Title

A Case of Thrombotic Thrombocytopenic Purpura

Journal

Proceedings of the UCLA Department of Medicine, 18(1)

Authors

Cox, Nathan

Khorsan, Reza

Publication Date

2014-07-25

CLINICAL VIGNETTE

A Case of Thrombotic Thrombocytopenic Purpura

Nathan Cox, MD and Reza Khorsan, MD

Introduction

Thrombotic thrombocytopenic purpura (TTP) is a syndrome involving pathology within multiple organ systems brought about by microangiopathic hemolytic anemia with thrombocytopenia. TTP can arise idiopathically or as a result of numerous hereditary or acquired conditions. Incidence of suspected TTP cases has been estimated in the range of 10 cases per million persons per year. We present a case of an HIV-positive man presenting with multiple vague complaints and ultimately being discovered to have TTP.

Case Report

A 39-year-old man with a past medical history significant for untreated HIV infection presented with 2 days of abdominal pain and 1 day of left-sided chest pain. The patient had been in his usual state of health until he began noting crampy, non-radiating, constant diffuse abdominal pain about 2 days prior to presentation. This discomfort was initially tolerable, but over the subsequent 24 hours became associated with nausea and vomiting. The patient experienced no diarrhea. On the day prior to presentation, he also began to note associated dull, achy left-sided chest pain, without palpitations or shortness of breath. He also noted dark discoloration of his urine, without appreciable change in urine output. He denied fevers and chills, and by his own report had not experienced confusion or mental status changes prior to presentation.

His most recent CD4 count was 177 with an HIV viral load of 71,000 approximately 8-months prior to presentation. He had deferred anti-retroviral therapy, and had had only irregular outpatient follow-up. He denied prior HIV-related infections.

On arrival to the emergency room, the patient was afebrile with mild sinus tachycardia. His labs were notable for anemia, with hemoglobin of 7.5 g/dL (mean corpuscular volume was borderline low), thrombocytopenia, with platelet count of 6,000, and renal insufficiency, with serum creatinine 2.3 mg/dL. Coagulation studies were within normal limits. Computed tomography of the abdomen and pelvis showed no acute abnormality, and ECG was unremarkable. While in the emergency room the patient received 2 units of packed red blood cells and 1 unit of platelets – post-transfusion hemoglobin was 6.6 g/dL, and platelet count was 10,000.

The patient was admitted with presumptive diagnosis of thrombotic thrombocytopenic purpura (TTP). Peripheral blood smear showed occasional schistocytes. Initial LDH was markedly elevated at 1146 U/L, and haptoglobin was low at <8 mg/dL. Within the first 24 hours of hospitalization, he developed confusion as well as fever. He was treated with six inpatient sessions of plasmapheresis, with improvement in hemoglobin level and platelet count. ADAMTS13 level was undetectable, and serum ADAMTS13 antibody was present. Ultimately the patient was discharged to continue outpatient treatment for TTP.

Since discharge the patient has continued to require regular plasmapheresis to maintain blood counts. His renal function has stabilized. Anti-retroviral therapy has been started, though it remains to be seen whether this will improve the underlying hematologic situation. Repeated measurements of ADAMTS13 levels have shown recurrence of downtrend when plasmapheresis is withheld.

Discussion

Pathology: The underlying pathologic injury in TTP is formation of platelet-rich thrombi in affected organs. These thrombi form because of large multimers of von Willebrand factor (vWf) that are not properly broken down within the vasculature. Lack of breakdown of these multimers is due to absent or deficient activity of a specific protease, ADAMTS13[1]. ADAMTS13 deficiency allows accumulation of vWf multimers, which leads to platelet aggregation, and ultimately to formation of typical platelet thrombi. These thrombi lead to

microangiopathic hemolytic anemia (via mechanical "shearing" of red blood cells, causing formation of schistocytes which can be seen on peripheral smear), thrombocytopenia (through consumption), and organ dysfunction (through microvascular damage).

Causes: TTP has been noted idiopathically and with numerous underlying pathologies. Idiopathic cases are attributable most often to either a lack of ADAMTS13 activity or to an antibody directed against ADAMTS13[2, 3]. Multiple other underlying abnormalities have been implicated in development of TTP, including disseminated malignancy, multiple chemotherapeutic and immunosuppressive agents (such as cisplatin, oxaliplatin, gemcitabine, cyclosporine, and tacrolimus among many others), following infection with Shiga toxin-producing E. coli, during or following pregnancy, in autoimmune disorders (especially when anti-phospholipid antibodies are present, such as in systemic lupus erythematosus), secondary to numerous medications (among them clopidogrel and valacyclovir), and finally in the setting of HIV[4-14]. Many of these secondary causes of TTP still involve absent or deficient ADAMTS13. In cases of TTP without ADAMTS13 deficiency, pathogenesis has not been fully elucidated, but has been postulated to involve endothelial injury and genetic factors. Specifically, HIV-related TTP in which ADAMTS13 level is not depressed has been attributed at least in part to endothelial injury, which would presumably favor formation of microthrombi[15].

Diagnosis: A 1964 review of all published cases yielded a "classic pentad" of clinical findings present in TTP cases: thrombocytopenia, microangiopathic hemolytic anemia, neurologic signs and symptoms, renal function abnormalities, and fever[16]. However, as therapeutic measures have emerged and evolved, improving prognosis of patients diagnosed and treated promptly, the importance of early diagnosis has become paramount. As such, it is now considered appropriate to initiate treatment for those patients found to have only otherwise-unexplained microangiopathic hemolytic anemia and thrombocytopenia[9].

Treatment: The cornerstone of treatment of TTP has been therapeutic plasma exchange[17]. Prior to plasma exchange, the survival rate in adults was dismal, around 5%. Since the introduction of plasma exchange over 30 years ago, this has risen to around 80%. The mode of action in plasma exchange is thought to be the removal of large vWF multimers, with replacement by fresh frozen plasma (FFP) or cryoprecipitate, which have therapeutic levels of ADAMTS13. A case series has shown benefit of cryoprecipitate over FFP in plasma exchange therapy[18] but another study did not show a difference[19]. Simple plasma infusion can be performed if timely plasma exchange is not feasible, however, outcomes are inferior[17].

Treatment protocols are largely empirical, with few formal guidelines. Most typically, plasma exchange is performed on a daily basis, using 1 to 1.5 plasma volumes per exchange for five to seven days. Progress is monitored by following the platelet count, serum LDH and neurologic symptoms – as these three parameters improve first. Correction of the micro-angiopathic hemolytic anemia and kidney dysfunction lag.

After five to seven treatments, daily plasma exchange can be stopped, with monitoring of platelets thereafter. Patients will frequently have exacerbations and need additional plasma exchanges 2 to 3 times weekly. If, after two weeks of monitoring, platelets are stable and there are no other clinical indications for continued treatment, the central venous catheter can be removed. Remission is defined as 30 days of normal platelet counts without the need for plasma exchange. Occasionally patients will have relapse after remission, necessitating a new cycle of plasmapheresis.

Plasma exchange is not without risk. Most of the morbidity and mortality are due to central venous catheter infections and thrombosis, or problems related to catheter insertion, hemorrhage, or pneumothorax[20]. Furthermore, the procedure can precipitate hypocalcemia and hypotension.

In addition to the cornerstone plasma exchange, there seems to be a role for glucocorticoids. They are most commonly given to patients with idiopathic TTP, concurrent with plasma exchange, or to patients who have relapsed. Doses are usually 1 to 2 mg of prednisone per kg per day, or one gram of methylprednisolone per day for three days intravenously[21].

In patients with refractory or relapsing disease, other immunosuppressive agents may be tried. Rituximab has shown some benefit[22, 23], as has cyclosporine in a few case reports[24-26]. Vincristine, cyclophosphamide and IVIG may also have a role in refractory cases[27, 28]. However, none of these medications should be a substitute for plasma exchange.

REFERENCES

1. **Levy GG, Nichols WC, Lian EC, Foroud T, McClintick JN, McGee BM, Yang AY, Siemieniak DR, Stark KR, Gruppo R, Sarode R, Shurin SB, Chandrasekaran V, Stabler SP, Sabio H, Bouhassira EE, Upshaw JD Jr, Ginsburg D, Tsai HM**. Mutations in a member of the ADAMTS gene family cause thrombotic thrombocytopenic purpura. *Nature*. 2001 Oct 4;413(6855):488-94. PubMed PMID: 11586351.
2. **Furlan M, Robles R, Galbusera M, Remuzzi G, Kyrle PA, Brenner B, Krause M, Scharrer I, Aumann V, Mittler U, Solenthaler M, Lämmle B**. von Willebrand factor-cleaving protease in thrombotic thrombocytopenic purpura and the hemolytic-uremic syndrome. *N Engl J Med*. 1998 Nov 26;339(22):1578-84. PubMed PMID: 9828245.
3. **Kremer Hovinga JA, Vesely SK, Terrell DR, Lämmle B, George JN**. Survival and relapse in patients with thrombotic thrombocytopenic purpura. *Blood*. 2010 Feb 25;115(8):1500-11; quiz 1662. doi: 10.1182/blood-2009-09-243790. Epub 2009 Dec 23. PubMed PMID: 20032506.
4. **Lesesne JB, Rothschild N, Erickson B, Korec S, Sisk R, Keller J, Arbus M, Woolley PV, Chiazze L, Schein PS, et al**. Cancer-associated hemolytic-uremic syndrome: analysis of 85 cases from a national registry. *J Clin Oncol*. 1989 Jun;7(6):781-9. Review. PubMed PMID: 2497229.
5. **Canpolat C, Pearson P, Jaffe N**. Cisplatin-associated hemolytic uremic syndrome. Cancer. 1994 Dec 1;74(11):3059-62. *Review*. PubMed PMID: 7954269.
6. **Zupancic M, Shah PC, Shah-Khan F**. Gemcitabine-associated thrombotic thrombocytopenic purpura. *Lancet Oncol*. 2007 Jul;8(7):634-41. Review. PubMed PMID: 17613425.
7. **Beaufils H, de Groc F, Gubler MC, Wechsler B, Le Hoang P, Baumelou A, Chomette G, Jacobs C**. Hemolytic uremic syndrome in patients with Behçet's disease treated with cyclosporin A: report of 2 cases. *Clin Nephrol*. 1990 Oct;34(4):157-62. PubMed PMID: 2257701.
8. **Trimarchi HM, Truong LD, Brennan S, Gonzalez JM, Suki WN**. FK506-associated thrombotic microangiopathy: report of two cases and review of the literature. *Transplantation*. 1999 Feb 27;67(4):539-44. Review. PubMed PMID: 10071024.
9. **George JN**. How I treat patients with thrombotic thrombocytopenic purpura: 2010. *Blood*. 2010 Nov 18;116(20):4060-9. doi: 10.1182/blood-2010-07-271445. Epub 2010 Aug 4. Erratum in: Blood. 2011 May 19;117(20):5551. PubMed PMID: 20686117.
10. **Vesely SK, Li X, McMinn JR, Terrell DR, George JN**. Pregnancy outcomes after recovery from thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. *Transfusion*. 2004 Aug;44(8):1149-58. PubMed PMID: 15265118.
11. **Nesher G, Hanna VE, Moore TL, Hersh M, Osborn TG**. Thrombotic microangiographic hemolytic anemia in systemic lupus erythematosus. *Semin Arthritis Rheum*. 1994 Dec;24(3):165-72. Review. PubMed PMID: 7899874.
12. **Bennett CL, Connors JM, Carwile JM, Moake JL, Bell WR, Tarantolo SR, McCarthy LJ, Sarode R, Hatfield AJ, Feldman MD, Davidson CJ, Tsai HM**. Thrombotic thrombocytopenic purpura associated with clopidogrel. *N Engl J Med*. 2000 Jun 15;342(24):1773-7. PubMed PMID: 10852999.
13. **Feinberg JE, Hurwitz S, Cooper D, Sattler FR, MacGregor RR, Powderly W, Holland GN, Griffiths PD, Pollard RB, Youle M, Gill MJ, Holland FJ, Power ME, Owens S, Coakley D, Fry J, Jacobson MA**. A randomized, double-blind trial of valaciclovir prophylaxis for cytomegalovirus disease in patients with advanced human immunodeficiency virus infection. AIDS Clinical Trials Group Protocol 204/Glaxo Wellcome 123-014 International CMV Prophylaxis Study Group. *J Infect Dis*. 1998 Jan;177(1):48-56. PubMed PMID: 9419169.
14. **Gervasoni C, Ridolfo AL, Vaccarezza M, Parravicini C, Vago L, Adorni F, Cappelletti A, d'Arminio Monforte A, Galli M**. Thrombotic microangiopathy in patients with acquired immunodeficiency syndrome before and during the era of introduction of highly active antiretroviral therapy. *Clin Infect Dis*. 2002 Dec 15;35(12):1534-40. Epub 2002 Dec 2. PubMed PMID: 12471574.
15. **Alpers CE**. Light at the end of the TUNEL: HIV-associated thrombotic microangiopathy. *Kidney Int*. 2003 Jan;63(1):385-96. PubMed PMID: 12472814.
16. **Amorosi EL, Ultmann JE**. Thrombotic thrombocytopenic purpura: Report of 16 cases and review of the literature. *J Medicine*. 1966;45:139.
17. **Rock GA, Shumak KH, Buskard NA, Blanchette VS, Kelton JG, Nair RC, Spasoff RA.** Comparison of plasma exchange with plasma infusion in the treatment of thrombotic thrombocytopenic purpura. Canadian Apheresis Study Group. *N Engl J Med*. 1991 Aug 8;325(6):393-7. PubMed PMID: 2062330.
18. **Rock G, Shumak KH, Sutton DM, Buskard NA, Nair RC**. Cryosupernatant as replacement fluid for plasma exchange in thrombotic thrombocytopenic purpura. Members of the Canadian Apheresis Group. *Br J Haematol*. 1996 Aug;94(2):383-6. PubMed PMID: 8759902.
19. **Rock G, Anderson D, Clark W, Leblond P, Palmer D, Sternbach M, Sutton D, Wells G**; Canadian Apheresis Group; Canadian Association of Apheresis Nurses. Does cryosupernatant plasma improve outcome in thrombotic thrombocytopenic purpura? No answer yet. *Br J Haematol*. 2005 Apr;129(1):79-86. PubMed PMID: 15801959.
20. **Howard MA, Williams LA, Terrell DR, Duvall D, Vesely SK, George JN**. Complications of plasma exchange in patients treated for clinically suspected thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. *Transfusion*. 2006 Jan;46(1):154-6. PubMed PMID: 16398746.
21. **Allford SL, Hunt BJ, Rose P, Machin SJ**; Haemostasis and Thrombosis Task Force, British Committee for Standards in Haematology. Guidelines on the diagnosis and management of the thrombotic microangiopathic haemolytic anaemias. *Br J Haematol*. 2003 Feb;120(4):556-73. PubMed PMID: 12588343
22. **George JN, Woodson RD, Kiss JE, Kojouri K, Vesely SK**. Rituximab therapy for thrombotic thrombocytopenic purpura: a proposed study of the Transfusion Medicine/Hemostasis Clinical Trials Network with a systematic review of rituximab therapy for immune-mediated disorders. *J Clin Apher*. 2006 Apr;21(1):49-56. PubMed PMID: 16619232.
23. **Caramazza D, Quintini G, Abbene I, Malato A, Saccullo G, Lo Coco L, Di Trapani R, Palazzolo R, Barone R, Mazzola G, Rizzo S, Ragonese P, Aridon P, Abbadessa V, Siragusa S**. Relapsing or refractory idiopathic thrombotic thrombocytopenic purpura-hemolytic uremic syndrome: the role of rituximab. *Transfusion*. 2010 Dec;50(12):2753-60. doi: 10.1111/j.1537-2995.2010.02763.x. Review. PubMed PMID:20576013.
24. **Kierdorf H, Maurin N, Heintz B**. Cyclosporine for thrombotic thrombocytopenic purpura. *Ann Intern Med*. 1993 Jun 15;118(12):987-8. PubMed PMID: 8489121.

25. **Cataland SR, Jin M, Ferketich AK, Kennedy MS, Kraut EH, George JN, Wu HM**. An evaluation of cyclosporin and corticosteroids individually as adjuncts to plasma exchange in the treatment of thrombotic thrombocytopenic purpura. *Br J Haematol*. 2007 Jan;136(1):146-9. Epub 2006 Oct 27. PubMed PMID: 17069579.
26. **Cataland SR, Jin M, Zheng XL, George JN, Wu HM**. An evaluation of cyclosporine alone for the treatment of early recurrences of thombotic thrombocytopenic purpura. *J Thromb Haemost*. 2006 May;4(5):1162-4. PubMed PMID: 16689782.
27. **Ziman A, Mitri M, Klapper E, Pepkowitz SH, Goldfinger D**. Combination vincristine and plasma exchange as initial therapy in patients with thrombotic thrombocytopenic purpura: one institution's experience and review of the literature. *Transfusion*. 2005 Jan;45(1):41-9. PubMed PMID: 15647017.
28. **Wong P, Itoh K, Yoshida S**. Treatment of thrombotic thrombocytopenic purpura with intravenous gamma globulin. *N Engl J Med*. 1986 Feb 6;314(6):385-6. PubMed PMID: 2418354.

Submitted on July 25, 2014