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Original article

Case Presentation: Remission of an Acute Thrombotic Thrombocytopenic Purpura in a Previously Healthy Female Adult

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Abstract

We reported a female patient presenting with headache, right side body weakness with multiple bruises all over her body. Over reviewing of her laboratory investigations, the patient had evidence of microangiopathic haemolytic anaemia (MAHA) and thrombocytopenia. Thrombotic thrombocytopenic purpura (TTP) was suspected. Corticosteroids and rituximab were started urgently. The patient had a dramatic improvement to the treatment of rituximab. A disintegrin and metalloproteinase with thrombospondin type 1 motifs, member 13 (ADAMTS 13) activity was remarkably low with a positive inhibitory ADAMTS 13 antibody. Subsequently, the patient routine investigations showed a complete remission of her pancytopenia with excellent improvement of her overall health to rituximab as a first line treatment.

Keywords: *Remission, TTP, Rituximab*

Introduction

Thrombotic thrombocytopenic purpura is a syndromic disease characterized by a pentad of fever, renal impairment, neurological manifestations, thrombocytopenia and a picture of microangiopathic haemolytic anaemia [1]. An accurate diagnosis of the underlying disease is essential to guide the appropriate management. As it could be induced by autoimmune diseases such as SLE (Systemic Lupus Erythematous), congenital or caused by malignancy [2]. It's pathophysiology still unknown completely but may be corresponded to severe deficiency of ADAMTS13 (a disuntegrin and metalloprotease with thrombopondin type 1 repeats, member 13), a specific von Willebrand factor-cleaving protease [3,4]. Although the main stay of treatment of TTP is plasma exchange. Even with treatment, SLE associated TTP still has a high mortality rate compared to TTP (34-62.5%) [5]. Diagnosis of SLE is important for the wellbeing of the patient. As it was supported by the presence of anti-ADAMTS13 abs, ANA and successful treatment with immunosuppressive such as rituximab [6-8]. 7% of patients with aTTP may develop SLE in future follow-ups. There for, screening surveillance post TTP treatment is essential for SLE whole picture of diagnosis to be established [9].

Case presentation

A 45-year-old Libyan black woman presented with headache, right-side body weakness, unilateral right side decrease of her visual acuity and bruises all over her body, all for one day. The patient had no significant past medical history. The headache started abruptly in the back of her head, intermittent in course, severe with no radiation. The right-side body weakness started gradually after the headache along with right side blurred vision, in which the patient couldn't move her upper and lower limbs. She also felt some numbness in her fingers and toes. No history of an oral, vaginal or rectal bleeding. Her review of systems was otherwise insignificant. The patient has three healthy children, no history of miscarriages, and her last normal menstrual period was a week since her presentation. There is no history of autoimmune diseases in her family. Both of her surgical and social histories were unremarkable. The patient didn't have any history of tobacco smoking, alcohol drinking or using of any illicit or chronic illnesses drugs. She also didn't have any recent travel history outside the country. Upon physical examination, the patient looked irritable, vital signs showed an elevated blood pressure 200/110 mmHg, febrile 38.2 C°, RR of 22/min with

pulse rate of 120/min. Pale conjunctiva and gallop rhythm was heard with an audible first and second heart sounds with no murmur. No hepatosplenomegaly. Diffuse purpura all over her body (petechia and ecchymosis). No malar flush. No tenderness or deformities were present in the joins. Neurological examination revealed an intact gag reflex, power (2/5) of her right upper and lower limbs; with normal tone and reflexes. After the evaluation of her case in the emergency room, the patient was admitted to the medical ICU duo to persistent high blood pressure, severe anemia and severe thrombocytopenia along with high renal profile.

The patient was investigated thoroughly; with the results of severe anaemia (haemoglobin 6 gm/dL) and platelets of 8000/µL. Multiple fragmented RBCs (shistocytes) were seen in peripheral blood film. High LDH and low haptoglobin that supported haemolysis. Bone marrow aspiration and biopsy showed a reactive process with no underlying malignancy. Summary of the investigations and imaging are shown in table 1.

Table 1: Patient diagnostic data

Invistigation	**Result**
CBC	Hb: 6g/dL, MCV:90 fL, MCHC: 32 pg, platelet count: 8000/microL, WBC:8000/microL
Haemolysis evaluation	Haptoglobin: 3 mg/dL (low), Reticulocyte count: 3% (high), serum leukocytic LDH: 645 U/L (high).
Serology	ANA: 640 (high) Anti-CL IgM: 11 (relatively high), Anti-CL IgG: negative, Anti-ds Abs: negative, Anti-La: negative.
Renal function and urine R/E	BUN: 100 mg/dL, serum creatinine: 8 mg/dL, serum sodium: 136 mmol/L, serum potassium: 3.7 mmol/L and serum calcium: 9.1 (corrected), urine R/E: showed profound number of RBCs (more than 300 and non-dysmorphic), WBC: 40 cell/hpf, no protein and no casts.
ADAMTS 13	ADAMTS 13 activity: less than 1% (very low), Anti-ADAMTS13 Ab: more than 15 U/mL (high).
Coagulation	Normal PT, INR, aPTT and serum fibrinogen levels, while D-dimer was elevated to (7.6).
Infection work-up	CRP: 5 mg/dL, ESR: 150 mm/hr, Negative urine culture, HAV IgM: negative, anti-HIV, anti-HBV and anti-HCV were all negative.
Miscellaneous studies of additional pertinence	Normal liver function test, troponin (I) level: (0.012) (negative),

	TFT: normal, serum amylase and lipase both normal, ECG showed multiple ischemic changes (inverted T waves in V4-5-6) with PSVT in another performed ECG, figure 1. CXR: unremarkable, Trans-abdominal U/S: unremarkable, Chest, abdomen and pelvis CT scan: unremarkable except for a single intramural endometrial fibroid, Echocardiogram was unremarkable, MRI brain (controlled): unremarkable except for multiple small periventricular ischemic changes, figure 2.

There are many causes that may lead to thrombocytopenia. Varying from primary to secondary causes. These include: infectious, drug induced, hypersplenism duo to chronic liver disease, alcohol consumption, vitamin B12 deficiency, pregnancy and malignancy. Infectious causes can be acute or chronic. As in viremia, bacteremia (sepsis) and protozoan. One of most common causes of acute viral thrombocytopenia is Epstein-Barr virus (EBV). Our patient didn't have the classical infectious mononucleosis symptoms (kissing fever common symptoms and signs of malaise, fever, arthralgia, sore throat and tender cervical lymphadenopathy. Her blood film showed schistocytes that unlikely to go with the illness. Her examination also didn't elicit hepatosplenomaly as in a reactive process to the disease [10]. HIV, HBV and HCV were the first to be excluded also (negative viral screen) [11]. Helicobacter pylori were also excluded duo to lack of symptoms of dyspepsia, peptic ulcer, unremarkable upper esophagogastroduodenoscopy and negative H pylori stool antigen [12]. Sepsis is very important. Our patient had normal lactic acid serum result with improved signs and symptoms in her follow-ups that made sepsis unlikely to be the cause [13]. Malaria is also another crucial cause duo to its endemic state in the sub-Saharan region [14]. Mycobacterium tuberculosis was one of the essentials in her differentials. The patient lacks a history of cough, night sweats, night fever and weight loss, also along with her investigations results, the disease was excluded [15].

Our patient lacked the history of taking any of the following drugs: heparin, quinine, sulphonamides, ibuprofen, naproxen, ampicillin, piperacillin, vancomycin nor any of the glycoprotein IIb/IIIa inhibitors (e.g abciximab) [16,17]. The patient's liver function tests and coagulation profile were all normal and lack any history nor clinical manifestations of chronic liver disease [18]. She also lacked any history of alcohol consumption in her lifetime [19]. And her serum vitamin B12 were within the normal limits [20]. Duo to one week duration of her last normal menstrual period in history, pregnancy was excluded. Her bone marrow aspiration and biopsy showed a reactive process and no underlying malignant features. Malignancy was also excluded duo to unremarkable CXR, CT scans of chest, abdomen and pelvis (table 1, figure 1,2).

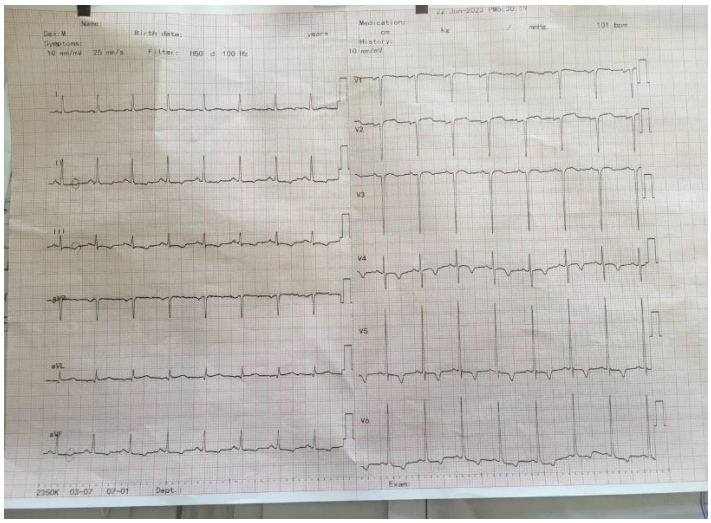

Figure 1: 12 leads electrocardiograph ischemic changes (multiple inverted T waves in V4-5-6)

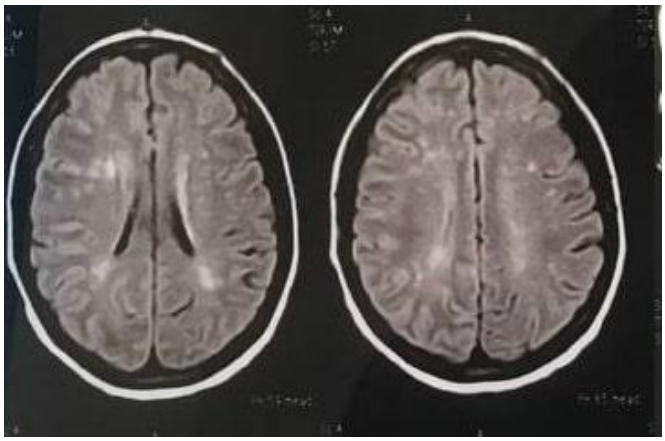

Figure 2. MRI brain without contrast (controlled - coronal plain): showing evidence of bilateral periventricular small vascular ischemic changes.

Another very important cause of severe thrombocytopenia is autoimmune diseases and its's accompanied of thrombotic microangiopathies. Such as systemic lupus erythematous, antiphospholipid syndrome, along with thrombotic thrombocytopenic purpura and its differentials of HUS and DIC. Peripheral blood smear and bone marrow biopsy revealed reticulocytotic escorted by a picture of reactive bone marrow and schistocytes going with microangiopathic thrombocytopenia (MAT). Accompanied by high renal profile and lack of history of diarrhea, a diarrheal negative HUS was also suspected. Idiopathic TTP was diagnosed after excluding similar TTP-like diseases such as disseminated intravascular coagulation (DIC; due to normal coagulation profile). A concern about SLE induced TTP was raised in consideration of high Anti-nuclear antibodies (ANA) serum level and the relative elevation of IgM anti-cardiolipin antibodies. Despite the lack of SLE current required accumulation of criteria to diagnose, it is very important to watch carefully for its emergence to prevent its catastrophic and tragic complications.

Methylprednisolone (1 gm) was trailed orally and intravenously for two days to elevate the platelets count. Due to patients' lack of improvement, Rituximab (375mg/m2) was started in a regimen of once weekly for a month. The platelet count rose dramatically from 8000/microL to 350'000/microL. Her symptomatic treatment contained of nifedipine (60mg) to lower her high blood pressure, along with Bisoprolol (2.5mg) to control the paroxysmal ventricular tachycardia. Multiple packed red blood cells were also transfused. She was discharged generally well, with no residual neurological deficit on day 20 while continuing folic acid (5 mg) (P.O), low molecular weight heparin (0.3 I.U) (S/C) and aspirin (75mg) (P.O). She had followed up with a haematologist, rheumatologist. Advised to daily measure her blood pressure, continue same treatment of nifedipine, bisoprolol, and to monthly

perform CBC, CRP, ESR, urea/creatinine and electrolytes, liver function test and urine routine examination.

Discussion

TTP is a serious disease, with a marked variability in its clinical presentation. Early diagnosis is vital due to its high mortality rate and catastrophic complications. TTP is characterized by fever, microangiopathic hemolytic anemia, thrombocytopenia with neurological and renal manifestations. Thrombotic events occur due to platelet aggregation with the subendothelial layer of the blood vessels (microvasculature) along with the association of large numbers of Von Willebrand factor, due to severe deficiency of a disintegrin and metalloproteinase with thrombospondin type 1 motifs, number 13 (ADAMTS-13). Which is responsible for the cleavage of von Willebrand factor (21). To diagnose a patient with hemolytic anemia and thrombocytopenia of unknown etiology, ADAMTS-13 activity is the fundamental test in the diagnostic process. Patients in whom ADAMTS-13 activity is reduced to (<10%) are diagnosed with TTP and excluded hemolytic uremic syndrome (HUS). Among patients with TTP, those positive for the anti-ADAMTS-13 antibodies are diagnosed with acquired TTP (22). Our patient has a high anti-nuclear antibodies (ANA) serum titre, which make her highly suspected of the presence of an autoimmune diseases such as SLE as the causative agent of aTTP. Few case reports have described the simultaneous presentation of Thrombotic Thrombocytopenic Purpura (TTP) and Systemic Lupus Erythematous (SLE). Connective tissue diseases, especially SLE, are associated with aTTP. Almost 170 patients with SLE-related TTP were reported in literature. In the other reviews, both conditions occurred simultaneously in about (12-45%) (5-9-27). The American College of Rheumatologists stated that SLE classification system is based on several criteria. One must include a positive ANA test to initially begin with. Seven grouped criteria include constitutional symptoms, hematologic, neuropsychiatric, mucocutaneous, serosal, musculoskeletal and renal. Three immunological laboratory exams, including antiphospholipid antibodies, complement proteins, and SLE-specific antibodies, are weighted 2 to 10. An accumulation of 10 or more points between immunological and grouped criteria leads to a diagnosis of SLE (23). Our patient met the high ANA titre along with a slight increase of anti-cardio-lipin antibody (IgM). It's very important to mention that the criteria for SLE don't have to occur simultaneously. As it has been hypothesized that the given rituximab treatment had suppressed the active phase of TTP, and therefore, some of the diagnostic parameters of SLE. The main treatment of TTP is rapid plasma exchange (PLEX), the goal is to exchange circulating anti-ADAMTS13 for fresh ADAMTS13. PLEX is continued daily until the platelet counts have normalized to more than 150'000/μL. Due to the lack of its presence in the developing countries, other modules of therapy have been used as first-line treatment, such as steroids and immunosuppressive (24). Rituximab as an example, the monoclonal antibody against CD20+ B cells. RTX is used in refractory and/or relapsed TTP with a high response rate. It's functioning through the CD-20 molecule that is expressed on the surface of B lymphocytes. By binding to them, fewer antibodies against ADAMTS-13 will be produced. Thus, normalizing ADAMTS-13 activity levels and ultimately reducing thrombotic events formation. Treatment with rituximab was associated with prompt clinical remission before completion of the 4 weekly infusions and normalization of routine laboratory parameters. Although further follow-up is required to determine the length of benefit of a 4-week course of rituximab, as it determined by ADAMTS-13 activity and disappearance of antibody activity, in which we didn't seek to provide in this study (25-26). Therefore, rituximab treatment for TTP should be more considered to highlight its incorporation into the guidelines as one of the first line agents. In conclusion, measurement of ADAMTS-13 activity and the anti-ADAMTS13 antibody titter is necessary for the diagnosis and proper management of TTP; however, in the acute phase of the disease, it's important to initiate whatever is available of treatments to counteract the irreversible and fatal complications of TTP. A 4-week course of rituximab was associated with complete clinical remission. There were no infectious complications despite continuous leukopenia (neutropenia) for 3 months after discharge. Acquired TTP cases need to be accumulated to elucidate appropriate treatment and to improve long-term prognosis. To maintain remission, it's advised to continue rituximab (375mg/m2) every 3 months, for two consecutive years.

References

1. Letchumanan P, Ng HJ, Lee LH, Thumboo J. A comparison of thrombotic thrombocytopenic purpura in an inception cohort of patients with and without systemic lupus erythematosus. Rheumatology (Oxford). 2009;48(4):399-403. doi:10.1093/rheumatology/ken510.
2. George JN, Nester CM. Syndromes of thrombotic microangiopathy. N Engl J Med. 2014;371(7):654-666. doi:10.1056/NEJMra1312353.
3. Stanley M, Killeen RB, Michalski JM. Thrombotic thrombocytopenic purpura. StatPearls [https://www.ncbi.nlm.nih.gov/books/NBK430721/]. StatPearls Publishing; 2022.
4. Lansigan F, Isufi I, Tagoe CE. Microangiopathic haemolytic anaemia resembling thrombotic thrombocytopenic purpura in systemic lupus erythematosus: the role of ADAMTS13. Rheumatology (Oxford). 2011;50(5):824-829. doi:10.1093/rheumatology/keq395
5. Jiang H, An X, Li Y, et al. Clinical features and prognostic factors of thrombotic thrombocytopenic purpura associated with systemic lupus erythematosus: a literature review of 105 cases from 1999 to 2011. Clin Rheumatol. 2014;33(3):419-427. doi:10.1007/s10067-013-2312-5
6. Scully M, Cohen H, Cavenagh J, et al. Remission in acute refractory and relapsing thrombotic thrombocytopenic purpura following rituximab is associated with a reduction in IgG antibodies to ADAMTS-13. Br J Haematol. 2007;136(3):451-461. doi:10.1111/j.1365-2141.2006.06448.x
7. Crawley JT, Scully MA. Thrombotic thrombocytopenic purpura: basic pathophysiology and therapeutic strategies. Hematology Am Soc Hematol Educ Program. 2013;2013:292-299. doi:10.1182/asheducation-2013.1.292
8. Changcharoen B, Bolger DT. Thrombotic thrombocytopenic purpura as an initial presentation of systemic lupus erythematosus with acquired ADAMTS 13 antibody. Case Reports. 2015;2015(feb20 1):bcr2014208477-bcr2014208477. doi:https://doi.org/10.1136/bcr-2014-208477
9. George JN. How I treat patients with thrombotic thrombocytopenic purpura: 2010 [published correction appears in Blood. 2011 May 19;117(20):5551]. Blood. 2010;116(20):4060-4069. doi:10.1182/blood-2010-07-271445
10. Páez-Guillán EM, Campos-Franco J, Alende R, Gonzalez-Quintela A. Hematological Abnormalities Beyond Lymphocytosis During Infectious Mononucleosis: Epstein-Barr Virus-Induced Thrombocytopenia. Mediterr J Hematol Infect Dis. 2023;15(1):e2023023. Published 2023 Mar 1. doi:10.4084/MJHID.2023.023
11. Stasi R, Chia LW, Kalkur P, Lowe R, Shannon MS. Pathobiology and treatment of hepatitis virus-related thrombocytopenia. Mediterr J Hematol Infect Dis. 2009;1(3):e2009023. Published 2009 Nov 25. doi:10.4084/MJHID.2009.023
12. Kuwana M. Helicobacter pylori-associated immune thrombocytopenia: clinical features and pathogenic mechanisms. World J Gastroenterol. 2014;20(3):714-723. doi:10.3748/wjg.v20.i3.714
13. Gonzalez DA, Kumar R, Asif S, Bali A, Dang AK. Sepsis and Thrombocytopenia: A Nowadays Problem. Cureus. 2022;14(5):e25421. Published 2022 May 27. doi:10.7759/cureus.25421
14. Horstmann RD, Dietrich M, Bienzle U, Rasche H. Malaria-induced thrombocytopenia. Blut. 1981;42(3):157-164. doi:10.1007/BF01026385
15. Jurak SS, Aster R, Sawaf H. Immune thrombocytopenia associated with tuberculosis. Clin Pediatr (Phila). 1983;22(4):318-319. doi:10.1177/000992288302200416
16. van den Bemt PM, Meyboom RH, Egberts AC. Drug-induced immune thrombocytopenia. Drug Saf. 2004;27(15):1243-1252. doi:10.2165/00002018-200427150-00007
17. Visentin GP, Liu CY. Drug-induced thrombocytopenia. Hematol Oncol Clin North Am. 2007;21(4):685-vi. doi:10.1016/j.hoc.2007.06.005
18. Peck-Radosavljevic M. Thrombocytopenia in chronic liver disease. Liver Int. 2017;37(6):778-793. doi:10.1111/liv.13317
19. Silczuk A, Habrat B. Alcohol-induced thrombocytopenia: Current review. Alcohol. 2020;86:9-16. doi:10.1016/j.alcohol.2020.02.166
20. Ganipisetti VM, Bollimunta P, Tun NN, et al. Concomitant Vitamin B1 and Vitamin B12 Deficiency Mimicking Thrombotic Thrombocytopenic Purpura. Cureus. 2023;15(1):e34421. Published 2023 Jan 31. doi:10.7759/cureus.34421
21. George JN. Clinical practice. Thrombotic thrombocytopenic purpura. N Engl J Med. 2006;354(18):1927-1935. doi:10.1056/NEJMcp053024.
22. Takagi Y, Kobayashi Y, Hirakata A, et al. Systemic Lupus Erythematosus Presenting With Thrombotic Thrombocytopenic Purpura at Onset: A Case Report. Front Pediatr. 2022;10:931669. Published 2022 Aug 1. doi:10.3389/fped.2022.931669.
23. Uczkowski D, Milonas H. Initial presentation of Systemic Lupus Erythematosus coinciding with Thrombotic Thrombocytopenic Purpura. Thrombosis Update. 2022;8:100118.
24. Scully M, Hunt BJ, Benjamin S, et al. Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies. Br J Haematol. 2012;158(3):323-335. doi:10.1111/j.1365-2141.2012.09167.x
25. Chen H, Fu A, Wang J, et al. Rituximab as first-line treatment for acquired thrombotic thrombocytopenic purpura. J Int Med Res. 2017;45(3):1253-1260. doi:10.1177/0300060517695646

26. Lim W, Vesely SK, George JN. The role of rituximab in the management of patients with acquired thrombotic thrombocytopenic purpura. Blood. 2015;125(10):1526-1531. doi:10.1182/blood-2014-10-559211
27. Musio F, Bohen EM, Yuan CM, Welch PG. Review of thrombotic thrombocytopenic purpura in the setting of systemic lupus erythematosus. Semin Arthritis Rheum. 1998;28(1):1-19. doi:10.1016/s0049-0172(98)80023-1