Anemia and thrombocytopenia: attention and care that the pediatrician must have during the service

Abstract
Thrombotic microangiopathies encompass a set of pathologies that evolve with nonimmune hemolytic anemia and thrombocytopenia, but underdiagnosed in the pediatric age group. This article reports the case of a child with a diagnosis of systemic lupus erythematosus (SLE), macrophagic activation syndrome (MAS) and thrombotic thrombocytopenic purpura (TTP), which evolved to death. Due to the severity of thrombotic microangiopathies and their underdiagnosis, we propose a flowchart of ducts in the anemic and thrombocytopenic patients, with careful care in platelet transfusion.

Introduction
Thrombotic microangiopathies (TMA), defined by microangiopathic hemolytic anemia (MAHA), associated with thrombocytopenia and ischemic lesion in microvascular target organs, are hematological emergencies that require urgent intervention. In MAHA, a non-immune anemia occurs due to intravascular hemolysis, secondary to endothelial cell aggression, platelet thrombi and fibrin, with consequent vascular lesion, resulting in increased LDH (lactic dehydrogenase), presence of schizocytes, indirect hyperbilirubinemia, low haptoglobin, reticulocytosis and negative Coombs direct test. Due to the severity and the underdiagnosis of TMA, requiring early treatment, patients with anemia and thrombocytopenia without definite cause should be investigated early. The study aims to propose a flowchart for management and/or referral to a reference center, in cases of anemia with thrombocytopenia.

Case report
A 9-year-old female patient, weighing 26kg, height 1.32m, was transferred from another service to the pediatric prompt service of the Children’s Institute of Hospital das Clinicas of the Medical School of the University of São Paulo (ICr - HCFMUSP) by the hypothesis diagnosis of meningococcemia, after a history of skin rash, fever and seizure. At the anamnesis, the mother reported appearance of erythematos; purpura; TMA, Thrombotic Microangiopathy; SLE, Systemic Lupus Erythematosus.

Abbreviations:
- TTP, Thrombotic Thrombocytopenic Purpura; TMA, Thrombotic Microangiopathy; SLE, Systemic Lupus Erythematosus;

First, performed laboratory tests, showing hemoglobin (Hb) 6.0g/dL (11.7-14.4g/dL); Hematocrit 18.9% (38-50%); 12100 leukocytes/mm³ (4500-14500/mm³); Platelets 6k/μL (150-450k/μL); serum potassium (K+) 4.2mEq/L (3.5-5.0mEq/L); serum sodium (Na+) 130mEq/L (135-145mEq/L). Initiated antibiotic therapy with ceftriaxone and amikacin. She received a transfusion of red blood cells and platelets when she presented a new seizure. Computed tomography (CT) of the skull was performed, and the report was normal. We chose to transfer the patient to a reference center (ICr - HCFMUSP) for diagnostic evaluation. Mother still reported unquantified discrete weight loss. She denied other complaints, traumas, contact with sick people, comorbidities, drug use, family illness and allergies.

In the ICr, also evidenced a right pleural effusion and a discrete pericardial effusion with preserved cardiac function, with a diagnostic hypothesis of Systemic Lupus Erythematosus (SLE), being requested evaluation of the team of rheumatology and hematology. Relevant laboratory tests: Electrolytes within the normal range, C-reactive protein: 1.01mg/L (<5), corrected reticulocytes: 7.5% (0.8-2.1), indirect bilirubin 1.21mg/dL (<0.6), LDH 1911U/L (143-190), Hb 8.4g/dL (11.7-14.4), 8070leukocytes/mm³ (4500-14500), Platelets 4k/μL (150-450k/μL); urea 63mg/dL (11-38), creatinine 0.86mg/dL (0.39-0.73), APT 29.4s (25.4-38.9), INR 1.0 (0.9-1.2), fibrinogen 168mg/dL (238-498), ferritin 2825mg/mL (20-200), triglycerides 173mg/dL (<130), proteinuria/creatinuria ratio 2.8 (<2.0), FAN: fine dotted pattern 1:320, Coombs direct positive, C4 and C3 low, Anti-SM positive and partial negative cultures. In conjunction with the specialties, diagnosed SLE and Macrophagic Activation Syndrome (MAS) by the criteria of the American College of Rheumatology (1997). Transferred to the Intensive Care Unit (ICU) for treatment with pulse therapy and hydroxychloroquine. In the ICU, She continued pulse therapy, removed antibiotic therapy and remained under observation due to anemia and thrombocytopenia. The next day, She presented a new generalized tonic-clonic seizure, improved with benzodiazepines. Passed central venous catheter into right femoral vein. Patient evolved with symptomatic bradycardia, with return of the circulation after 2 minutes and cardiopulmonary resuscitation (CPR). After 5 minutes,
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she presented cardiorespiratory arrest, with intense bleeding (oral mucosa, conjunctiva, nasal), cardiopulmonary resuscitation for 25 minutes, without return of spontaneous circulation. Declared death without definite cause. Autopsy report showed thrombosing coagulopathy secondary to SLE, with multisystemic arterial thrombosis and severe cardiac involvement. Plasma activity of ADAMTS-13 by fluorescence of <0.02 IU / mL (> 0.5). A peripheral blood slide with numerous schizocytes (Figure 1). These findings corroborate with the diagnosis of Systemic Lupus Erythematosus, Macrophagic Activation Syndrome (MAS) and Thrombotic Thrombocytopenic Purpura (TTP).

Figure 1 Numerous schizocytes in a peripheral blood slide

Discussion

Classification and presentation of TMA

Thrombotic microangiopathies (TMA) can be classified as: primary thrombotic thrombocytopenic purpura - TTP (acquired and congenital) and hemolytic uremic syndrome - HUS (STEC-HUS, pneumococcal HUS, atypical HUS); and secondary to malignant hypertension, pregnancy-related, drug-related and toxin-related forms of infection (HIV, Influenza, Epstein-Barr virus), cancer and bone marrow transplantation, disseminated intravascular coagulation (DIC), metabolic vitamin B12 and secondary to vasculitis.1,2,4,7,9 The treatment of these secondary forms is the treatment of the causative pathology itself, for example, in the case of vitamin B12 deficiency, the conduct is replacement of this vitamin. In the primary forms, the treatment will depend on the type. HUS typical or associated with diarrhea.9 is so named because it is most commonly caused by Shiga-Toxin-producing Escherichia coli (STEC), which mainly affects the age group below 5 years and is the main cause of acute renal dysfunction in children north.9 The HUS caused by Streptococcus pneumoniae is classified by some authors as another typical form of HUS, since the neurominidase released by this bacterium, as well as the Shiga-toxin, act directly on the endothelium (mainly renal), causing AHMA, thrombocytopenia, and important acute renal injury, often dysalteric.2,4 Atypical HUS (HUSa) is considered an atypical form due to the fact that it is a deregulation of the complement system (mainly due to factor H deficiency), generating excessive activation of the alternative pathway of the complement and important endothelial injury, consequently to TMA and also renal injury important. George JN et al.11 stresses that the atypical designation does not denote specificity nor does it report the cause, preferring the term “complement-related TMA.”

TTP is a rare disease, mainly in pediatrics (3% of cases),12 but with important mortality if not diagnosed and treated quickly. It is caused by a severe deficiency of ADAMTS 13 (disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13), usually below 10%12,13 or 5%.12 It can be acquired (IgG auto antibodies against said enzyme) or congenital deficiency (Upshaw-Schulman Syndrome). With the deficiency of ADAMTS 13, the von Willebrand factor (VWF) present in the endothelium is not cleaved, generating thrombi in the microcirculation due to the accumulation of these multimers, consequently to TMA and its aggressions in several organs. According to Deroux A et al.,11 the main lesions found were: renal lesion (48%), neurological alteration (66%), fever (30%) and classic findings with these three alterations+MAHA+thrombocytopenia (11%).13 Another secondary cause of TMA is DIC, making an important differential diagnosis with HUS and TTP, with high morbidity and mortality. The DIC is caused by the massive activation of the coagulation system, generating deposition of circulating fibrin, leading to the consumption of coagulation factors and platelets, with subsequent bleeding. In the DIC, in addition to thrombocytopenia, hypofibrinogenemia, enlargement of APTT and INR, and increase of D-dimer5 occur.

Treatment of TMA

As for treatment, typical HUS is hemodynamic and dialytic support, whereas in HUSa, Eculizumab9 is indicated as a treatment due to inhibition of the excessive activation of the alternative complement pathway.5,9,12 Plasmapheresis is the treatment of choice in TTP acquired by removing IgG antibodies from the circulation and replenishing ADAMTS 13 during plasma transfusion. Corticosteroids are also recommended as first-line treatment, followed by rituximab and other alternative treatments in refractory forms. In congenital TTP, the treatment is plasma transfusion or recombinant ADAMTS 13 in order to increase the circulation of ADAMTS 13 in the bloodstream. The misinterpretation of the diagnosis can determine platelet transfusion in TTP, which will increase microthromboses, arterial thromboses, acute myocardial infarction, ischemic stroke and acute renal injury, leading to greater morbidity and mortality.14,15 This is due to the accumulation of Von Willebrand factor multimers in the vascular endothelium, which were not broken by the ADAMTS 13 deficiency, forming platelet thrombi and its consumption, being aggravated by the incorporation of more platelets that are transfused.

Handling suggestion

Due to the difficulty in the differential diagnosis between TMA and its adequate treatment, with relevance to TTP, where platelet transfusion increases morbidity and mortality, we propose an initial investigation and management flowchart for patients with anemia and thrombocytopenia to be clarified (Figure 2).

Initial Investigation

Firstly, we are faced with a potentially serious patient with no cause for anemia and thrombocytopenia, in need of rapid diagnosis. After this blood count confirmation, we should investigate TMA, with the expected results.2

1. Research of schizocytes: generally greater than 1% in TMA (or greater than 2 per field of increase of peripheral blood smear), 0.5-1% in DIC and less than 0.5% as normal value3,6; examination and shows the intravascular destruction of red blood cells
2. Increased LDH, whereas Barcellini W et al.6 reports that the value of falling LDH is an important marker of disease improvement and that the LDH/TGO ratio=22.12 is suggestive of TTP. Already Beris P et al.,7 suggests that very high values of LDH are suggestive of
intravascular hemolysis, whereas those slightly increased suggest extravascular hemolysis
3. Increased indirect bilirubinemia due to heme conversion after hemolysis
4. Decreased Haptoglobin, since this protein produced in the liver binds to the erythrocyte and is destroyed along with it during hemolysis. In hepatic dysfunction, haptoglobin is low because of lack of production
5. Corrected reticulocytes above 1%; showing increased production by the bone marrow
6. Generally normal INR, APTT, fibrinogen and D-dimer, for the differential diagnosis with DIC
7. Direct Antiglobulin Test (Coombs) negative, to exclude autoimmune cause
If the TMA hypothesis is confirmed, a referral center with a hematologist should be sent to discuss the case and assess the need for a myelogram.

Figure 2 Flowchart of ducts in front of the patient with anemia+thrombocytopenia.

Initial care
Before starting therapy, we must collect sample for dosage of ADAMTS 13, complement genetic research, coproculture and Shiga toxin research. After collection of the above exams, and without the diagnosis, we must initiate plasmapheresis (in the available places) or transfuse fresh plasma, avoiding to transfuse platelets before the correct diagnosis. This concern is due, as already reported, to the increase in morbidity and mortality when transfusing platelets in TTP. In addition, in cases of HUS and DIC there is no worsening with plasmapheresis or transfusion of fresh plasma. Anamnesis and physical examination will help differentiate between HUS, TTP and DIC, but proper treatment and transfer to a specialized hematology center as soon as possible can change patient outcomes. All this concern is due to the important decrease in mortality in TTP, evolving from 90% to 20% when plasmapheresis is performed.

Conclusion
In the initial diagnosis of anemia and thrombocytopenia, we must keep in mind the TMA, mainly thrombotic thrombocytopenic purpura, in view of its important morbidity and mortality. The great concern is due to the fact that it is not recommended to transfuse platelets in these patients, despite the intense thrombocytopenia, which can be catastrophic in clinical evolution.

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None.

Conflict of interest
The authors declare there is no conflict of interest.

References

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