Heparin-induced thrombocytopenia and COVID-19

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Abstract

Heparin-induced thrombocytopenia (HIT) has not been included as a possible cause of thrombocytopenia in Coronavirus Disease 2019 (COVID-19) patients. We report a case of HIT in a patient with COVID-19 treated with heparin. A 78-year-old man was admitted to our hospital for acute respiratory failure and acute renal failure due to SARS-CoV-2 infection; in intensive care unit, one 5000IU heparin dose (day 0, platelet count 305000/μL). On day 2, haemoglobin started to decrease and heparin was stopped. On day 10, platelet count was 153000/μL and 5000IU calcium heparin subcutaneously twice daily was started. The platelet further decreased, reaching 49000/μL on day 17, and the patient was investigated for suspected HIT: an IgG specific chemiluminescence test for heparin-PF4 antibodies was positive and a femoral DVT was found at ultrasound. Argatroban was started, platelet count increased without any bleeding and thrombosis complication. Our experience shows that HIT may develop in heparin treated COVID-19 patients and should be included among the possible cause of thrombocytopenia in such patients.

Introduction

Recent reports indicate that Coronavirus Disease 2019 (COVID-19) is a prothrombotic disease and the presence of the "Covid-19-associated coagulopathy" is associated with adverse outcomes.[1] The incidence of thrombosis in patients with COVID-19 is high and varies considerably according to the severity of disease and the presence of additional thrombotic risk factors.[2,3] A very high venous thromboembolic (VTE) prevalence, including a high proportion of potentially life-threatening proximal deep vein thrombosis (DVT), in mechanically ventilated SARS-CoV-2 patients was observed despite standard pharmacological thromboprophylaxis.[4] Anticoagulant treatment seems to confer a survival benefit in hospitalized patients with COVID-19,[5] in particular the administration of heparin was associated with lower mortality in hospitalized patients with COVID-19.[6] As a result, more intense antithrombotic regimens have been suggested in this population.[7] The Italian Society on Thrombosis and Haemostasis suggests the use of intermediate-dose of heparin in COVID-19 patients with previous VTE.[8] Patients with COVID-19 admitted to the intensive care unit (ICU) of our hospital are treated with intermediate-therapeutic heparin doses even in the absence of documented VTE. Heparin-induced thrombocytopenia (HIT) is a rare complication of heparin treatment.[9] It is associated with increased in vivo thrombin generation provoking both arterial and venous thrombosis. In case of HIT, heparin in any form should be immediately withdrawn. Patients with HIT require non-heparin anticoagulants and high therapeutic levels of anticoagulation are needed to control such hypercoagulable state. Pooled analyses of prospective cohort studies with historical controls have shown that untreated HIT can be complicated by further thrombotic events in 30-75% of cases with 5-10% mortality.[9,10] Since thrombocytopenia is a common finding in patients in ICU, and severe COVID-19 is often associated with thrombocytopenia,[11] HIT is seldom suspected and investigated. Here, we report a case of HIT in a patient with severe COVID-19 that received unfractionated heparin (UFH) treatment, highlighting that HIT may occur also in such patients.

Case Report

A 78-year-old man (weight 76 Kg) with a history of chronic kidney disease, arterial hypertension and recurrent deep vein thrombosis was admitted to our hospital for acute respiratory and renal failure. He was on therapy with warfarin, amlodipine 5 mg once a day, atorvastatin 20 mg once a day, cinacalcet 30 mg three times a week, calcium and vit D supplementation. He described generalized malaise, muscle ache and fever the week before. In the emergency department, the patient's temperature was 37.8 °C, he had sinus tachycardia with 108 beats per minute, blood pressure was 190/90 mm Hg, respiratory rate 18 breaths per minute, and oxygen saturation 97% on room air. Laboratory findings showed a hypocapnic hypoxemia with metabolic acidosis, serum creatinine was 9 mg/dL, sodium 126 mmol/L, kalium 5.7 mmol/L, INR was 8.37. Warfarin was stopped and he received intravenous Vit K. A diagnosis of viral pneumonia was based on computed tomographic (CT) scan and the patient was transferred to ICU. A nasopharyngeal swab for SARS-CoV-2 was performed but was negative, nevertheless a treatment based on hydroxychloroquine, azithromycin, steroids, tocilizumab was started given to the high COVID-19 suspicion. During the following two days, INR decreased from 3.04 to 1.5, renal function did not improve and hemodialysis was started three days after admission with the insertion of a catheter in the right femoral vein. One bolus dose of 5000IU sodium UFH was used during the first dialysis treatment (Day 0, platelet count: 305×10^3/μL). The trend of platelet count is shown in Figure. 1 On day 1 he received one dose of 40 mg enoxaparin. On day 2, haemoglobin started to decrease and heparin was stopped. On day 4 hemoglobin was 8.5

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g/dL and melena were observed. On day 5, hemoglobin was 7.8 g/dL, platelet count was 219×10^3/μL and he underwent a transfusion of packed red blood cells. From day 5 to day 9, no bleeding was observed and haemoglobin values were stable. On day 10, platelet count was 153×10^3/μL, the femoral catheter was removed, and 5000IU calcium heparin subcutaneously twice a day was started. As shown in the figure, the platelet count further decreased: on day 17 platelet count was 49×10^3/μL, calcium heparin was stopped and HIT was suspected. The pretest clinical score (4 T's)[12] for the diagnosis of HIT was 4 (viral pneumonia and tocilizumab as a possible cause for thrombocytopenia) and the patient was investigated for a diagnosis of HIT. An IgG specific chemiluminescence test for heparin-PF4 antibodies (AcuStar; HIT-IgGPF4-H) was positive (9.44 U/ml). The presence of HIT could not be confirmed by a platelet aggregation test because the platelet aggregation test is no longer available in the Bologna area. On day 18 (platelet count 41×10^3/μL), he complained of right lower extremity pain, a whole leg ultrasound showed a right common femoral DVT (4T's score 6) and argatroban was started. During argatroban treatment, platelet increased: from 51×10^3/μL on day 19 to 267×10^3/μL on day 31 and no recurrent thrombotic event or bleeding complication was observed. The patient was discharged on warfarin. In ICU, the patient required 48 hours of non-invasive ventilation, a nasopharyngeal swab for SARS-CoV-2 was repeated and the RT-PCR for SARS-CoV-2 was positive; on day 14, serological test showed positive IgG and IgM against SARS-CoV-2. Thus, the diagnosis of acute renal failure and pneumonia due to SARS-CoV-2 infection was confirmed. When he was discharged, serum creatinine was 6.14 mg/dL, sodium 137 mmol/L, kalium 5 mmol/L, INR 2.7. During the 12-week follow-up by our anticoagulation clinic, there were neither thrombotic nor bleeding events.

Discussion

We describe a HIT case occurred during SARS-CoV-2 infection. Despite the obvious limitations of a case report, our experience demonstrates that HIT may develop in patients with COVID-19 treated with heparin and it should be considered among the possible cause of thrombocytopenia in such patients.

Guidelines recommend prophylactic or intermediate doses of low-molecular-weight heparin to prevent venous thromboembolism in patients with COVID-19.[8] In Italian hospitals, heparin was used at intermediate or anticoagulant doses in most of the COVID-19 patients. The prevalence of HIT increases in parallel with the dose and the type of heparin and can reach 1% in medical patients.[13] In line with the risk of HIT that is higher for unfractionated heparin than for low molecular weight heparin,[9] HIT occurred in a patient treated with calcium heparin. Despite the widespread use of unfractionated heparin and low molecular weight heparin in COVID-19 patients, few cases have been described so far.[14-16] It is a common finding that patients in ICU have a decreased platelet count,[17] as well as coagulation disorders. Moreover, thrombocytopenia is common in COVID-19 patients: it has been detected in 5-41.7% of patients,[18] and a meta-analysis of 7163 COVID-19 patients showed that thrombocytopenia might be a risk factor for COVID-19 progressing into a more severe state.[11] The cause of thrombocytopenia in COVID-19 patients is not clear and several pathophysiological processes have been postulated: a direct infection of hematopoietic stem cell, a damage to the lungs by autoantibodies and immune complexes by coronavirus, a decreased thrombopoietin production, an increased platelet clearance and platelet consumption.[18] Interestingly, there is no data on the role of thrombocytopenia in increasing the risk of bleeding in COVID-19 patients. Nevertheless, HIT has never been included as a possible cause of thrombocytopenia in COVID-19 patients. In our experience, HIT has been seldom investigated during SARS-CoV-2 infection, probably because thrombocytopenia is always ascribed to SARS-CoV-2 infection.

Several drugs used in patients with COVID-19 may lead to thrombocytopenia. Tocilizumab is often used and thrombocytopenia is one of its most common adverse events. In a recent study, 14% of COVID-19 patients treated with tocilizumab developed thrombocytopenia.[19] A tocilizumab associated thrombocytopenia was highly unlikely in the present case. The presence of HIT antibodies, the platelet trend and the thrombotic complication at the lowest platelet level were compatible with HIT and not with tocilizumab associated thrombocytopenia.

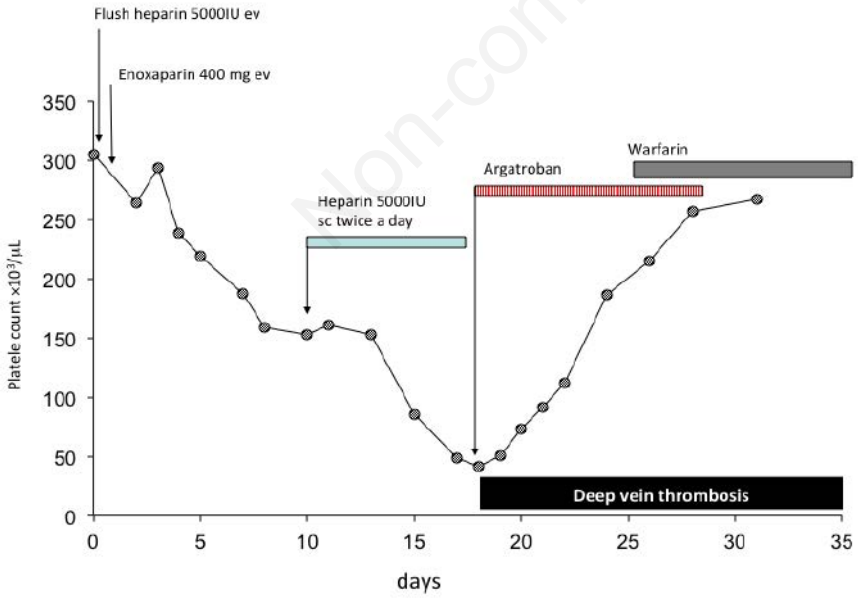

Figure 1. Trend in platelet counts in a patient with acute renal failure and pneumonia due to SARS-CoV-2 infection. On day 0, a bolus of heparin dose of 5000 IU was used; major bleeding occurred on day 5. On day 10, calcium heparin 5000IU subcutaneously twice a day was started. On day 17, calcium heparin was stopped and IgG specific chemiluminescence test was positive for heparin PF4-antibodies. On day 18, a whole leg ultrasound showed a femoral DVT and argatroban was started.

Conclusions

Several limitations of the present case report should be acknowledged. Firstly, a platelet aggregation test could not be performed. Thus, HIT diagnosis was not confirmed. However, the chemiluminescent

test yielded a moderate-strong result and, taking in the account the 4T's score result (at least 6), our patient had more than 90% chance of HIT,[20] which strongly supports a diagnosis of HIT. Whole leg ultrasound was performed only when HIT was suspected, and we cannot exclude that thrombosis was already present, even if DVT symptom occurred during platelet fall. Despite the limitation of a single case report, our observations reveal that HIT occurs in COVID-19 patients treated with heparin and support the intriguing hypothesis that in some COVID-19 patients the thrombo-embolic events may be secondary to anti-PF4-heparin antibodies. In summary, HIT should be suspected and investigated also in heparin treated COVID-19 patients who develop thrombocytopenia.

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