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Case report

Spontaneous abdominal bleeding associated with SARS-CoV-2 infection: causality or coincidence?

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Summary. Authors present 6 cases of abdominal bleeding associated with COVID-19, representing 1.35% of all hospitalized COVID-19 patients and hypothesize that there could be, although not very frequently, a relationship between SARS-CoV2 and bleeding. They excluded a side effect of the low molecular weight heparin therapy that all patients underwent during the course of the disease or other possible causes. Alterations of the coagulation state or a weakness of the vascular wall due toa presumed endotheliitis SARS-CoV-2 infection induced, are hypothesized by the authors. Investigation and follow-up for possible hemorrhagic problems in patients with COVID-19 is recommended. In particular, clinicians should be vigilant about retroperitoneal hemorrhage in COVID-19 patients. In addition to the fact that these patients are being treated with anticoagulants, anemia and abdominal pain are the signs that should lead us to suspect this type of haemorrhage. More studies are needed to understand if COVID-19 can be directly associated with bleeding. (www.actabiomedica.it)

Key words: COVID-19, SARS-CoV-2, bleeding, abdominal, pneumonia

Introduction

Coronavirus disease 2019 (COVID-19) is caused by a novel strain of coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that was first discovered in Wuhan, China, in December 2019. The virus quickly spread around the globe and was declared a global pandemic by the World Health Organization. As of May 26, 2020, there were 86 million confirmed cases of COVID-19 in 231 between sovereign states and territories, with about 1.86 million deaths.

The lungs are the target organ for SARS-CoV2; patients develop acute lung injury which can progress to respiratory failure, although multi-organ failure can also occur. SARS-CoV-2 infection can

be also associated with a coagulopathy, findings consistent with infection-induced inflammatory changes as observed in patients with disseminated intravascular coagulopathy (DIC). High incidence of thromboembolic events suggests an important role of COVID-19-induced coagulopathy (1). Autopsy revealed deep venous thrombosis in 7 of 12 patients (58%) in whom venous thromboembolism was not suspected before death; pulmonary embolism was the direct cause of death in 4 patients (2). Another study performed on 388 consecutive COVID-19 patients, in thrombo-prophylaxis treatment, thromboembolic events occurred in 21% of them (3). Therefore, currently low molecular weight heparin (LMWH) has become part of the clinical management of hospitalized COVID-19 patients, even if evidence about the right prophylactic dose is still lacking. Although there is an associated coagulopathy with COVID-19, bleeding manifestations clearly connected to COVID-19, even in those with DIC, have not been reported.

Below, are reported 6 clinical cases of retroperitoneal/abdominal bleeding associated with COVID-19 infection**,** apparently unrelated to adverse events from thromboembolic prophylaxis.

Case series

On 30 December, in the Grosseto province**,** we had 4,175 cases of COVID-19 infection of which 443 of them had been hospitalized for respiratory failure. 6 patients (1.35% of severe COVID-19 cases) showed abdominal bleeding during hospitalization. The CT images concerning the individual cases are shown in figure 1. A brief description of the clinical cases follows.

Case 1: an obese 60-year-old female was hospitalized for respiratory failure from SARS-CoV2 pneumonia. Hemoglobin (Hb) (14.7 g/dl), coagulation (PTT=27.3 sec; INR=1.23), platelet (PLT) count (185,000/μL) and fibrinogen (232 mg/dL) were normal. After 10 days, she was transferred to the Intensive Care Unit for respiratory failure deterioration. In ICU, the patient was treated with invasive ventilation and showed normal Hb and aPTT/INR values but high D-Dimer rate (5.01 mg/L). After 17 days of hospitalization, hemorrhagic shock (Hb=5 g/dl) from abdominal bleeding appeared, with hematoma of the right abdominal rectus muscle plus a 102x88 mm hematoma in the pelvic excavation. Initially**,** a conservative approach was taken. Later, another abdomen CT scan was performed, because of the appearance of abdominal pain, which showed a right hydronephrosis due to compression caused by the increase of the pelvic hematoma. Consequently, percutaneous drainage was placed for 10 days. The subsequent CT scan showed a reduction in size (65x35 mm) of the hematoma and resolution of hydronephrosis. The patient had always taken prophylactic doses of enoxaparin (4000 IU/day).

Case 2: a 79-year-old male with mono-kidney, chronic renal failure, chronic atrial fibrillation, previous gastric neoplasia, dilated cardiomyopathy, prostatectomy (IPB), diabetes and COPD was hospitalized for acute respiratory failure from SARS-CoV-2 pneumonia. Tests showed pancytopenia (was found) (Hb = 6.8 g/dl; PLT = 112,000 μL; WBC= 2320/mmc), normal coagulation parameters (INR = 1.42; aPTT 32.3 sec.; fibrinogen 209 mg/dL) and 1.36 mg/L D-Dimer. Hemotransfusion was then performed. The patient, who had been treated with enoxaparin 4000 IU/day at home continued his therapy even during hospitalization. After 8 days he underwent abdominal CT for the appearance of abdominal pain radiating to the left lower limb with the presence of pluri-concamerated hematoma in correspondence of the iliac muscle and left psoas (50x38 mm). A conservative approach was taken.

Case 3: an 86-year-old female was hospitalized for acute respiratory failure from SARS-CoV-2 pneumonia. After two days, pulmonary embolism (D-Dimer was 12.36 mg/L) was detected, for which an enoxaparin therapy**,** (6000 IU, twice a day)**,** was prescribed. Coagulation tests were normal (INR, 1.08; aPTT = 27.3 sec; fibrinogen= 338 mg/dL) as well as hemoglobin values (Hb =13.9 g/dl) and PLT value (163,000/μL). An abdominal CT scan was performed after 2 days for the appearance of abdominal pain. This showed a massive retro-peritoneal hematoma at the left posterior para-renal space, about 9x8.5x15 cm in size, with active bleeding. She underwent two embolization operations at the level of the left lumbar arteries. Hemoglobin values dropped to 8.1 g/dl. The hematoma still compressed the left kidney and ipsilateral psoas muscle.

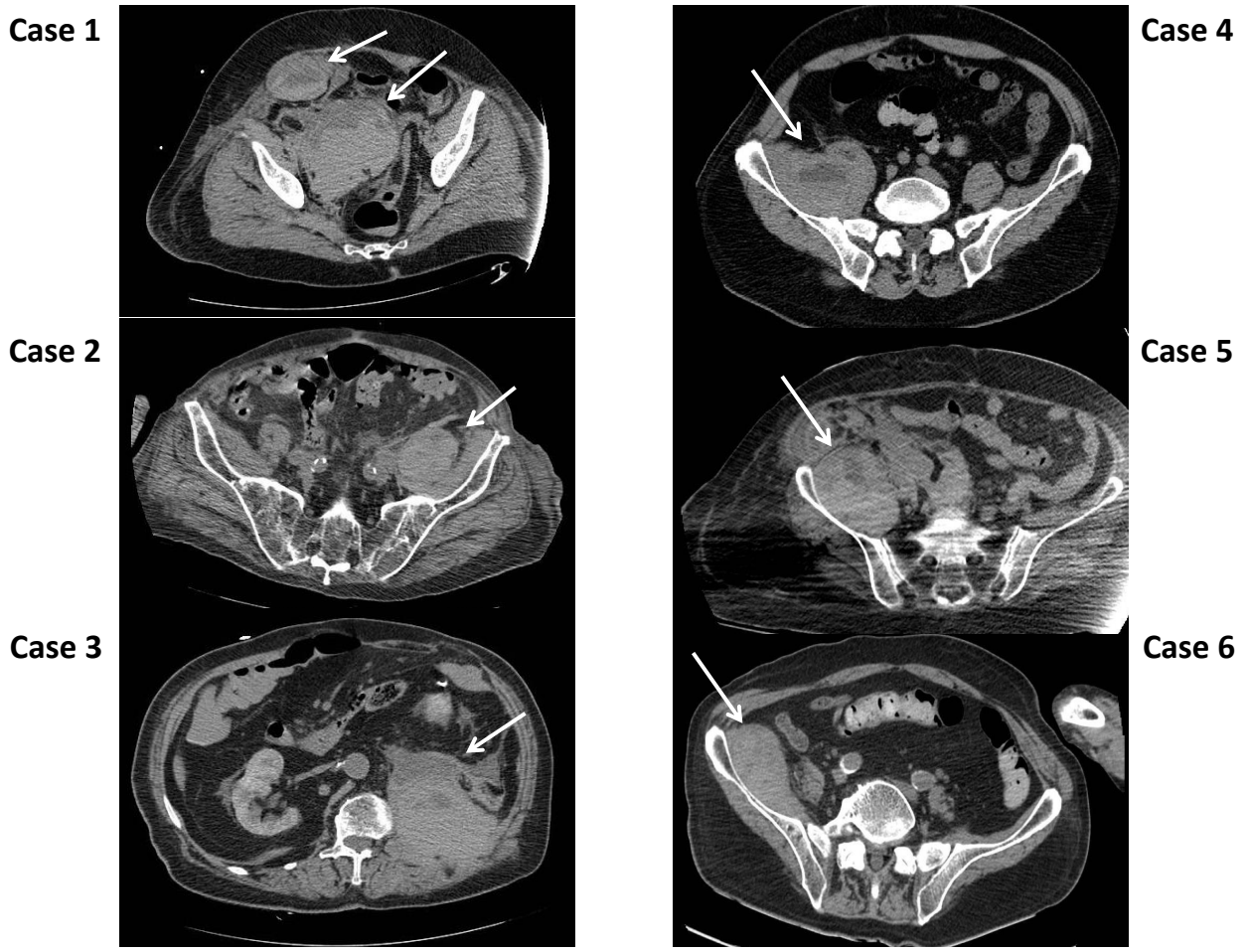

Figure 1. CT scan showing the abdominal hematoma in the 6 cases described. The arrows indicate bleeding.

Case 4: a 68-year-old male affected by chronic renal failure was hospitalized for acute respiratory failure from SARS-CoV-2 pneumonia. About 15 days after admission, while the respiratory failure was improving, the patient presented pain and weakness of the right lower limb. He then performed a CT of the abdomen/lower limb which revealed a massive hematoma (25x5x10 cm in size) of the ileo-psoas muscle with signs of active bleeding. Then an embolization of the right iliac-lumbar artery was performed. The patient had been treated only with low dose enoxaparin during the previous days. Blood tests in the days preceding the onset of the hematoma did not reveal any abnormalities of coagulation (INR, 1.08; aPTT = 26.6 sec; fibrinogen= 297 mg/dL; D-Dimer=1 mg/L) as well as of hemoglobin (12.8 g/dl) and platelets (214,000/μL).

Case 5: a 79-year-old female was hospitalized for acute respiratory failure from SARS-CoV-2 pneumonia. She was also affected by arterial hypertension and diabetes mellitus. About 10 days after hospitalization, she suddenly showed abdominal pain accompanied by severe anemia (hemoglobin: 5.8 g/dl) for which the patient had to undergo several blood transfusions. CT of the abdomen showed an extensive hematoma located posterior to the right kidney, with a hemorrhagic focus at the level of the eleventh rib. CT showed another hematoma in the right ileo-psoas muscle of 80 mm diameter with evidence of active bleeding. Embolization of the intercostal vessels of the 11th and 12th

ribs, the L2 lumbar and the ileo-lumbar arteries was carried out with resolution of the bleeding. Before the bleeding, the patient had been treated with low-dose heparin and had no evidence of coagulation abnormalities (INR, 1.11; aPTT = 30.1 sec; fibrinogen= 296 mg/dL; D-Dimer=0.51 mg/L) and low levels of platelets (240,000/μL).

Case 6: a patient affected by chronic atrial fibrillation, arterial hypertension and diabetes mellitus was hospitalized for acute respiratory failure from SARS-CoV-2 pneumonia. Due to clinical deterioration, the patient was transferred to intensive care. During hospitalization in intensive care, edoxaban therapy was suspended for anemia and replaced with medium-dose fondaparinux. About 7 days after the suspension of edoxaban a CT scan of the abdomen showed a hematoma of the right iliac muscle of about 8x4 cm with no apparent signs of bleeding. The subsequent CT check showed no evolution of the hemorrhage. With the exception of anemia (Hb=11.3 g/dl), the coagulation status during the days prior to the hematoma diagnosis was normal (INR, 1.1; aPTT = 25.8 sec; fibrinogen= 595 mg/L; D-Dimer=0.9 mg/L), as was the number of platelets (147,000/μL).

Discussion

We reported 6 rare cases of bleeding associated to COVID-19 infection (1.35% of the entire hospitalized COVID-19 patients). Another study involving 400 patients observed that overall bleeding rate was 4.8% (7.6% in the critically ill), with a major bleeding rate of 2.3% (4), results comparable to ours. As already said**,** we know that this infection is frequently related to venous thromboembolism and not with bleeding. This led us to hypothesize a possible SARS-CoV-2-induced complication which was not just a mere fortuity. In our cases, five of them used low/medium dosage heparin while the other took a high dose for pulmonary embolism. All of them showed a PTT, INR normal range, excluding a possible adverse effect from anticoagulant therapy. Furthermore, all patients had D-Dimer above the normal range at the time of the complication, confirming that all subjects were, on the contrary, predisposed to thrombotic events and not to the occurrence of bleeding. Furthermore when the hemorrhage occurred, all patients had no signs of bacterial infection or DIC that could justify bleeding.

Recently, some authors describe the experience of a clinical case with retroperitoneal hemorrhage, hypothesizing a possible adverse effect of anticoagulant therapy. However, these authors report that this patient was in fact being treated with a low dose of enoxaparin, not fully justifying the authors' hypothesis (5). Other researchers described two cases of spontaneous abdominal bleeding in hospitalized patients with SARS-CoV-2 bilateral interstitial pneumonia (6). Also these above said researchers did not attribute the bleeding to an adverse event of heparin. As already said, COVID-19 can trigger a thrombotic coagulopathy (1-4), although it cannot be excluded that it may also promote bleeding events as highlighted by the patients described. In fact, other cases of bleeding in other organs have been reported, without apparently being explained by a well-defined cause. As already said, some authors have described hemorrhagic events in 19 patients out of 400 COVID-19 hospitalized subjects (4). A case of a patient with bleeding (petechiae) has been recently reported as an initial presentation of COVID-19 (7). Some authors observed that major pulmonary thromboembolic events with pulmonary infarcts and/or hemorrhage occurred in 5 of the 23 autopsies (8). Others described 2 cases of devastating intracranial hemorrhage in patients being treated with VV-ECMO for COVID-19, without any partial thromboplastin times (aPTT) change or other risk factor**s** that could predict such complication (9). An analysis of 92 deaths for COVID-19 showed that one patient died of recurrent gastrointestinal bleeding (10). Literature reports another case of COVID-19 that presented hematochezia as initial symptom of the infection (11). Rare cases of hemoptysis have also been described as isolated and initial symptoms of COVID-19 (12-14). Therefore, SARS-CoV-2 could be associated also to bleeding.

Apparently**,** there is not a clear cause that could justify retroperitoneal bleeding. Thrombocytopenia being common in patients with COVID-19 appears associated to an increased risk of hemorrhages and in-hospital mortality (4,15). Low fibrinogen values also seem to be associated with an increased risk of

bleeding (4). However, none of our patients had significant trobocytopenia or low fibrinogen values that could explain spontaneous bleeding. Diffuse microvascular damage was described as an important cause of death in critically ill patients with COVID-19, which was related to the "cytokine storm" syndrome caused by immune disorders (16-17). In fact, next to an increased risk of thrombosis, patients seem to have an increased risk of bleeding as well, due to imbalances in platelet production and disruption, and disorders of the coagulation system (16) probably influenced by COVID-19 induced cytokine disorder; however, none of the patients showed alterations of the coagulation parameters. Furthermore, apparently none of our patients had splanchnic arteries aneurysms or retroperitoneal masses that could explain the bleeding. Not even trauma can justify it because patients were bedridden all the time during hospitalization. Therefore, a direct relationship between COVID-19 infection and spontaneous bleeding may be possible. Recently, some authors have found evidence that the virus can directly infect the endothelial cell thus developing endothelial inflammation (18). The ACE2 receptor is not only expressed by pneumocytes but also widely expressed on endothelial cells that can favor endothelial infection (19). Recruitment of immune cells, either by direct viral infection of the endothelium or immune-mediated, can result in widespread endothelial dysfunction associated with apoptosis (18). Endothelial inflammation may induce vasoconstriction with subsequent organ ischaemia, inflammation with associated tissue edema, and a pro-coagulant state. We hypothesize that such inflammation may also induce a weakness of the vascular wall favoring aneurisms development and then possible bleeding.

All COVID-19 patients, in addition to anemia, had abdominal pain at the onset, which is the main symptom of retroperitoneal hematoma (20,21). Consequently, in the presence of sudden abdominal pain, it is always necessary to think about possible bleeding and therefore to perform an abdominal CT scan urgently. Early recognition and treatment is critical for such patients.

In conclusion, although rarely, abdominal bleeding complications may be associated with COVID-19 infection apparently without predisposing causes. SARS-CoV-2 probably favors these spontaneous bleeding. Investigation and follow-up for possible hemorrhagic problems in patients with COVID-19 are recommended. More studies are needed to understand if COVID-19 can be directly associated with bleeding.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

References

1. Wang T, Chen R, Liu C, Liang W, Guan W, Tang R. Attention should be paid to venous thromboembolism prophylaxis in the management of COVID-19. Lancet Haematol 2020; 7: e362-e363.
2. Wichmann D, Sperhake JP, Lütgehetmann M, et al. Autopsy Findings and Venous Thromboembolism in Patients With COVID-19. Ann Intern Med 2020; 173: 268-277.
3. Lodigiani C, Iapichino G, Carenzo L, et al; Humanitas COVID-19 Task Force. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. Thromb Res 2020; 191: 9-14.
4. Al-Samkari H, Karp Leaf RS, Dzik WH, et al. COVID and Coagulation: Bleeding and Thrombotic Manifestations of SARS-CoV2 Infection. Blood 2020; 136: 489-500.
5. Patel I, Akoluk A, Douedi S, et al. Life-Threatening Psoas Hematoma due to Retroperitoneal Hemorrhage in a COVID-19 Patient on Enoxaparin Treated With Arterial Embolization: A Case Report. J Clin Med Res. 2020; 12: 458-461.
6. Conti CB, Henchi S, Coppeta GP, Testa S, Grassia R. Bleeding in COVID-19 severe pneumonia: The other side of abnormal coagulation pattern? Eur J Int Med 2020; 77: 147-149.
7. Joob B, Wiwanitkit V. Hemorrhagic Problem Among the Patients With COVID-19: Clinical Summary of 41 Thai Infected Patients. Clin Appl Thromb Hemost 2020; 26: 1076029620918308.
8. Buja LM, Wolf D, Zhao B, et al. The Emerging Spectrum of Cardiopulmonary Pathology of the Coronavirus Disease 2019 (COVID-19): Report of 3 Autopsies From Houston, Texas, and Review of Autopsy Findings From Other United States Cities. Cardiovasc Pathol 2020; 48: 107233.
9. Heman-Ackah SM, Su YS, Spadola M, et al. Neurologically Devastating Intraparenchymal Hemorrhage in COVID-19 Patients on Extracorporeal Membrane Oxygenation: A Case Series. Neurosurgery 2020; 87: E147-E151.
10. Yang F, Shi S, Zhu J, Shi J, Dai K, Chen X. Analysis of 92 Deceased Patients With COVID-19. J Med Virol 2020; 92: 2511-2515.

11. Guotao L, Xingpeng Z, Zhihui D, Huirui W. SARS-CoV-2 infection presenting with hematochezia. Med Mal Infect 2020; 50: 293-296.
12. Shi F, Yu Q, Huang W, Tan C. 2019 Novel Coronavirus (COVID-19) Pneumonia With Hemoptysis as the Initial Symptom: CT and Clinical Features. Korean J Radiol. 2020; 21: 537-540.
13. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395: 497–506.
14. Guan WJ, Ni ZY, Hu Y, et al; China Medical Treatment Expert Group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020; 382: 1708-1720.
15. Yang X, Yang Q, Wang Y, et al. Thrombocytopenia and its association with mortality in patients with COVID-19. J Thromb Haemost 2020; 18: 1469-1472.
16. Tang N, Li D, Wang X. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost 2020; 18: 844-847.
17. Jiang H, Liu L, Guo T. Improving the safety of CAR-T cell therapy by controlling CRS-related coagulopathy. Ann Hematol 2019; 98: 1721-1732.
18. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endhothelitis in COVID-19. Lancet 2020; 395: 1417-1418.
19. Ferrario CM, Jessup J, Chappell MC, et al. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. Circulation 2005; 111: 2605–2610.
20. Artzner T, Clere-Jehl R, Schenck M, et al. Spontaneous ilio-psoas hematomas complicating intensive care unit hospitalizations. PLoS One 2019; 14: e0211680.
21. Sunga KL, Bellolio MF, Gilmore RM, Cabrera D. Spontaneous retroperitoneal hematoma: etiology, characteristics, management, and outcome. J Emerg Med 2012; 43: e157-61.

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