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Hospital Infantil de México

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CLINICAL CASE

Thrombotic thrombocytopenic purpura associated with COVID-19 in a critically ill child: a Peruvian case report

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Abstract

Background: *Acquired thrombotic thrombocytopenic purpura (TTP) is a rare disease. In middle and low-income countries, specific resources are required for its diagnosis due to the lack of diagnostic tests and the variable response to plasma exchange, especially in the context of the new SARS-CoV-2 pandemic.* **Case report:** *We report the case of a 9-year-old male Hispanic patient with SARS-CoV-2 infection, atypical presentation, and multisystem involvement, thrombotic microangiopathy with dermal manifestations, hematologic, renal, and neurologic involvement. The patient was followed up after SARS-CoV-2 infection, the PLASMIC score was applied, and a genetic study was performed. Ventilation and hemodynamic support, corticotherapy, immunoglobulins, plasma exchange, renal replacement therapy, and monoclonal antibodies were given without favorable response.* **Conclusions:** *TTP associated with SARS-CoV-2 in the pediatric population is rare. However, resources for the diagnosis, support, and management of patients with TTP are required to avoid fatal outcomes.*

Keywords: *Thrombotic thrombocytopenic purpura. COVID-19. SARS-CoV-2. Child. Peru.*

Púrpura trombocitopénica trombótica asociada con COVID-19 en un niño críticamente enfermo: reporte de un caso peruano

Resumen

Introducción: *La púrpura trombocitopénica trombótica (PTT) adquirida es una enfermedad poco frecuente. En los países de mediano y bajo estatus económico se requieren recursos para el diagnóstico de la PTT, debido a la falta de pruebas diagnósticas y a la respuesta variable al recambio plasmático, especialmente en el contexto de la pandemia por el nuevo SARS-CoV-2.* **Caso clínico:** *Paciente de sexo masculino, de 9 años, hispano, con infección por SARS-CoV-2, presentación atípica y afectación multisistémica, microangiopatía trombótica con manifestaciones dérmicas, y compromiso hematológico, renal y neurológico. Se dio seguimiento posinfección por SARS-CoV-2, se aplicó la escala PLASMIC y se realizó un estudio genético. Se aplicaron soporte ventilatorio y hemodinámico, corticoterapia, inmunoglobulinas, recambio plasmático, terapia de reemplazo renal y anticuerpos monoclonales, sin respuesta favorable.* **Conclusiones:** *La PTT asociada al SARS-CoV-2*

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Date of reception: 05-04-2021
Date of acceptance: 29-07-2021
DOI: 10.24875/BMHIM.21000061

Available online: 21-04-2022
Bol Med Hosp Infant Mex. 2022;79(2):123-128
www.bmhim.com

en la población pediátrica es poco frecuente. Aun así, se requieren recursos para el diagnóstico, el soporte y el manejo de los pacientes con PTT para evitar desenlaces fatales.

Palabras clave: *Púrpura trombocitopénica trombótica. COVID-19. SARS-CoV-2. Niño. Perú.*

Introduction

Thrombotic microangiopathy (TMA) is characterized by microthrombus formation associated with subsequent thrombocytopenia, microangiopathic hemolytic anemia (MAHA), and target organ injury[1]. Thrombotic microangiopathies are a group of disorders primarily related to endothelial dysfunction. This category of endothelial dysfunction results from various imbalances between platelets, the endothelial and immune systems, and cytokine production[2]. Thrombotic thrombocytopenic purpura (TTP) is a fatal condition, rare among hematological diseases, characterized by microvascular thrombosis with platelet aggregation in patients with severe functional deficiency of ADAMTS13 (activity < 10%)[3].

Furthermore, COVID-19 is a new disease with different clinical manifestations observed in children[4,5]. During SARS-CoV-2 infection, hematological diseases such as immune thrombocytopenia and TTP were reported in adults[2,6]. However, information in children is still limited. Hidalgo et al. reported a 14-year-old patient with COVID-19-associated TTP, with a favorable outcome after treatment with plasma exchange therapy (PEX)[7]. Verma et al. described another case of COVID-19 complicated with hemophagocytic lymphohistiocytosis and TTP in a 21-year-old male patient, who died despite treatment[8]. This study aimed to describe the unusual presentation of TTP associated with COVID-19 in a pediatric patient with a fatal outcome.

Clinical case

We describe the case of a 9-year-old male Hispanic patient who presented with abdominal pain and fever of 14 days of evolution to the pediatric emergency department. Five weeks earlier, the mother was positive for SARS-CoV-2 by RT-PCR (reverse transcription-polymerase chain reaction) test; on admission to the hospital, the patient's serological test (IgG) for SARS-CoV-2 antibodies was positive. He had no previous hospitalizations or any report of illness or surgical interventions and had complete immunizations. Vital functions on admission were the following: heart rate 120 beats/min, respiratory rate 22/min, temperature 38°C, weight 30 kg, height 128 cm. On clinical examination, we detected pallor of the skin and mucous membranes, chapped lips, erythematous macular lesions symmetrically distributed on the neck, forehead, and inguinal area. Abdominal pain was present on palpation of the mesogastrium. The results of clinical tests showed hemoglobin, 13.3 g/dL; leukocytes, 18.9 x 10^3/μL; platelets, 528 x 10^3/μL; C-reactive protein, 4.6 mg/dL; normal coagulation profile; fibrinogen, 581.3 mg/dL; lactate dehydrogenase, 1317 U/L; D-dimer, 1.6 mg/L; normal complement C3 and C4; urea, 18 mg/dL; creatinine, 0.4 mg/dL; albumin, 3.7 g/dL; triglycerides, 130 mg/dL; creatine kinase, 25 mg/dL; ferritin, 1016 ng/mL; serum electrolytes with normal values and urinalysis showed hematuria. Abdominal ultrasound showed hepatomegaly, and echocardiography showed no alterations. He received exogenous human immunoglobulin 2 g/kg/day, acetylsalicylic acid 3 mg/kg/day for 7 days, prednisone 2 mg/kg/day for 5 days to treat the probable multisystem inflammatory syndrome. On the second day of treatment, he was afebrile, and on the fourth day, the erythematous lesions decreased; also, there was no hematuria, and he presented a decrease in acute phase reactants, so he was discharged. Five days after discharge, abdominal pain and fever persisted. Clinical laboratory findings were as follows: hemoglobin, 11.3 g/dL; leukocytes, 10 x 10^3/μL; eosinophils, 1305/μL; absolute neutrophil count, 5321/μL; lymphocytes, 2710/μL; platelets, 606 x 10^3/μL; C-reactive protein, 8.2 mg/dL; fibrinogen, 664 mg/dL; D-dimer, 2 μg/mL; ferritin, 1030 ng/mL; lactate dehydrogenase, 890 U/L; coagulation profile, urea, creatinine, and serum electrolytes were normal. Immunological tests were performed: negative antinuclear antibodies (ANA), negative anti-dsDNA, negative antineutrophil cytoplasmic antibodies (ANCA), negative anti-cyclic citrullinated peptide antibodies (anti-CCP), negative rheumatoid factor, negative lupus antibodies, negative antiphospholipid profile, and negative IgG antibodies against *Toxocara*. The patient was treated with methylprednisolone at a dose of 2 mg/kg/day for 7 days, then at a dose of 30 mg/kg for 3 days, and then with prednisone at a dose of 2 mg/kg/day for 15 days. During hospitalization, he presented decreased abdominal pain and absence of fever, so he was discharged with an indication of follow-up control by rheumatology.

Four months later, the patient was readmitted to the pediatric emergency room with 12 days of evolution characterized by fever, abdominal pain, and generalized edema. On admission, he presented a heart rate

of 140 beats/min, respiratory rate of 29/min, blood pressure (p90-95), and edema of the face, genitals, hands, and feet. The skin was cold, turgid, with erythematous macular lesions of urticarial appearance (positive dermographism) associated with diffuse hematic crusts and fine desquamation on the face, neck, thorax, arms, and legs. Examinations found the following values: hemoglobin, 11.6 g/dL; platelet count, 170 x 10^3/μL; prothrombin time (PT), 13.1 s; INR (international normalized ratio), 1.1; activated partial thromboplastin time (aPTT), 34 s; fibrinogen, 432 mg/dL; urea, 16 mg/dL; creatinine, 0.34 mg/dL; D-dimer, 4.32 mg/L; lactate dehydrogenase, 1862 U/L; serum calcium, 7.2 mg/dL; complement C3, 120 mg/dL, and C4, 28 mg/dL, and hemoglobinuria. The patient was transferred to the dermatology department due to the dermatological lesions described. Three days later, the dermal lesions increased (Figure 1), so a skin biopsy of the lesions was performed. The biopsy results described an acute spongiotic dermatitis with intraepidermal vesicles and numerous necrotic keratinocytes in the epidermis, associated with a superficial and deep perivascular and periadnexal inflammatory infiltrate, with numerous eosinophils and extravasation of red blood cells. Histochemical study with periodic acid-Schiff and Alcian blue was negative. He presented with oliguria and generalized tonic-clonic seizures associated with 86% desaturation (fraction of inspired oxygen (FiO_2) 21%) on three occasions. Due to unstable hemodynamic compromise, it was decided to perform endotracheal intubation and transfer him to the Pediatric Intensive Care Unit (PICU) for ventilation and hemodynamic management. The following results were obtained in the PICU: hemoglobin, 10.6 g/dL; schistocytes, 6+/field (blood); positive direct Coombs test; leukocytes, 13.4 x 10^3/μL; platelets, 19 x10^3/μL; haptoglobin not detectable; triglycerides, 280 mg/dL; ferritin, 3442 ng/mL; lactate dehydrogenase, 1862 U/L; D-dimer, 4 mg/L; complement C3, 120 mg/dL, and C4, 28 mg/dL; creatinine, 1.23 mg/dL; creatine kinase, 248 mg/dL; erythrocyte sedimentation rate, 19 s, and ADAMTS13 activity (von Willebrand factor-cleaving protease) in 54% (RV: 40-130%) after transfusion support of blood products. Flow cytometry showed a decrease in T lymphocytes, CD4+ lymphocytes, CD8+ lymphocytes, an increase in CD4/CD8 ratio for age, and a decrease in natural killer (NK) cell count. Viral load for Epstein-Barr virus, cytomegalovirus, and parvovirus B19 was negative.

Renal ultrasound showed the left kidney with asymmetry compared to the contralateral one; in the Doppler study, a decreased wave depth was identified, suggesting left renal hypoperfusion. With the clinical and laboratory manifestations described, the patient was diagnosed with TTP. The PLASMIC score was 7 (Table 1). He received fresh frozen plasma, renal replacement therapy, methylprednisolone cycles, human immunoglobulin, and rituximab (Table 1). Due to persistent severe thrombocytopenia, it was decided to initiate plasma exchange (PEX), and the patient received 14 sessions. Although the patient received platelet transfusion to compensate for the platelet deficit, he did not respond well.

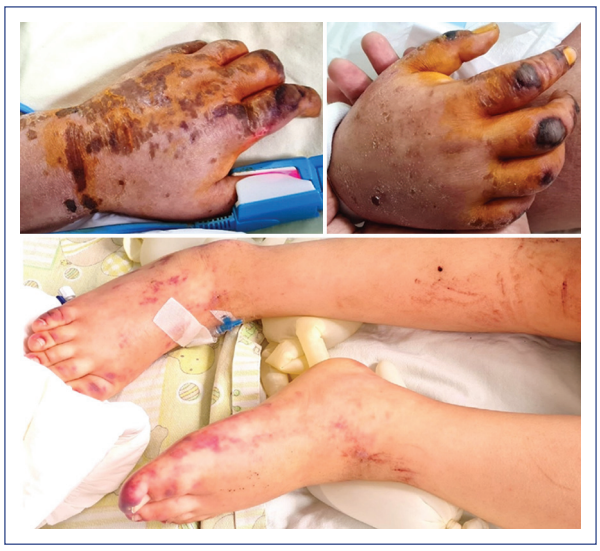

Figure 1. Erythematous macular lesions with excoriated hematic scabs in the hands associated with purpuric dermatosis in the patient's lower limbs on the Pediatric Intensive Care Unit admission day.

The patient presented sensorium deterioration during the PICU stay, and an intracerebral hemorrhage was detected one month after the last PEX session in a CT scan. The patient evolved unfavorably with a fatal outcome in the second month of hospitalization. Gene sequence analysis and deletion/duplication test of 13 genes (ADAMTS13, C3, CD46, CD55, CD59, CFB, CFH, CFI, DGKE, INF2, MMACHC, PLG, THBD) for atypical hemolytic uremic syndrome and thrombotic microangiopathy were negative.

Discussion

Acquired TTP has been described as a clinical presentation associated with COVID-19 in adults[6]. However, since TTP in children is rare[3], only a few cases have been reported in children[7].

Table 1. Laboratory test results during hospitalization

Hospital admissions	1st	2nd	3rd							
Department	Medicine	Medicine	Dermatology	PICU						
Hospitalization day	1	1	1	1*	3+	11	16	23	30	37
Treatment					MTP+Ig/ Rtmb/ PD	MTP/ PEX/ PD	MTP/ Rtmb/ PEX/ HD	PDN/ Rtmb/ PEX/ HD	PDN/ Rtmb/ HD	PDN/ HD
Hematology results										
Hemoglobin (g/dL)	13.3	11.3	11.6	10.6	8	10	7.8	9.1	7.8	8.4
Leukocytes ($10^3/\mu L$)	18.9	10	16.4	13.4	9.2	17.4	11.6	5.4	2.2	5.3
Platelets ($10^3/\mu L$)	528	606	170	19	14	68	40	32	99	51
Prothrombin time (s)	12.8	12.4	13	16	13	12.4	13.1	13.5	—	13.8
INR	1.1	1.0	1.1	1.4	1.1	1	1.1	1.1	—	1.2
Thromboplastin time (s)	29.6	28.5	34	44	29	33.5	37.2	43.7	—	42.7
Thrombin time (s)	17	17	18.7	27	23	21	19.8	25.8	—	24
Fibrinogen (mg/dL)	581.3	664	432	300	335	230	253.4	226.6	—	164.1
D-dimer (mg/L)	1.6	2.0	4.32	6.8	12.2	—	—	3.6	—	
Biochemical results										
Ferritin (ng/mL)	1016	1030	—	3442	23943	3254	—	—	—	—
C3 (mg/dL)	101		120	—		—	—	—	—	—
C4 (mg/dL)	24	32	28	—		—	—	—	—	—
Lactate dehydrogenase (U/L)	1317	890	1862	—	10,562	2279	1780	754	494	—
Urea (mg/dL)	18	23	16	49	173	177	245	84	54	57
Creatinine (mg/dL)	0.4	0.32	0.34	1.23	4	3.6	4.14	1.9	1.8	1.8
GOT (U/L)	34	50	48	233	360	—	—	32	—	—
GPT (U/L)	17	49	9	61	—	—	—	42	—	—
CPK (mg/dL)		44	248	—	1883	—	—	31	—	—
CPK-MB (U/L)	25	14	26	—	102	—	—	12	—	—
C-reactive protein (mg/dL)	4.6	8.17	4.76	5.9	6	2.6	—	2.2	—	12.8

(*) PLASMIC score: platelet count < 30,000/μL: 1; hemolysis: 1; no active cancer: 1; no solid organ or stem cell transplantation: 1; no diarrhea: 1; INR < 1.5: 1; creatinine < 2.0 mg/dL: 1 (score 7). Corticosteroid onset: MTP (1 g) + Ig 5% (30 g) for 5 days. Then it was decreased to MTP (125 mg) every 6 hours for 5 days and MTP (125 mg) every 8 hours for 5 days, then moved to PDN (1 mg/kg) equivalent dose in dexamethasone. Initiation of Rtmb (375 mg/m^2/dose each week*4 doses). (+) Indication of fresh frozen plasma (10 cc/kg/dose every 8 hours).
CPK, creatine phosphokinase; GOT, aspartate aminotransferase; GPT, alanine aminotransferase; HD, hemodialysis; Ig, immunoglobulin; MTP, methylprednisolone; PD, peritoneal dialysis; PDN, prednisone; PEX, plasma exchange: received 14 cycles; Rtmb, rituximab.

On our patient's first hospital admission, he was diagnosed with the multisystem inflammatory syndrome (MIS-C), for which he received MIS-C therapy. He was readmitted to the hospital four months later with multiple organ damage, probably of autoimmune origin, triggered by SARS-COV-2 post-infection.

After PEX, our patient underwent ADAMTS13 dosing. This procedure delivers the deficient enzyme (ADAMTS13) and eliminates autoantibodies that inhibit ADAMTS13 activity. In some cases of acquired TTP with ADAMTS13 deficiency, antibodies may be undetectable, probably related to the lack of sensitivity of the available methods[9] and the sensitivity of anti-ADAMTS13 antibodies of IgM or IgA type[10], or due to altered synthesis or secretion of ADAMTS13[11]. Therefore, the result was interpreted in normal ranges.

Additionally, the patient presented features of MAHA associated with TMA in the clinical context of anemia, reticulocytosis, schistocytosis, elevated lactate dehydrogenase, undetectable haptoglobin, hemoglobinuria, and severe thrombocytopenia.

The PLASMIC score discriminates between PTT and other TMA, such as atypical uremic syndrome, reliably assesses the likelihood of a severe deficit of ADAMTS13 activity in patients with TMA and could help improve the accuracy of clinical assessment and be beneficial when ADAMTS13 testing is unavailable[12,13]. Gupta et al. reported that the PLASMIC score could also be a good predictor to identify pediatric patients with an ADAMTS13 activity less than 10%[14].

On admission to the PICU, a PLASMIC score of 7 we obtained in the patient (platelet count < 30,000/μL, hemolysis, no active cancer, no solid organ or stem

cell transplantation, no diarrhea, INR < 1.5, creatinine < 2.0 mg/dL). Therefore, the PLASMIC score predicted ADAMST13 deficiency and high suspicion of TTP and guided the management of PEX according to its score.

RT-PCR for SARS-CoV-2 was negative on readmission, but serologic testing was positive for SARS-CoV-2 IgG, similar to a 14-year-old male with a previous infection with SARS-COV-2 who developed a TTP with a favorable evolution after PEX sessions[7].

The association of other viruses, such as human immunodeficiency virus, human lymphotropic lymphoma virus-1, hepatitis C, dengue, influenza, cytomegalovirus, human herpesvirus 8, human herpesvirus 6, and parvovirus B19, with the acute development of TTP has been described[15]. The late development of this complication, however, is unclear. Oka and Nohgawa described a case of acquired TTP associated with EBV reactivation in a 37-year-old healthy male who recovered spontaneously without any treatment[16]. As the mechanism is still under study, further clinical reports and studies are needed.

In the PICU, management was performed with hemodynamic support, corticosteroids, immunoglobulin, rituximab, and fresh frozen plasma. The patient showed a gradual but ineffective response while waiting for the initiation of PEX, which began 11 days after the diagnosis of TTP. It has been shown that the use of immunosuppressive therapy together with PEX improves the therapeutic response and decreases the days of PEX, avoiding the complications of this procedure[17].

During PEX, a partial response was evidenced with a decrease in MAHA and partial clinical improvement of the patient. Unfortunately, due to the lack of resources needed to maintain PEX, the patient only received 14 cycles, and the target platelet count > 150 x 10^3/μL on two control measurements, or more days as a cut-off point for completion of this procedure, was not achieved (Table 1). PEX is used in patients with a presumptive or confirmed clinical diagnosis of TTP. It is used in all patients because, if left untreated, they progress to neurologic deterioration or renal failure. Mintz et al. have described the use of up to two cycles of PEX in patients with TTP in a clinical trial. In this study, of seven patients with a second cycle of PEX, four achieved remission[18]. Another report described up to 25 daily sessions of PEX without complications and with a favorable evolution[7]. A recent study on the use of PEX in a PICU in Chile reported complications related to the apheresis circuit, hypotension, anaphylaxis, or transfusion-related acute lung injury[19]. Although the mean number of PEX sessions in this study was lower than that in our patient because the pathologies evaluated were different, no hemorrhagic complications were reported[19].

The delay in the initiation of treatment, the premature interruption of PEX, and the suspicion of recurrent acquired TTP were the possible causes of the patient's poor response to treatment, with severe renal and neurological compromise. Analysis of the disease course suggested TMA diagnosis that was partially treated with corticosteroids, immunomodulatory therapy with immunoglobulin, rituximab, and PEX. The genetic panel to rule out hereditary TTP, complement-associated hemolytic uremic syndrome, and alterations of vitamin B12 metabolism tested negative, confirming acquired TTP.

One of the limitations of this report is the insufficient evidence in the literature to conclude that the immune response to SARS-CoV-2 caused acquired TTP. Further studies are required to confirm a causal relationship between these two conditions.

In conclusion, the presentation and clinical course of acquired TTP probably associated with SARS-CoV-2 was severe. Early diagnosis and prompt initiation of combination therapy are essential for a better prognosis.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author has this document.

Conflicts of interest

The authors declare no conflict of interest.

Funding

None.

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