and lack of appetite.	Hypertension.	Splenic infarction of 70% of splenic parenchyma.	1523 ng/mL	Distal thrombus in splenic artery.	Enoxaparin 1 mg/kg BD changed to oral rivaroxaban later on.	Resolution of symptoms.
57.	Pitliya *et al.* 2023 India Patient 3 [62]	29/F	Fever, vomiting, cough, abdominal pain, and myalgia.	Sickle cell trait.	Splenic hypo-density and peri-splenic edema consistent with splenic infarct.	2822 ng/mL	None	Hydroxy-chloroquine, tocilizumab and continuous Heparin infusion in ICU.	Not stated.
58.	Pitliya *et al.* 2023 India Patient 4 [62]	58/M	Shortness of breath, cough, and tachypnea.	Dyslipidemia.	Angiography shows no flow in the left posterior, left anterior, and mid-peritoneal artery.	3012 ng/mL	None	Hydroxychloro-quine, Azithromycin, Anakinra, LMWH.	Not stated.
59.	Pitliya *et al.* 2023 India Patient 5 [62]	57/M	Fever, cough, and dyspnea.	Obesity. Diabetes mellitus type 2.	Splenic and renal ischemic lesions.	1169 ng/mL	Aortic thrombi with occlusion of superior mesenteric artery.	Hydroxy-chloroquine, antibiotics, LMWH, tocilizumab.	Resolution of symptoms in a month.
60.	Pitliya *et al.* 2023 India Patient 6 [62]	70/M	Fever, dyspnea, cough, nausea, and weakness.	Hypertension, benign prostatic hyperplasia, GERD, and depression.	4 cm well demarcated area of non-enhancement in antero-superior spleen.	1441 ng/mL	Large hematoma within the bilateral rectus sheath.	Enoxaparin, dexamethasone, Remdesivir, radiologic embolization for hematoma.	Bleeding stopped and patient stable on day 2.
61.	Karakök 2023 Turkey [63]	35/M	Severe left upper quadrant pain on third day of antimalarial treatment.	Malaria (Plasmodium falciparum) and typhoid fever, contracted in Sierra Leone.	CT showed spleno-megaly and 8 cm diameter hypodense areas (infarct).	7383 µg/L	None	Antimalarial drugs. Antipyretics and LMWH.	Discharged with LMWH.
62.	de Godoy *et al.* 2023 Brazil Case 3 [64]	29/F	Precordial, epigastric pain and pain in the lower limbs at rest following AstraZeneca vaccine for COVID-19.	Polycystic ovarian syndrome, obesity, smoking, and miscarriage.	Angio-tomography revealed a hypodense thrombus in the descending thoracic aorta.	NA	Embolic infarction in the spleen, liver, and kidneys.	Conservative anticoagulant treatment was initiated with non-fractionated heparin.	Discharged and was counseled to maintain anticoagulant therapy with war-farin.
63.	Amr *et al.* 2024 Jordan Current Case	63/M	Chronic productive cough, dysuria, and generalized weakness.	Hypertension.	Hypoattenuated parenchyma 12.5 × 9 × 13 cm (splenic infarction).	NA	None.	Laparoscopic splenectomy.	Discharged six days following splenectomy on empirical antibiotics and an antifungal agent.

NA: Not available; LMWH: Low molecular weight heparin.

Most patients were treated conservatively, and were discharged on anticoagulant therapy or empiric antibiotics with recovery. However, 6 patients expired due to extensive thromboembolic complications, severe hypoxia, or sepsis [17] [42] (four patients) [53]. There were no available data on the outcome of five patients [15] [38] [54] [57].

Splenectomy was performed in five patients only [14] [44] [49] [55] [61]. One patient had resection of segment of infarcted small bowel and massively infarcted spleen [14]. Another patient developed fluid and gas in the infarcted spleen, pointing to superimposed splenic abscess formation. Antibiotics (piperacillin-tazobactam and clindamycin) were administered. An attempt to drain the splenic abscess by CT-guided drainage failed. Splenectomy was eventually performed [44]. A third patient had a large splenic infarct with perisplenic hematoma and hemoperitoneum. Splenectomy was done revealing the presence of splenic lacerations that resulted in intraperitoneal hemorrhage [49]. The fourth patient had splenectomy but later on he developed fluid collection in the left sub-diaphragmatic space. A hematoma was evacuated by a second surgical intervention [55]. The fifth patient underwent splenectomy due to massive intra-abdominal bleeding, with large areas of splenic infarction and necrosis.

There are many underlying conditions and etiologies that can cause splenic infarction. In one series of 32 patients with splenic infarction published in 2015 before the COVID-19 pandemic, cardiogenic emboli, particularly related to atrial fibrillation, were the dominant cause, seen in 20 patients (62.5%) [68]. In a study of 96 cases of splenic infarction that had been diagnosed at autopsy between February 1982 and February 1985 at Mayo Clinic, embolic events were considered to be responsible for splenic infarction in 64 cases (67%). Non-embolic causes accounted for 29 cases (30%). Embolic causes were mostly related to underlying cardiovascular conditions, mainly aortic atheroemboli, dilated cardiomyopathy, acute myocardial infarction, and infective endocarditis [69].

A recent study from Japan of 18 patients who had splenic infarction, Hakoshima *et al.* reported that six patients (33.3%) had cancer, four patients (22.2%) had atrial fibrillation, and four patients (22.2%) had infection but no cases of COVID-19 infection. The authors reviewed cases of splenic infarction published from 2019 to 2022, and found 65 case reports. The leading conditions in these reports were infectious agents, with COVID-19 as the main cause in 13 reports. Other infectious conditions included infective endocarditis (7 reports); Epstein-Barr virus (7 reports); cytomegalovirus (3 reports); Mycoplasma pneumoniae; malaria; scrub typhus (2 reports each), dengue virus; aspergillus pericarditis; and babesiosis (one report each). Other etiological factors included malignant tumors; abnormal red blood cells and hemoglobin, and coagulation abnormality; and atrial fibrillation [70].

As shown in **Table 1**, the listed cases of splenic infarction associated with COVID-19 infection were reported from many countries worldwide, reflecting the nature of this global pandemic. USA had the lead in reporting cases of splenic

infarction (11 cases), followed by India (10 cases); Turkey (8 cases); and Brazil (6 cases). Other countries reported four or less cases. There were 5 cases, including the current one from Jordan, reported from Arab countries, namely Qatar [34], United Arab Emirates [45], Saudi Arabia [49], and Morocco [59]. Few cases were reported from Jordan emphasizing the pathological aspects of COVID-19 infection, including a recent autopsy study of lung and heart involvement in 13 patients who died of their disease [71].

In conclusion, we presented a patient who had leukocytosis and large area of hypoattenuated splenic parenchyma suspected of infarction or abscess, but blood and urine cultures for bacteria were negative. Laparoscopic splenectomy was done, and it showed infarction, with thrombosis of splenic vessels. We made a comprehensive review of the literature related to this unusual and uncommon finding in patients infected with COVID-19.

Data Availability

The case report data used to support the findings of this study are included within the article.

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Consent

Written informed consent was obtained from the patient for publication of this case report.

Authors' Contributions

Yousef Amr contributed to conceptualization, data collection, organizing the table, and writing of the manuscript.

Aseel Al-Omari contributed to histopathological description and images.

Mousa Saadeh contributed to radiological description and images.

Samir Amr contributed to conceptualization, verifying references, organizing the table, and writing of the manuscript.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

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