Case Report

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Severe thrombocytopenia in COVID-19

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ABSTRACT

Covid-19 besides pneumonia, may be associated with hematological disorders. Among these is thrombocytopenia, and when severe thrombocytopenia occurs, it may have impact on patient's survival. One of the possible reasons may be immune associated thrombocytopenia. Prompt treatment of this condition is required with steroids and intravenous immune globulin. Herein, we report the case of an 83-year-old man with extremely low platelet count (1 x 10^9/L), which was attributed to immune thrombocytopenia.

KEY WORDS: *COVID-19, thrombocytopenia, SARS-CoV-2, platelets*

INTRODUCTION

COVID-19 pandemic is characterized by pneumonia, but also is associated with a variety of hematological complications[1]. Among these, thrombocytopenia is quite often: it has been observed in one third of COVID-19 patients, even up to 57.7% in those with severe disease[2]. When severe thrombocytopenia occurs, the clinician must consider the likelihood of immune thrombocytopenic purpura (ITP)[2]. Besides, viral infections are known to induce autoimmune phenomena[3]. It has to be reminded that ITP remains a diagnosis of exclusion. When treating ITP, the primary goal is to acquire a safe level of platelets[4], and in COVID-19 patients it is important to balance the thrombotic complications of the virus and the hemorrhagic complications of thrombocytopenia[5].

CASE REPORT

An 83-year-old man was admitted in the COVID-19 clinic of the University Hospital of Ioannina, Ioannina, Greece, with fever, cough, and diarrhea. A polymerase chain reaction (PCR) for SARS-CoV-2 was positive. His past medical history comprised several comorbidities, including heart failure, atrial fibrillation, mechanical aortic valve, implanted pacemaker, chronic obstructive pulmonary disease (COPD), dyslipidemia, chronic kidney disease and anemia of chronic disease. He was receiving pantoprazole, allopurinol, acenocoumarol, eplerenone, amlodipine, digoxin, atorvastatin, furosemide, mirabegron and salmeterol-fluticasone inhaler.

On physical examination, the patient was febrile (37.8 °C), hemodynamically stable with an arterial oxygen saturation of 94% on ambient air. Lung auscultation revealed rales bilaterally. On a chest computed tomography (CT) scan, there was evidence of 25-50% pulmonary involvement. Ceftriaxone and doxycycline were initiated per treatment protocol.

On the 6th day of hospitalization, complete blood count revealed thrombocytopenia (39x10^9/L), with a further decline the next day to 1x10^9/L. The international normalized ratio (INR) was severely prolonged (INR=7.22) but was reversed to normal after stopping acenocoumarol and starting vitamin K intravenously. Vitamin K was administered to avoid severe hemorrhagic complications

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because patient experienced prolonged bleeding from venipuncture site, and platelet count and INR were both extremely affected. Laboratory tests are shown in Table. Peripheral blood smear confirmed thrombocytopenia with no schistocytes or dysplasia. Direct antiglobulin test was negative. Serology tests for hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), and varicella-zoster virus (VZV) were negative. An abdominal ultrasound revealed no specific intra-abdominal pathology. All medications except amlodipine and furosemide were stopped.

The patient was started on intravenous dexamethasone (24 mg/day) and IVIG (25 g/day) with gradual increase in the platelet count. When platelet count reached 85x10^9/L, acenocoumarol was restarted and the patient was discharged. Unfortunately, he suffered a hip fracture 3 weeks after discharge and was lost to follow-up.

DISCUSSION

This is a case of an 83-year-old male patient who presented with extremely low platelet count, which, to our knowledge, is one of the lowest reported in COVID-19 patients.

COVID-19 is characterized by a number of hematological complications, such as lymphopenia and thrombocytopenia[2,6]. Up to 58% of patients with severe COVID-19 will manifest mild thrombocytopenia[2]. As the platelet count drops, mortality increases[7].

Admittedly, immune thrombocytopenia remains largely a diagnosis of exclusion. Disseminated intravascular coagulation (DIC) did not seem to be the case as peripheral blood smear did not show microangiopathic changes, fibrinogen was within normal range and d-dimers were only slightly elevated. INR prolongation was associated with the administration of antibiotics in a patient on acenocoumarol and was reversed with the administration of vitamin K. Moreover, no evidence of sepsis, another viral infection, chronic liver disease or hypersplenism was present.

Heparin-induced thrombocytopenia (HIT) was not considered in this case, as the patient was not receiving any form of heparin. Drug induced immune thrombocytopenia can be expressed with severe degree of thrombocytopenia (<20x 10^9/L); nonetheless, cephalosporin and doxycycline are rarely associated with thrombocytopenia[2].

Several mechanisms have been suggested for SARS-CoV-2-associated thrombocytopenia. These include:

i) *Reduced platelet production*: It is assumed that SARS-CoV-2 enters bone marrow cells and inhibits platelet production and promotes platelet apoptosis[6]. In addition, SARS-CoV-2 impairs thrombopoietin production[2].

ii) *Increased platelet consumption*: SARS-CoV-2 causes

TABLE

	5 days before current admission	On admission	6th day	7th day	9th Day	Discharge	Normal Values
HCT (%)	31.2	28.9	29.0	28.2	29.8	34.1	40-50
Hb (g/dL)	9.9	9.2	9.5	9.1	9.8	11.2	14-16
WBC (10^9/L)	8.64	4.18	3.37	4.90	2.98	9.53	4-10
PLT (10^9/L)	107	142	39	1	12	85	150-400
FIB (mg/dL)		376		399	351		200-400
d-dimers (μg/mL)		0.47		1.12	0.44		<0.5
INR	1.95	2.79	5.2	7.22	1.24	2.05	<1.2
aPTT (sec)	40.3	42.8	58.0	58.6	34.0		30-40
Fragmented red cells (/field)				1-2	3-4		0-2
Cre (mg/dL)	1.78	1.54	1.48	1.58	1.68	1.33	0.6-1.2
Urea (mg/dL)	154	112	94	95	131	141	11-55
CRP (mg/L)	2	3	8	9	5	1	<6
B_{12} (pg/mL)		223					145-914
FOL (ng/mL)		14.3					3.1-19.9

Abbreviations: HCT: Hematocrite, Hb: hemoglobulin, WBC: White Blood Cells, PLT: Platelets, FIB: Fibrinogen, INR: International Normalized Ratio, aPTT: activated Partial Thromboplastin Time, Cre: Creatinine, CRP: C-Reactive Protein, FOL: folic acid

lung damage, platelet aggregate in alveoli and create microthrombi, thus increasing platelet consumption[6]. SARS-CoV-2-associated DIC is another mechanism leading to platelet destruction.

iii) *Increased platelet destruction from immune causes*: Patients with severe COVID-19 have lower levels of regulatory $CD4^+$ T cells, so that they allow cytotoxic $CD8^+$ T cells to cause platelet destruction, apoptosis and hinder platelet production[2]. In addition, increased C-reactive protein (CRP) eases IgG-mediated phagocytic actions against platelets[8]. Another potential mechanism is molecular mimicry, namely development of cross-reactive antibodies to specific components of platelet surface, which results in platelet destruction in the reticuloendothelial system[2].

When severe thrombocytopenia appears (<20 x 10^9/L or a sudden drop >50% over 24-48h), the clinician must consider the possibility of immune thrombocytopenia[2]. The first case suggesting COVID-19 as causal factor of immune thrombocytopenia was described in April 2020[9]. Our patient fits the demographic and clinical characteristics most frequently encountered by a recent systematic review on SARS-CoV-2 immune thrombocytopenia: male, older than 50 years of age, with several comorbidities, and COVID-19 of moderate severity [2]. The lowest platelet count reported was 5x10^9/L.

What seems to be very important in COVID-19 associated immune thrombocytopenia is to weigh the risk between the thrombotic complications of COVID-19 and the bleeding risks of ITP. Practical guidance for the management of adults with immune thrombocytopenia during the COVID-19 pandemic has been recently published[5]. Transfused platelets are of little value as they are probably destroyed and may worsen a prothrombotic state in a patient with coagulopathy[5]. The use of thrombopoietin receptor agonists may increase thrombotic risk, and therefore should be avoided. Steroids are the best choice of treatment for COVID-19 associated immune thrombocytopenia. The optimal dose is 20 mg/day and tapering after 2 weeks is recommended[5]. IVIG is recommended when immediate platelet elevation is required, or in cases of therapeutic failure with steroids[5]. Rapid increase of platelet count after administration of intravenous steroids and IVIG in our patient points to immune thrombocytopenia as the possible cause of thrombocytopenia.

In conclusion, physicians should be aware of COVID-19-associated immune thrombocytopenia, especially as it may carry a high risk of fatal complications and may be masked by concurrent steroid treatment used in the context of COVID-19. Clinical suspicion and prompt diagnosis facilitate timely initiation of appropriate treatment.

Conflict of interest

None to declare.

ΠΕΡΙΛΗΨΗ

Σοβαρή θρομβοπενία σε ασθενή με COVID-19

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Η Covid-19 εκτός από πνευμονία συσχετίζεται και με αιματολογικές διαταραχές. Μία εξ αυτών είναι η θρομβοπενία, και όταν αυτή εμφανισθεί σε σοβαρό βαθμό, απειλείται η ζωή του ασθενούς. Στα πιθανά αίτια συγκαταλέγεται η αυτοάνοση θρομβοπενία. Σε αυτή την περίπτωση απαιτείται άμεση θεραπεία με κορτικοστεροειδή και ενδοφλέβια ανοσοσφαιρίνη. Αναφέρουμε την περίπτωση 83χρονου ασθενή με σοβαρού βαθμού θρομβοπενία (1 x 10^9/L) που αποδόθηκε σε αυτοάνοση θρομβοπενία.

ΛΕΞΕΙΣ ΚΛΕΙΔΙΑ: *COVID-19, θρομβοπενία, SARS-CoV-2, αιμοπετάλια*

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