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Letters to the Editor

Asymptomatic inmune thrombocytopenia associated with COVID-19

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Abstract

The SARS-CoV-2 virus causes a disease that produces multiple clinical manifestations. Abnormal hematologic findings, such as thrombocytopenia, have emerged as a complication of COVID-19.

Worldwide, a series of cases of association between the SARS-CoV-2 virus and immune thrombocytopenia has been described; however, reported to date, it is the first case published in Costa Rica.

This clinical report describes the case of an elderly female patient admitted in the Centro Especializado para la Atención de Pacientes COVID-19, one of the hospitals of the Caja Costarricense de Seguro Social. She was admitted with severe COVID-19, and during her hospital stay, she developed asymptomatic acute thrombocytopenia. The diagnosis of immune thrombocytopenia was made after excluding other diagnoses causing this clinical sign. In addition to the protocolized management of COVID-19 with steroids and enoxaparin, she was treated with an additional cycle of dexamethasone and a dose of intravenous immunoglobulin. After this, she showed a complete recovery of the platelet count.

Keywords: COVID-19; SARS-CoV-2; Thrombocytopenia; Thrombocytopenic purpura.

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Abbreviations:
ITP - immune thrombocytopenic purpura

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In late 2019 in Wuhan, China, an acute respiratory system infection caused by the coronavirus called SARS-CoV-2 emerged in humans, which subsequently became a global pandemic. COVID-19 is known to cause severe pulmonary symptoms and complications; however, the disease has been seen to involve other systems, including the hematopoietic system.[1]

Immune thrombocytopenic purpura" (ITP) or also called immune thrombocytopenia, since many of these patients have no symptoms of bleeding, is defined as an autoimmune disease associated with isolated thrombocytopenia, after excluding other causes of plateletopenia.[2] The classic cutoff for the diagnosis of ITP is <100 x 10^3/µL platelets.[3] It is classified as primary or secondary, depending on whether a causative factor is found.[2] Causes of secondary ITP, which correspond to approximately 18-20% of all cases in adults, include some viral infections.[3] Multiple mechanisms have been described to explain the relationship

between SARS-CoV-2 and thrombocytopenia, the most relevant being the molecular mimicry between viral components and platelet glycoproteins.[6]

Presentation of the case

A 67-year-old female patient, independent for basic and instrumental activities of daily living, diagnosed with poorly controlled type II diabetes mellitus**,** who showed a history of 6 days of abdominal pain, diarrhea, respiratory distress, headache, and unquantified fever. Her chronic treatment included only metformin. A real-time polymerase chain reaction or RT-PCR test for SARS-CoV-2 was performed, with a positive result.

On admission to the hospital, the patient had a temperature of 36°C, respiratory rate of 27 rpm, heart rate of 64 bpm, glycemia by micro method at 258 mg/dl, blood pressure at 126/74 mmHg and oxygen saturation of 93%; with supplementary oxygen requirements by high flow cannula with the following parameters: inspired oxygen fraction (FiO2) of 70% and flow rate of 60 liters per minute (lpm). The rest of the physical examination showed no relevant pathological findings. Her initial and subsequent laboratory examinations are shown in Table 1. The initial chest X-ray showed bilateral diffuse infiltrates with peripheral distribution and basal predominance. The patient was dewormed with albendazole (400 mg every day for three days orally) and ivermectin (12 mg every week for two weeks) and treatment was started according to the local protocol for severe COVID-19 patients with 10 days of dexamethasone (20 mg for 5 days, 10 mg for 5 days intravenously) and thromboprophylaxis with enoxaparin (40 mg every 12 hours subcutaneously).

Table 1. Profile of laboratory results, according to the day of COVID-19 evolution from the date of symptom onset, during a hospital stay at the Specialized Center for COVID-19 patient care of the Caja Costarricense del Seguro Social de Costa Rica, the year 2021.

Day of symptoms	Hemoglobin (g/DL)	Leukocytes (X 10^3/ML)	Lymphocytes (%)	Platelets (X 10^3/ML)	Creat MG/DL	BT (mg/DL)	INR	aTTP (s)	LHD (IU/L)	PCT ng/ML	D Dimer (ng/ML FEU)	Fibrinogen (mg/DL)	Presepsin pg/ML	CRP (mg/L)	FIO2 (%)
6	12.3	10.4	18.1	422	-	0.6	-	-	-	0.1	909	-	767	64	70
8	12.2	16.0	10.6	508	0.5	-	-	-	-	-	-	-	-	70	50
18	13.2	11.6	24.6	422	0.5	-	-	-	-	-	-	-	-	25	40
21	12.5	11.2	26.9	102	0.6	-	-	-	-	-	-	-	-	30	28
22	12.1	8.6	24.7	50	-	-	-	-	-	-	-	-	-	-	28
23	11.7	8.7	25.3	25	0.6	-	-	-	-	0.1	-	-	334	13	24
24	12.3	8.1	31.6	18	0.6	0.5	-		-	-	-	-	-	-	24
25	12.1	10.9	25.2	10	0.6	-	1.07	33	194	-	1037	414	-	-	21
29	13.5	19.4	16.1	23	0.5	-	-	-	-	-	-	-	-	5	21
35	14.2	11.2	34.3	305	0.6	-	-	-	-	-	-	-	-	-	21

Creat: creatinine, BT: total bilirubin, LHD: lactate dehydrogenase, FiO2: inspired oxygen fraction, INR: international normalized ratio, CRP: C-reactive protein, PCT: procalcitonin, aPTT: activated partial thromboplastin time.

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During her hospital stay, there was a slow and gradual reduction of oxygen requirements and improvement of inflammatory markers together with an increase in absolute lymphocyte count. By day 21, from the date of symptom onset, the patient met clinical criteria for COVID-19 recoverability according to Ministry of Health Guidelines version 17: more than 20 days of evolution from symptom onset with more than 72 hours of being asymptomatic.[5] RT-PCR was not performed since it was no longer required according to current legislation. However, before discharge, a sharp drop in platelet count was observed. The count dropped from 422 x 10^3/µL platelets, reported on day 18 of COVID-19 evolution, to a nadir of 10.00 x 10^3/ µL platelets on day 25 (see Table 1 and Figure 1). The hemogram showed no alteration of other cell lines. The only finding reported in the peripheral blood smear was macro platelets. There were no clinical signs of bleeding. The ultrasound approach of the abdomen did not show viscero-megaly or adenopathy.

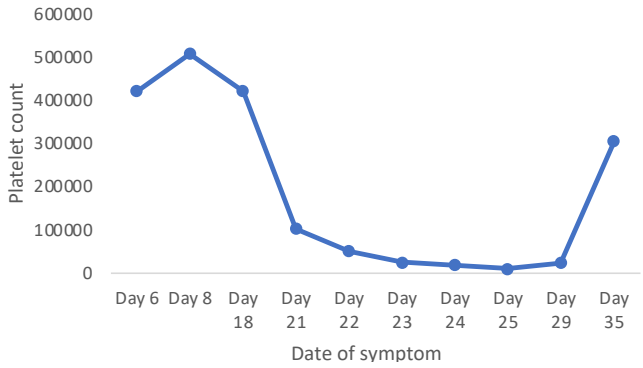

Figure 1. Temporal evolution of platelet count, according to the day of evolution of COVID-19 from the date of symptom onset, during the hospitalization of the patient at the Specialized Center for patient care COVID-19 of the Caja Costarricense de Seguro Social, the year 2021.

Case discussion and analysis

We begin the analysis of the case by characterizing the picture as an isolated acute thrombocytopenia. The first step in the diagnostic approach corresponds to the exclusion of pseudo thrombocytopenia. This is an entity characterized by a false decrease in the automated platelet count.[7] Ethylene diamine tetra acetic acid (EDTA) in blood count collection tubes induces a conformational change in the platelet GpIIB-IIIa complex, which renders it susceptible to autoantibody binding, causing subsequent platelet agglutination. On most occasions (83%) the use of a non-EDTA anticoagulant allows an accurate platelet count.[7] In this case, no platelet clumps were documented in the smear of peripheral blood and it was evidenced that thrombocytopenia persisted, after measuring it in a tube with sodium citrate.

Subsequently, it was necessary to consider etiologies suggestive of a chronic neoplastic inflammatory process of hematologic origin.[8] No compatible clinical manifestations such as weight loss, night sweats, constitutional symptoms, lymphadenopathy, hepatosplenomegaly, blasts, or other relevant findings on peripheral blood smear were reported. In addition, lactate dehydrogenase and erythrocyte sedimentation rate values, which tend to be elevated in several of these entities, were normal.

The hyperinflammatory and coagulopathic state observed in patients with COVID-19 makes it necessary to consider processes such as disseminated intravascular coagulation (DIC) and thrombotic microangiopathy.[3] The patient showed no signs of fragmentation anemia, which excludes the possibility of microangiopathic mechanisms as the etiology of thrombocytopenia. In addition, there was no evidence of bleeding and no evidence of thrombotic organic damage. This, added to an International Society of Thrombosis and Hemostasis (ISTH) scale of fewer than 5 points, makes DIC unlikely.

Given the prolonged stay and the immune dysregulation found in COVID-19, the possibility of thrombocytopenia in the context of a bacterial or fungal superinfection should be examined. No fever or other clinical findings suggestive of a new infectious process such as urinary, respiratory, gastrointestinal symptoms, phlebitis, or signs of systemic inflammatory response were documented. Nor was there any elevation of markers such as presepsin, procalcitonin, or C-reactive protein, which made such an etiology unlikely.

Drug-induced thrombocytopenia occurs because of several mechanisms. The most described is the formation of antibodies against new epitopes generated by the interaction of the drug with platelets. Platelet desensitization can be rapid (within 2-3 days) if the patient is already previously sensitized to the drug, or it may require a latency of 1-3 weeks when a first exposure occurs.[8,9] Among the

drugs most attributed to this condition are antibiotics. The patient did not receive drugs that have been commonly associated with thrombocytopenia (such as antibacterial, and thiazides, among others). No cases of thrombocytopenia induced by ivermectin have been reported.[8] Regarding albendazole, its association is very sporadic. This compound tends to generate medullary suppression of several cell lines and has been described with prolonged use due to pathologies such as hydatid cyst.[10]

Heparin-induced thrombocytopenia (HIT) is an immunological complication that occurs because of the formation of autoantibodies against heparin-platelet factor 4 complexes. It manifests as thrombocytopenia with moderate counts (rarely less than 20.00 x 10^3/µL) and predisposition to thrombotic events. When the patient first receives treatment, thrombocytopenia usually presents in the first 5-10 days; however, when previous treatment has been received, the condition develops within the first 24 hours.[8] In this case, the patient received enoxaparin prophylaxis from admission and was transiently discontinued upon onset of thrombocytopenia; however, since the onset of plateletopenia was later than 14 days from heparin initiation, there was a platelet decline to a level of 10.00 x 10^3/µL, absence of thrombotic manifestations, and a negative antiplatelet factor 4 antibody results in conjunction with a "4T" scale of fewer than 3 points, this entity was ruled out as the etiology of the patient's current condition.

Thrombocytopenia may be associated with systemic diseases with an autoimmune mechanism.[8] In this case, no clinical manifestation compatible with skin rash, fever, alopecia, nephritis, arthralgias, arthritis, uveitis, ulcers on mucous membranes, serositis, hemolytic anemia, or thrombosis was demonstrated. In addition, a general autoimmunity panel was obtained with complement levels, hemolysis markers, antinuclear antibodies, and antiphospholipid antibodies all within the normal range.

Viral induction of autoimmunity can be explained by phenomena such as molecular mimicry, direct infection, and release of inflammatory factors, which could lead to the development of thrombocytopenia, usually after the first week of infection.[4,11] Given the above, the study of agents such as hepatitis B virus is relevant in the diagnostic approach (HBV), hepatitis C (HCV) and human immunodeficiency virus (HIV), as well as Epstein-Barr virus (EBV) and cytomegalovirus (CMV).[11] In this case, serologies for HBV, HCV, and HIV were negative. Concerning EBV and CMV, at no time were there any typical manifestations of this type of infection such as splenomegaly, hepatomegaly, lymphadenopathy, fever, pharyngitis, fatigue, elevated transaminases, increased lactate dehydrogenase or DHL, lymphocytosis, alteration of other cell lines in the hemogram or presence of atypical lymphocytes in the blood smear.[12, 13] This, together with negative serologies, leads to an unlikely diagnosis of acute infection by these pathogens.

Consequently, following an extensive etiopathogenic approach that did not document an alternative etiology of thrombocytopenia, it was classified as an ITP secondary to SARS-CoV-2. It was decided to initiate first-line treatment for ITP, endorsed by the American Society of Hematology in its latest 2019 recommendations.[14] A course of dexamethasone 40 mg IV over 4 days was used. In addition, it was decided to add an application of IV immunoglobulin (IVIG) at a dose of 1 g/kg. This was because a rapid and marked decrease in platelet count was observed with a risk of progressing to values below 10.00 x 10^3/µL. In these cases, the use of IVIG is recommended by some authors to reduce the risk of severe bleeding because it produces an increase in platelet count within 12-48 hours of initiating treatment, while glucocorticoids usually cause a more larval elevation in platelet count (in 2 to 5 days)[3,14,15] Seven days after initiation of treatment, complete platelet count recovery was shown (see Table 1 and Figure 1), meeting the definition of early response (elevation to more than 30.00 x 10^3/µL platelets within one week of initiation of treatment).[14]

The association between SARS-CoV-2 and PTI has already been described in multiple international publications. A systematic review published by Bhattacharjee and colleagues in 2020, which included a sample of 47 cases, describes the clinical profile of these patients. In general, this hematologic presentation is more frequent in patients older than 50 years, especially in patients with moderate or severe COVID-19. It tends to occur between the second and third weeks of evolution and the nadir is usually less than 20.00 x 10^3/µL platelets. Bleeding manifestations described are variable and range from petechiae to intracranial bleeding; however, up to 30% of patients have it asymptomatically.[3]

In this case, the causal association of SARS CoV-2 virus and thrombocytopenia is supported by several points: 1) the exclusion of other alternative etiologies, 2) the concordance of this case with the clinical profile reported internationally, and 3) the response to treatment.

In the case presented, the patient was discharged from the Center in excellent clinical condition to complete her follow-up by the hematology specialty of the hospital corresponding to the area of attraction and it is expected that the course of her disease will be favorable, as reported in the literature for ITP associated with both SARS-CoV-2 and other viruses.[4]

Finally, it is concluded that SARS-CoV-2, like other viruses, can cause immune thrombocytopenia, usually after two weeks of evolution in patients who were affected by the severe disease; it tends to be associated with a good response to treatment and has a good prognosis. To our knowledge, this is the first case of severe immune thrombocytopenia secondary to COVID-19 published in Costa Rica since the beginning of the pandemic, because of this pathogen.

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