Case Report

The paradox of thrombotic thrombocytopenic purpura and the TACO challenge!

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ABSTRACT

Thrombotic thrombocytopenic purpura (TTP) is a rare medical emergency characterized by the pentad of microangiopathic hemolytic anemia, thrombocytopenia, fever, renal failure, and neurological dysfunction. TTP is an infrequent condition and is a thrombotic microangiopathy. TTP is essentially a clinical diagnosis. As untreated TTP has a high mortality, diagnosis is usually presumptive and prompt treatment with plasma exchange is highly beneficial and reduces mortality significantly. Therapeutic plasma exchange with fresh frozen plasma is the standard treatment of choice for TTP. Transfusion-associated reactions may occur in some patients further complicating the disease picture and prolonging hospital stay and recovery. Transfusion-associated circulatory overload and transfusion-associated acute lung injury are the leading cause of transfusion-related mortality. We present here the diagnostic and therapeutic challenges that we faced with a young male patient who presented with fever, jaundice, and seizures.

Key words: Circulatory overload-transfusion associated, Plasma exchange, Thrombotic microangiopathies, Thrombotic thrombocytopenic purpura, Transfusion reactions

Thrombotic microangiopathy (TMA) syndromes are a group of disorders associated with microangiopathic hemolytic anemia, thrombocytopenia, as well as microthrombi which lead to ischemic tissue injury. The classical TMAs are hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) [1]. Other causes include malignant hypertension, systemic autoimmune disorders, antiphospholipid syndrome, and drug toxicities [2]. TTP could be congenital due to deficiency of ADAMTS13 (A disintegrin and metalloprotease with a thrombospondin-like domain) or acquired due to autoantibodies against ADAMTS13. TTP must be thought of when there is the presence of microangiopathic hemolytic anemia with thrombocytopenia in the absence of other contributing causes. The classical pentad consists of fever, changes in mental state, altered kidney function, microangiopathic hemolytic anemia, and thrombocytopenia occurs in less than 10% of the patients.

CASE REPORT

A 29-year-old male patient with no comorbid medical conditions presented with fever, jaundice, and diffuse abdominal pain for 2 days. He also had an episode of loss of consciousness lasting for 5 min. He had no history of vomiting, pruritis, or pale colored stools.

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On examination, the patient was icteric, conscious, and oriented. His temperature was 100° F, respiratory rate was 22 per min, heart rate was 110 per min, and blood pressure was 110/70 mmHg. He had bilateral subconjunctival hemorrhage and hematuria was noted on catheterization. Other systemic examinations were grossly normal.

On initial investigations, his complete blood picture showed normocytic normochromic red cells with the presence of fragmented red cells, neutrophilic leukocytosis, 9% blasts, and severe thrombocytopenia, as shown in Fig. 1. Elevated urea and creatinine, indirect hyperbilirubinemia were noted, as shown in Table 1. Apart from this, serum haptoglobin was reduced. His prothrombin time and activated partial thromboplastin time were normal. Tropical fever workup, namely, malaria, scrub typhus, dengue, leptospirosis, enteric fever, and hepatitis serology was negative. However, there was a serial decline in hemoglobin and platelets. Further investigations showed elevated lactate dehydrogenase (LDH), elevated reticulocyte count, and hemoglobinuria. Magnetic resonance imaging brain showed acute left gangliocapsular infarct. Electroencephalogram was normal.

Our differential diagnoses at this point were thrombotic microangiopathies, sepsis with disseminated intravascular coagulation, hematological malignancy, immune-mediated hemolytic anemia and thrombocytopenia, and paroxysmal nocturnal hemoglobinuria. Bone marrow aspiration showed

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normoblastic to megaloblastic erythroid hyperplasia and 2% atypical cells and biopsy showed normocellular marrow. Repeat peripheral smear showed no blast cells. The earlier blast picture was probably due to stress and the marrow's response to hemolysis. Autoimmune workup was negative and blood, urine cultures were sterile. Coagulation profile, prothrombotic workup (prothrombin, antithrombin III, and protein C and S activity), and flow cytometry (for CD55- and 59-deficient cells) were normal. Antiphospholipid antibodies, antinuclear antibodies, and anti-neutrophilic cytoplasmic autoantibody profiles were negative.

The classical clinical presentation and further investigations led us to the diagnosis of TMA. The patient was promptly started on therapeutic plasma exchange (TPE). Platelet counts showed a rising trend following the initiation of plasma exchange. His LDH, liver parameters, and reticulocyte count also stabilized subsequently. Urine became clear and subconjunctival hemorrhage started resolving. The patient was supported with antiepileptic drugs for seizures and required two sessions of hemodialysis as he was oliguric with acute kidney injury. However, 5 hours after the fourth plasma exchange, the patient developed dyspnea, tachypnoea, hypoxemia, hypertension with elevated jugular venous pressure, lung crepitations, and bilateral pedal edema. He did not have fever, chest pain, or palpitations. There was no worsening of hemolytic features clinically nor evidenced in laboratory parameters. His white cell counts, procalcitonin, and cultures were sterile ruling out any new infection. Electrocardiogram did not show any dynamic ST-T changes. The echocardiogram was normal and cardiac markers were elevated (NT-proBNP 515 pg/ml). Plasma transfusion-associated circulatory overload was considered and further plasma exchange was withheld. The patient was supported with fluid restriction, diuretics, and non-invasive ventilation. The patient improved gradually and was discharged. On further follow-up 2 and 4 weeks later, the patient was asymptomatic with normal blood counts, normalized bilirubin, LDH, and reticulocyte counts.

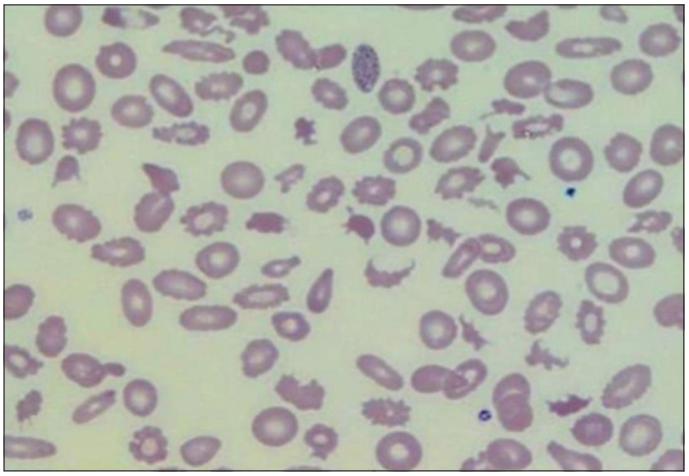

Figure 1: Peripheral smear (100×) by Leishman staining showing the presence of fragmented red cells

DISCUSSION

Fever, microangiopathic hemolytic anemia, and thrombocytopenia are central to both HUS and TTP – the classical TMAs, whereas, neurological manifestations are more common in TTP and acute kidney injury is commoner in HUS. HUS could be typical as in Shiga toxin-mediated STEC-HUS where it is preceded by infectious diarrhea or atypical where it is complement mediated. TTP is relatively uncommon before 20 years of age, with the peak incidence of 30–50 years with male: female ratio of 2:1 [3]. HUS tends to occur more in children and has no sex predilection and is associated with profound thrombocytopenia. Our patient's age group and the absence of gastrointestinal symptoms ruled out a typical HUS. Furthermore, neurologic abnormalities favored the diagnosis of TTP in this patient.

Acquired form or secondary TTP is due to autoantibodies against ADAMTS13 and is usually triggered by infections, autoimmune disorders, cancer, HIV, and pregnancy. The platelet- vWF complexes form microblood clots and shearing of the blood cells when passing through these blood vessels will result in schistocytes. Peripheral smear classically demonstrates schistocytes which are fragmented red cells. The hemolysis tends to stimulate the bone marrow and at times, leads to the formation of blast cells [4]. Therefore, probably, the first peripheral smear in our patient too had blast cells. However, subsequent smears or bone marrow biopsy ruled out atypical cells.

TTP is a medical emergency and the decision to initiate TPE solely lies on the presenting clinical features. Our patient had

Table 1: The serial laboratory parameters at admission and after plasma exchange

Laboratory parameters (reference range)	At admission	12 h after admission	24 h after admission	Plasma exchange D1	Plasma exchange D2	Plasma exchange D3	2 weeks later	4 weeks later
Hemoglobin (13–17g/dL)	13.7	8.6	5.3	7.9	7.3	7.6	9.3	9.6
White cell counts (4–10×10^3/uL)	28,000	12,300	8300	13,100	9900	9400	5500	7700
Platelets (150–400×10^3/uL)	14,000	22,000	15,000	30,000	52,000	94,000	271,000	231,000
Bilirubin total (0.2–1.0 mg/dL)	5.5				2.0	1.4		0.8
Bilirubin indirect (0.2–0.8)	4.9				1.5	0.6		0.4
Lactate dehydrogenase (135–225 U/L)	750		626	592	574	614		356
Reticulocyte count (0.5–2.5%)	3.5%	3.5%	3.0%	2.5%	2.0%	1.9%		1.2%
Urea (6.5–18.7 mg/dL)	60	96	75	197	175	124	34	18
Creatinine (0.8–1.25 mg/dL)	2.23	5.55	4.39	8.77	7.28	3.97	1.73	1.27

fever, an episode of loss of consciousness, hemolytic anemia, thrombocytopenia, acute kidney injury, and all these classical features favoring the diagnosis of TTP. Although severe deficiency of ADAMTS13 confirms the diagnosis, the *in vitro* measurements may not correlate with *in vivo* activity and its measurement is only supportive and not absolutely necessary for initiating management. The turnaround time for ADAMTS13 assays may be quite long and it may be disastrous to delay treatment based on the levels. However, drawing blood for ADAMTS13 measurement before the initiation of TPE will support the diagnosis, determine the severity of disease, duration of treatment, and has prognostic value.

The complement levels in our patient were normal and the patient showed a sustained favorable response following plasma exchange treatment, thereby ruling out atypical HUS [5]. Drug-induced TMA was not considered in view of negative drug history. The patient had normal fibrinogen levels and coagulation parameters were normal ruling out disseminated intravascular coagulation.

According to the guidelines of the American Society for Apheresis (ASFA), usage of TPE in TTP is a category 1 indication-accepted first-line therapy or predominantly stand-alone therapy [6]. ASFA suggests that in TTP, TPE be done daily and that the plasma volume replacement be 1–1.5 times the exchanged volume. Usually, around five plasma exchanges may be required. The initial response to TPE is said to be satisfactory once the neurological symptoms resolve and hemoglobin, platelet counts start improving along with normalization of LDH and bilirubin levels. Further exchanges may be discontinued when neurological symptoms resolve, platelets are above 150,000, and LDH becomes near normal for 2–3 consecutive days.

Corticosteroids are used as adjunctive therapy along with TPE in TTP. Other adjunctive therapies include rituximab, vincristine, cyclophosphamide, and intravenous immunoglobulin. Another drug Caplacizumab, an anti-von Willebrand factor humanized immunoglobulin, also has shown to halt disease progression but had major bleeding tendencies as an adverse effect.

Despite strict hemovigilance practices, transfusion-associated adverse reactions are grossly underreported throughout the globe. This is attributable to the failure to recognize symptoms and to temporarily correlate to blood product transfusion [7]. According to the Food and Drug Administration, 30% of the transfusion fatalities between 2012 and 2016 were attributed to transfusion-associated circulatory overload (TACO) [8]. TACO is characterized by cardiogenic-pulmonary hydrostatic edema, whereas, transfusion-associated acute lung injury is non-cardiogenic permeability edema. The revised 2018 ISBT criteria for TACO requires three of the following: Acute or worsening respiratory compromise up to within 12 h of the onset of transfusion, development of cardiovascular changes not explained by the patient's condition, and evidence of fluid overload and elevated NT-proBNP 1.5 times above the age-specific range [9]. The presence of hypertension, elevated venous pressure, and significant response to diuretics is some of the marked characteristics found in TACO in contrast to TRALI. The estimated frequency of TACO varies between 1 and 8% [10].

Risk factors for the development of TACO are pre-existing cardiac, renal failure, extremes of age, hypoalbuminemia, hypertension, emergency surgeries, and larger transfusion volume. Our patient developed signs of volume overload after 4 days of plasma exchange [11]. Suspecting TACO, we stopped further sessions and supported him with ventilator support and diuretics to which he promptly responded. Right when we decide to transfuse, we should also evaluate the risk versus benefit of transfusion, the transfusion rate, the fluid balance in the patient, and emphasis on vigilant monitoring during as well as after blood product transfusion [11].

CONCLUSION

TTP, although a well-known entity, is a rare disease. The classical pentad may not be present in all the patients. Prompt recognition and initiation of TPE are imperative to prevent the rapid progression of the disease. TACO is an often underreported and underdiagnosed complication of blood product transfusion and needs immediate addressal.

REFERENCES

1. Benz K, Amann K. Thrombotic microangiopathy: New insights. Curr Opin Nephrol Hypertens 2010;19:242-7.
2. Scully M, Hunt BJ, Benjamin S, Liesner R, Rose P, Peyvandi F, *et al*. Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies. Br J Haematol 2012;158:323-35.
3. George JN. Clinical practice. Thrombotic thrombocytopenic purpura. N Engl J Med 2006;354:1927-35.
4. Lynch EC. Peripheral blood smear. In: Walker HK, Hall WD, Hurst JW, editors. Clinical Methods: The History, Physical, and Laboratory Examinations. 3rd ed. Boston: Butterworths; 1990. p. 734.
5. Laurence J. Atypical hemolytic uremic syndrome (aHUS): Making the diagnosis. Clin Adv Hematol Oncol 2012;10 Suppl 17:1-12.
6. Mehmood T, Taylor M, Winters JL. Management of thrombotic microangiopathic hemolytic anemias with therapeutic plasma exchange: When it works and when it does not. Hematol Oncol Clin North Am 2016;30:679-94.
7. Narick C, Triulzi DJ, Yazer MH. Transfusion-associated circulatory overload after plasma transfusion. Transfusion 2012;52:160-5.
8. Fatalities Reported to Food and Drug Administration (FDA) Following Blood Collection and Transfusion; Annual Summary for Fiscal Year 2016; 2022. Available from: https://www.fda.gov/downloads/biologicsbloodvaccines/safetyavailability/reportaproblem/transfusiondonationfatalities/ucm598243.pdf [Last accessed on 2020 Feb 10].
9. van den Akker TA, Grimes ZM, Friedman MT. Transfusion-associated circulatory overload and transfusion-related acute lung injury. Am J Clin Pathol 2021;156:529-39.
10. Semple JW, Rebetz J, Kapur R. Transfusion-associated circulatory overload and transfusion-related acute lung injury. Blood 2019;133:1840-53.
11. Agnihotri N, Agnihotri A. Transfusion associated circulatory overload. Indian J Crit Care Med 2014;18:396-8.

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