

Review Article

Massive Spontaneous Retroperitoneal Hemorrhage Induced by COVID-19

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Abstract

Since the onset of the COVID-19 pandemic in 2019, the virus has exhibited a wide spectrum of clinical manifestations primarily affecting the respiratory system and vascular system induced endothelialitis¹ and often ends with respiratory failure and thromboembolism.

However, a patient with a massive spontaneous hemorrhage in the retroperitoneum without the above mentioned two systems involved presented a dilemma for timely correct diagnosis and effective treatment.

Spontaneous Retroperitoneal Bleeding (SRB) is usually caused by usage of anticoagulant, chronic illness or trauma therefore, it was very unusual to suspect Covid-19 as the cause. The uniqueness in this case, is the patient developed SRB in the absence of the above aforementioned induced factors, plus occurrence of a silent and severe thromboembolism simultaneously; however, an effective outcome was achieved despite the unusualness involved in this case. The most likely underlined pathogenesis on this case along with its effective therapeutic regime is illustrated in this article with a detailed clinical course, to make aware of this heterogenic nature of this constant mutated COVID-19, and help to facilitate a more comprehensive program in clinical management when encounter with this virus in the future.

This case study not only contributes to the evolving understanding of COVID-19's diverse clinical presentations, but also underscores the necessity for a comprehensive and dynamic approach to diagnosis and treatment. As we continue to navigate the complexities of the pandemic, unraveling the enigma of dual pathogenesis may pave the way for more targeted and effective therapeutic strategies in managing severe COVID-19 cases.

Keywords: COVID-19; Glycolalx; Thromboembolism; Spontaneous retroperitoneal bleeding; Nutrition

Introduction

The COVID-19 pandemic has brought forth a myriad of challenges for clinicians, as the virus showcases a broad spectrum of clinical manifestations, notably an elevated risk of thromboembolism. Acknowledging this heightened risk, the Center for Disease Control and Prevention (CDC) has advocated for the prophylactic use of anticoagulants, particularly in severe and critical COVID-19 cases, with reported reductions in mortality. Nevertheless, the administration of anticoagulants is not devoid of complications and adverse effects, notably bleeding complications that have been documented and associated with an increased risk of mortality [1-6].

Retroperitoneal bleeding typically arises from trauma or chronic illnesses that compromise the integrity of blood vessels, or in patients receiving anticoagulants as a preventive measure against diseases predisposing to thromboembolism, such as COVID-19. The occurrence of a massive spontaneous retroperitoneal hemorrhage

devoid of known induced factors poses a significant challenge in clinical management, particularly in the absence of respiratory system involvement. This clinical scenario demands a comprehensive and thoughtful approach, as the simultaneous presence of thromboembolism and spontaneous retroperitoneal bleeding complicates decision-making. Striking a delicate balance between preventing potentially fatal thromboembolic events and alleviating the risk of severe bleeding becomes paramount. Clinicians are faced with the challenge of navigating uncharted territory, where traditional diagnostic and treatment methods may not be directly applicable.

Present Illness

A previously healthy 52-year-old female presents with a recent history of exposure to a COVID-19 infected coworker. Three days following the exposure, she developed a high fever. Shortly thereafter, she experienced the sudden onset of spasmodic abdominal pain, intensifying in both frequency and severity within a span of 6 hours.

Initial laboratory investigations revealed a concerning finding of severe anemia, with a hemoglobin level of 5.6 g/dl. A Computed Tomography (CT) scan of the abdomen unveiled the presence of a retroperitoneal hematoma and bloody ascites. Notably, the patient tested positive for Covid-19 *via* Polymerase Chain Reaction (PCR). Chest x-ray was normal (Figure 1).

The patient was promptly admitted to an isolation room, where she received blood transfusions and underwent further laboratory tests and evaluations to determine the cause of bleeding, the patient denies any pre-existing chronic illnesses, including diabetes mellitus and hypertension. Additionally, she is not on any regular medication

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regimen and reports no history of recent trauma.

Physical Examination

Temp: 37.5°C, BP: 177/80 mmHg, HR: 74/min, RR: 18/min. High: 166 cm, Weight: 66 kg, BMI: 23.9. GCS: 15. Abdominal, soft, diffuse tender; guarding (-). Bowel sounds normal, others negative.

1. Chest x-ray was normal (Figure 1).
2. Abdominal CT is as follows (Figure 2).
 - The indistinct contour of the pancreatic head & uncinate process, with adjacent stranding and extensive hyperdense collection at retroperitoneal, peritoneum, and pelvis. DDx: pancreatitis with serous ascites, hemoperitoneum (but no definite bleeding point) or others.
 - Focal segmental hypoenhancement of 3rd portion duodenum. Nature to be determined (S/I 4/41).
 - Multiple hypodense lesions (size: <2.8 cm) at both lobe liver with centripetal enhancement, suspected hemangiomas.
3. CTA is showed as follows (Figure 4-6).
 - Intact vasculature of the main branches of the celiac trunk and superior mesenteric vessels.

Laboratory (Table 1), elevated D-dimer, fibrinogen and FDP etc.

Clinical Course

While in the isolation room, the patient's hemodynamic stability was closely monitored, and supportive measures were implemented to address the acute anemic state. Intravenous fluids and blood transfusions were administered to restore and maintain adequate hemoglobin levels. Since the patient was in a stable hemodynamic situation, there was no urgency to do surgical exploration before a clear diagnosis could be made; hence multiple units of packed red blood cells plus fresh frozen plasma were transfused accordingly to raise the hemoglobin level. Since the location of the retroperitoneal hematoma was in the pancreas, and the duodenal region was perfused by the celiac and superior mesenteric arteries, consequently, the integrity of the UGI tract needed to be ruled out. The entire GI tract was R/O from any injury or bleeding by an endoscopic examination and repeated negative stool occult blood tests. Three days later patient was off from isolation and in the meantime, her abdomen became more distended, which indicated more intra-abdominal bleeding hence, the patient was then explored. With the impression of ruptured liver hemangioma, the operative findings showed over 2200 ml of blood in the abdominal cavity with a marked bulging on the retroperitoneum, no rupture from the hemangioma, and no

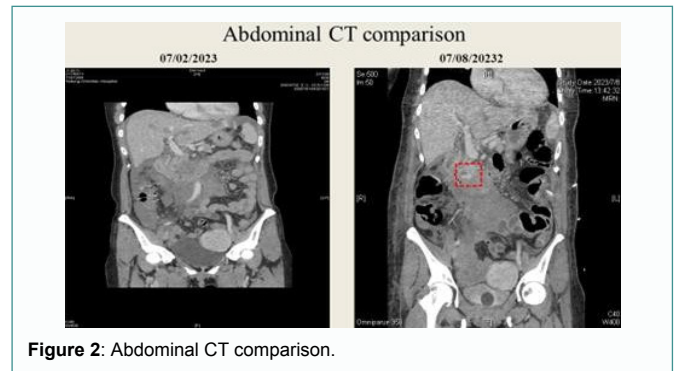


Figure 2: Abdominal CT comparison.

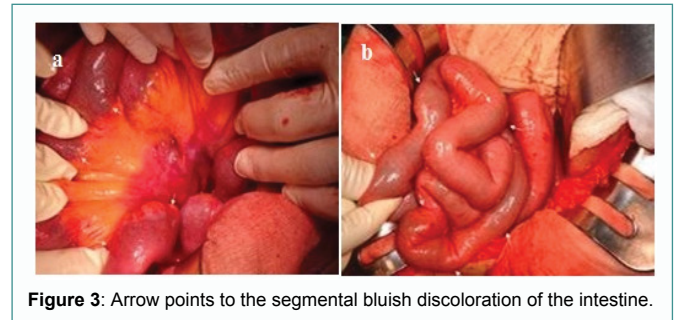


Figure 3: Arrow points to the segmental bluish discoloration of the intestine.

active bleeding was found, blood was evacuated completely from the abdominal cavity and hemovac drainage tube was put under the liver and under the spleen, post Operation (op) patient was stable, but on the 2nd day post op, the drainage from the splenic site was increased suddenly over 350 ml of blood in a 3 hour period. Emergency exploration was done, and over 550 ml of blood in the abdominal cavity evacuated, and multiple blood clots spread in the mesenteric space from the proximal jejunum down to the terminal ileum, and edematous swelling of the small bowel mesentery was noticed which was not present on the first op 2 days ago; the bulging retroperitoneal hematoma appeared slightly less, again no active bleeding site can be found, and while tracing the integrity of the small intestine from the proximal jejunum to the distal ileum, partial bluish to darkish color discoloration occurred in the wall of the small bowel was noticed (Figure 3), no serosa injury in the entire small bowel, colon grossly normal, three drains were inserted, one under the liver, one under the left side diaphragm, and one to the pelvic cavity, post op patient was admitted to the ICU, hemodynamic maintained stable by transfusion of packed red cell and FFP accordingly; and nutrition support with albumin and peripheral hyperalimentation with amino acid, lipid etc. and steroid initiated as per CDC recommendation (Chart 1). At this time, her newly developed hyperglycemia was monitored

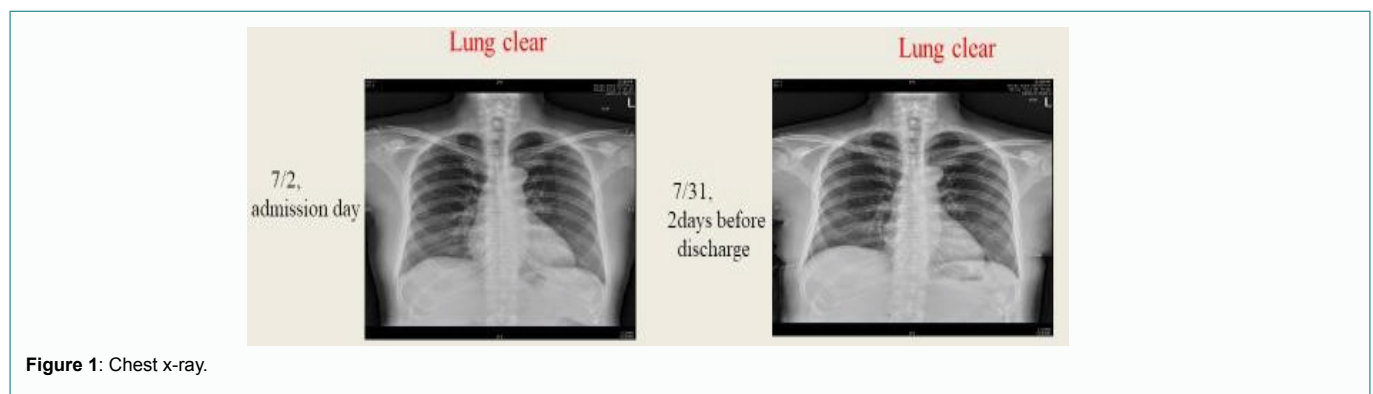


Figure 1: Chest x-ray.

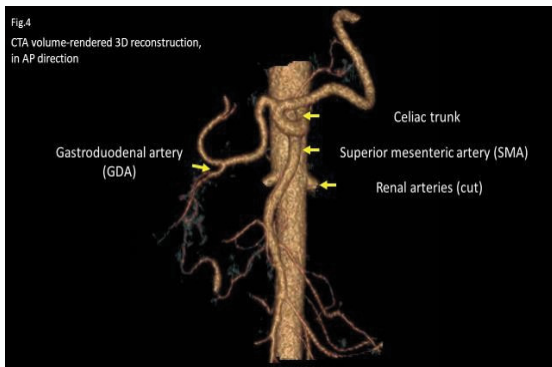


Figure 4: CTA volume rendered 3D reconstruction, in AP direction.

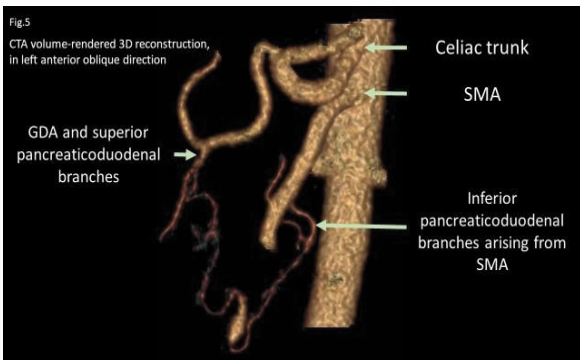


Figure 5: CTA volume-rendered 3D reconstruction, in left anterior oblique direction.

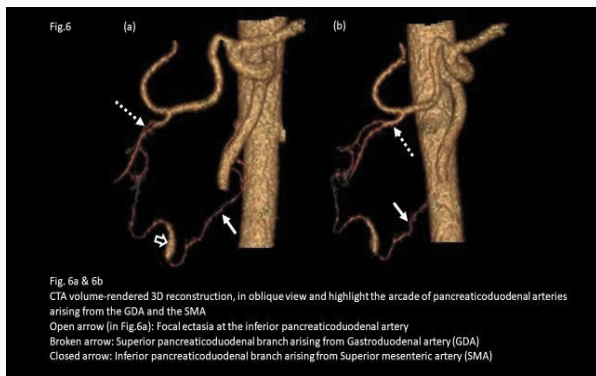


Figure 6: CTA volume-rendered 3D reconstruction, in oblique view and highlight the arcade of pancreaticoduodenal arteries arising from the GDA and the SMA.

and controlled with time scale insulin injection accordingly. The hemoglobin remained stable after 2nd surgery without any further packed red blood cell transfusion, but daily two units of FFP were given until the blood drainage from the hemovac was clear and was removed (Chart 2), her GI function recovered gradually, during this period, her mild abdominal and back pain from pancreatitis resolved slowly and prolonged decline of lipase level despite the bleeding had stopped (Table 1). Hypertension exhibited during the entire admission course gradually improved. Patient was discharged 30 days after admission: total blood loss 6389 ml, total packed red blood cell transfusion 26 units, FFP 60 units (Chart 3), discharged

diagnosis: COVID -19 induced massive spontaneous retroperitoneal hemorrhage, newly onset diabetes mellitus, and acute pancreatitis.

Discussion

Unusual thromboembolic and hemorrhagic events

The patient's clinical course was characterized by the co-occurrence of thromboembolic events and spontaneous retroperitoneal hemorrhage. The prolonged elevation of D-dimer, Fibrinogen and FDP levels (Table 1), even after the second surgical exploration, suggests an ongoing thromboembolic process. The ischemic changes observed in the small bowel wall during the second exploration point towards the occurrence of embolization in the mesenteric vessels. The absence of these changes during the first exploration, in addition with the lack of gross or occult bleeding from the gastrointestinal tract implies the embolization was partial and transient in nature.

Delayed presentation of retroperitoneal bleeding

The delayed onset of clinical evidence of retroperitoneal bleeding, occurring three days after contact with an infected coworker, the gradual and slow nature of bleeding, till the amount of blood accumulated enough to fully occupy the retroperitoneal space and stretch the retroperitoneal membrane and induced abdominal pain implies the bleeding source was from small and terminal branches of the superior mesenteric vessels.

Extended duration of thromboembolic events

The persistence of elevated D-dimer levels for an extended period, even two months after the operation, suggests the continued occurrence of thromboembolic events (Table 1). This highlights the potential for a prolonged prothrombotic state in COVID-19 patients, necessitating extended monitoring and providing anticoagulant therapy if clinically suitable.

Pancreatitis and diabetes mellitus newly developed

The occurrence of pancreatitis and the subsequent development of diabetes mellitus in the patient further indicate the extent of endothelialitis involve the pancreas, particularly the islet cells and pancreatic tissue. This broadens the spectrum of COVID-19 related complications, emphasizing the virus's potential to affect multiple organ systems beyond or in the absence of involvement of the respiratory system.

Hypertension and renin-angiotensin system dysfunction

The persistence of hypertension throughout the hospitalization period points to the marked dysfunction of Renin-Angiotensin system in the vascular system; this aligns with the growing understanding of ACE2 as a key player in the pathophysiology of COVID-19, affecting the regulation of blood pressure and potentially contributing to vascular complications.

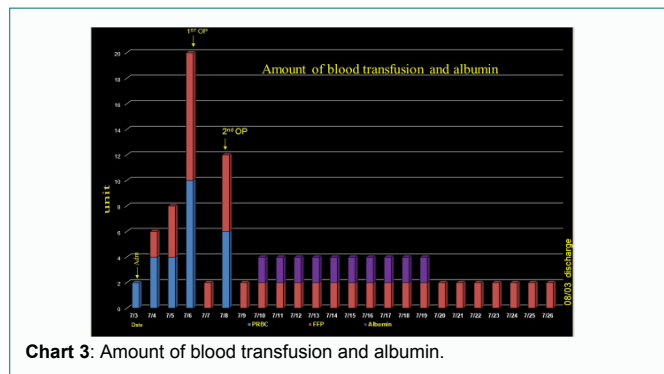
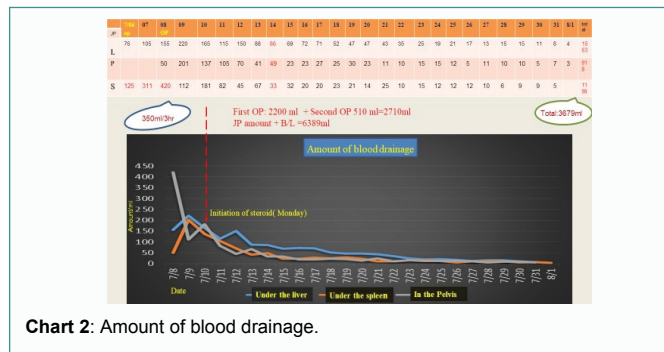
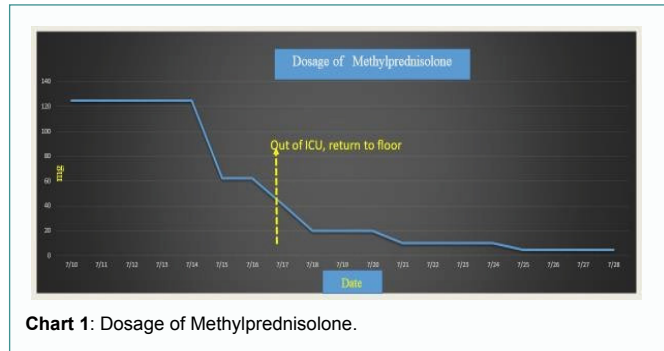
Structure damage of vasculature, glycocalyx degradation by COVID-19

Glycocalyx is a layer of membrane adhesive on the surface of the inner lumen of the vessels, serves as barrier between the flowing blood and inner vessel wall, composed mixture of glycoproteins and glycolipids, protecting the integrity of the vasculature.

The intact layer of the glycocalyx provides anticoagulant and antiadhesive effects on the surface of the endothelial cells of the vessels. Moreover, it can shield endothelial cells from oxidative stress. And preventing vasculitis, and thrombosis from various inflammatory factors. Glycocalyx degrades when under various

Table 1: Elevated D-dimer, fibrinogen and FDP etc.

Date	9-Jul	10-Jul	15-Jul	13-Jul	17-Jul	24-Jul	27-Jul	31-Jul	10-Aug	17-Aug	24-Aug	21-Sep	19-Oct
D-dimer (<500)	8420			10400		5060	5220	3460	2090	1300	1120	584	294
LDH (120-246)								365	335			197	150
Lipase (13-60)	20	25	478		306	240	173	154	143	116	110	78	62
Fibrinogen (200-393)	367.3			247		514.4				408.4			
FDP (<5)	40.4			48.6		20							
Ant thrombin activity (83-128)	71.7					101.6							



inflammatory insults; the degraded glycocalyx vessels cannot perform its normal function, which leads to enhanced vascular permeability, tissue edema, and rupture as shown in this case [7-10].

The patient's unique presentation raises the possibility that the invading virus specifically targeted the most vulnerable vasculature, particularly at the capillary end of the mesenteric vascular system. The intact main branches of the superior mesenteric artery and celiac trunk, as confirmed by CT angiography, suggest a localized and targeted impact on the vasculature, implicating at the capillary level of the mesentery vessels (Figure 4-6).

Nutritional supplement, role of albumin and Fresh Frozen Plasma (FFP)

Albumin is a good blood volume expander, also a major blood flow osmotic pressure modulator. It is a basic component of the structure

of the glycocalyx of the vessels, and bonds within the glycocalyx, thus contributing to the stability of the layer resisting glycocalyx degradation which then helps maintain vascular integrity and normal capillary permeability, Albumin also has immunomodulatory and anti-inflammation effects which smooth the surface of the vessel walls to enhance leukocyte rolling and diminish degree of cell adhesion to the wall, thus lessen the risk of thrombosis, effects that were comparable to FFP and have a repairing effect on the degraded layer of glycocalyx to help regain the functioning of vessels [11-13].

Conclusion

The occurrence of embolism and spontaneous retroperitoneal bleeding in a COVID-19 patient without respiratory system involvement suggests the possibility of preexisting vascular damage at the terminal end of the mesenteric vessels. The attack of COVID-19 may induce varying degrees of micro and macro-vasculitis, contributing to significant coagulopathy and weakening the integrity of blood vessels, leading to leakage and rupture. Efforts to counteract the immune dysfunction induced by the virus, along with the management of coagulopathy using steroids, are crucial in mitigating the damage to vessels [14]. The repair of these damaged and leaking vessels is essential to effectively halt any ongoing bleeding. The aggressive nutritional support provided, including Peripheral Parenteral Nutrition (PPN) combined with albumin until adequate oral intake was achieved, along with the daily administration of Fresh Frozen Plasma (FFP) until bleeding ceased, played a significant role in the patient's recovery. The beneficial effects of plasma and albumin in repairing damaged vessels have been established through decades of research [11-13]. This case emphasizes the importance of incorporating insights from basic science research into clinical practice. By focusing on interventions that promote vascular repair, such as nutritional support and the generous use of blood products, healthcare providers can enhance the quality of care for patients experiencing complex manifestations of COVID- 19.

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