



CASE REPORT

COVID-19 and Thrombocytopenia: Heparin or Sepsis-Induced?

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Introduction

The outbreak of a novel-coronavirus related pneumonia was officially identified in Wuhan, on January 2020 and it was declared a Public Health Emergency of International Concern on January 30th. On February, WHO named the virus SARS-CoV-2 and the subsequent disease COVID-19 [1]. On March 11th, WHO Director General, Dr. Tedros Adhanom Ghebreyesus, declared that “COVID-19 can be characterized as a pandemic” because “there are now more than 118,000 cases in 114 countries, and 4,291 people have lost their lives” [1].

About 40% of SARS-CoV-2 positive patients are asymptomatic but infectious. More common symptoms are fever, dry cough and dyspnea but some patients might experience also myalgia, diarrhea, anosmia and ageusia. Severe cases present a severe pneumonia that could exitate in an acute respiratory distress syndrome (ARDS) characterized by acute hypoxemic respiratory failure and bilateral lung infiltrates [2].

As recently published in severe COVID-19 patients there is a derangement of coagulation ranging from hypercoagulability to an overt disseminated intravascular coagulation (DIC) [3]. Some patients could experience venous thromboembolism that requires anticoagulation therapy with heparin [4].

The name heparin comprehends a group of glycosaminoglycans having anticoagulant properties used for prevention of clot formation. Common side effects are

bleeding or bruising, pain, redness or skin modification in injection-side. Heparin induce-thrombocytopenia (HIT) without or with thrombosis (HITT) is a known, potentially fatal, side effect caused by antibodies against complexes containing platelet factor 4 (PF4) and heparin. Only 0.2% to 3% of heparin-exposed patients present thrombocytopenia and/or thrombosis [5].

Most important tool is differential diagnosis that could be difficult due to the overlap of HIT with other medical conditions as DIC, immune thrombocytopenia, thrombotic microangiopathies including thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome, and drug-induced thrombocytopenia. The presumptive diagnosis of HIT is made by the so called 4Ts scoring system developed by Cuker, et al. [6].

Herein we report the first case, at the best of our knowledge, of suspected HIT in a patient positive for SARS-CoV-2.

Case Description

On March 14, 2020 a 79-years-old man was admitted to our Department due to dry cough and fever. His wife and daughter were SARS-CoV-2 positive. His nasopharyngeal swab-test for SARS-CoV-2 was positive and he was in quarantine at home.

His past medical history included non-insulin-dependent diabetes mellitus, right carotid endarterectomy, colorectal cancer and gastric ulcer. He was taking aspirin, furosemide, bisoprolol and linagliptin. On physical

examination there weren't lung crackles, pleural friction rubs or peripheral oedema. His arterial blood oxygen saturation (SO₂) was 95% on 9 liters of supplemental oxygen and he was pyretic (38 °C).

The computed tomography (CT) of the chest revealed bilateral, wide ground-glass opacity with a "crazy-paving" pattern. Laboratory data revealed lymphocytopenia (0.37 G/L) without abnormality of platelet count (320 G/L) and/or hemoglobin (113 g/L), elevation of lactate dehydrogenase (536 U/L), abnormal liver function with increased AST (72 U/L), ALT (40 U/L), GGT (159 U/L), high C-reactive protein (200 mg/L). HIV combo-test (HIV antibodies and p24 antigen), *Streptococcus pneumoniae* and *Legionella pneumophila* urinary antigen test were negative.

He started antibiotic treatment with Levofloxacin and Ceftazidime, antiviral therapy with lopinavir/ritonavir (Kaletra®), methylprednisolone, insulin and 4,000 IU of enoxaparin every 24 hours. He also continued his daily medications (furosemide, aspirin, bisoprolol).

During the following days he presented desaturation (SO₂ 88%) requiring treatment with continuous positive airway pressure (CPAP) delivered with a "helmet". The high suspicion for pulmonary embolism, due to clinical signs and elevation of D-dimer (4738 ug/L), was dispelled by CT-pulmonary angiography. During the following days, patient's symptoms improved and fifteen days after hospital admission CPAP was stopped and switched to high flow nasal cannula oxygen therapy.

The next day he experienced hypotension (90/50 mmHg), tachypnea, tachycardia (130 bpm), epigastric pain radiated to back and wrists, and Melaena. Laboratory data highlighted severe anemia (48 g/L), reduction of platelet count (157 G/L), moderate elevation of troponin (46 ng/L), elevation of C-reactive protein (51 mg/L), normal AST and ALT level (25 and 31 U/L respectively). The EKG revealed an anterolateral subepicardial ischemia. The patient underwent chest and abdominal CT-scan showing no aortic dissection but a 7 cm × 5 cm non-active bleeding hematoma at the level of iliopsoas muscle. Aspirin and heparin were immediately withdrawn.

Due to the presence of Melaena the patient also underwent to esophagogastroduodenoscopy showing duodenal ulcer without active bleeding (Forrest III) and hiatal hernia. He started proton pump drug intravenously and continue remaining therapy. In the following 2 days, laboratory data revealed a marked increase of troponin (up to 1260 ng/L) and a progressive reduction of platelets (up to 44 G/L) with stability of d-dimer (4575 ug/L) and hemoglobin at 105 g/L after blood transfusions.

In the next two days (22 days after hospital admission) he improved symptoms but he presented a new febrile episode with desaturation and he died. Blood culture collected around temperature elevation was negative.

Discussion

SARS-CoV-2 infection could be complicated by DIC subsequent to the septic status and Iba [7] proposed the name of "sepsis-induced coagulopathy" for this syndrome. COVID-19 patients, especially those with severe disease, are at high risk of venous thromboembolism requiring prophylactic dose of low molecular weight heparin [4].

Heparin induced-thrombocytopenia (HIT) is a potentially fatal complication during treatment with heparin - unfractionated or low-molecular weight - characterized by platelet count fall with or without new venous or arterial thrombosis [5]. This entity could be underestimated especially when platelet count falls > 50% without causing a real thrombocytopenia. Warkentin [8] recently reported that 15% to 20% of patients could suffer arterial events while 30% to 60% could develop venous thromboembolism.

Spontaneous retroperitoneal hematoma during anti-coagulation therapy is well known and usually they are self-limiting [9]. At first the clinical course of the patient could be explained by DIC or hypercoagulability related to a severe COVID-19 pneumonia in a comorbid old-patient.

Nevertheless, retrospectively evaluating this case, we could speculate that patient suffered from a HIT (thrombocytopenia complicated by acute coronary syndrome) associated with an iliopsoas muscle hematoma subsequent either thrombocytopenia than LMWH treatment. This hypothesis could be validated by the 4Ts score resulting in 6 point indicating a high HIT probability. Unfortunately the patient was not tested for PF4/H antibodies and he died before platelet recovery that, as reported by Warkentin, et al. [10], usually occurs 2 weeks after heparin withdrawal.

In conclusion, SARS-CoV-2 positive patients, especially more severe cases, could have a prothrombotic condition due to infection itself, cytokine release and subsequent DIC. It is of paramount importance to keep in mind that HIT can complicate SARS-CoV-2 infection being a life threatening condition.

Conflict of Interest

The authors declare they have no conflict of interest.

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