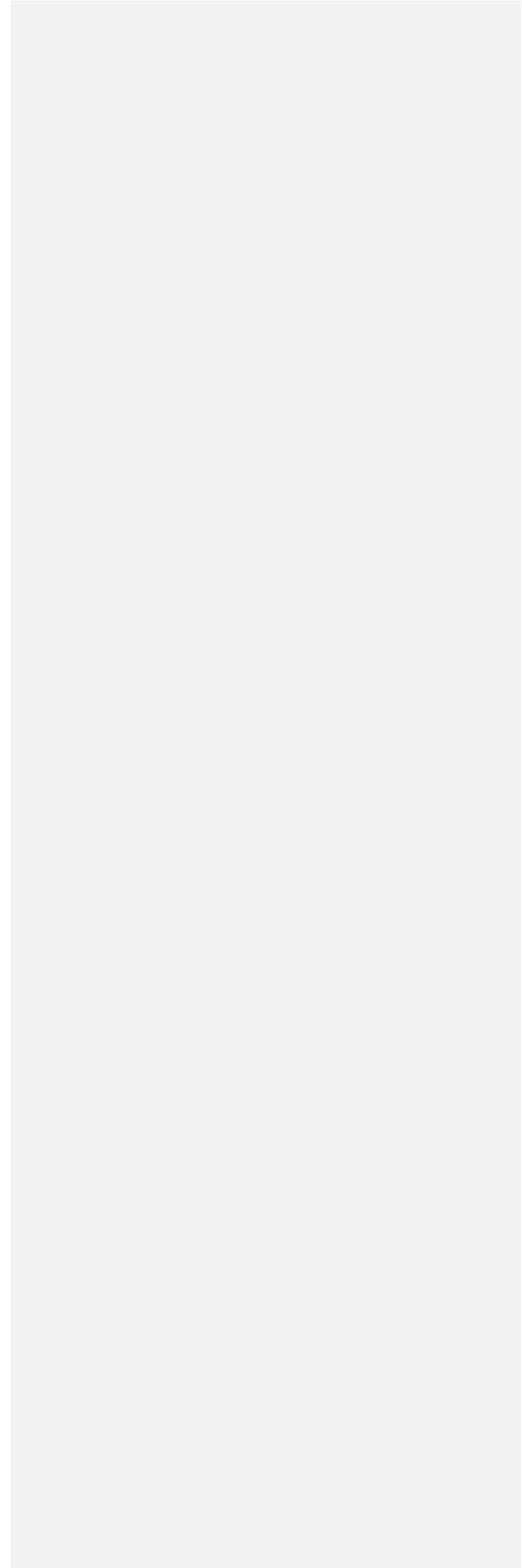


TTP Overview

Adam K. Morgan



TTP Overview

Thrombotic thrombocytopenic purpura (TTP) is a rare type of microangiopathic hemolytic anemia (MAHA), caused by microvascular platelet aggregates, which result from a severe deficiency of von Willebrand factor-cleaving protease ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) (Keohane et al. 2016). Another classification of TTP is as Thrombotic Microangiopathy (TMA). TMAs are caused by pathologic lesions in the walls of arterioles and capillaries that lead to microvascular thrombosis. Many authors will use the term's MAHA and TMA interchangeably (Keohane et al. p. 396), while others only include the related and variant disorders of TTP, Hemolytic Uremic Syndrome (HUS), under the category of TMAs (Wada et al 2018). The distinction seems to be made on the involvement of platelets and their depletion, which can vary in Disseminated Intervascular Coagulation (DIC).

TTP can be further subdivided into inherited TTP or acquired TTP. Approximately 5% of TTP cases are inherited, and 95% are acquired (Barbour et al 2012). Inherited TTP results from gene mutations that alter the function or abundance of ADAMTS13. Acquired TTP results from antibody formation to ADAMTS13. The cause of the antibody formation is currently unknown, but is associated with conditions including lupus, cancer, infections, or pregnancy, or certain medications associated with those conditions.

Clinical symptoms

TTP presents with five major categories of symptoms: classic symptoms of hemolytic anemia, thrombocytopenia, fever, renal symptoms, and cognitive symptoms. Anemia and thrombocytopenia are highly indicative for the condition, while renal and cognitive symptoms

Commented [AK1]: MLA style
3-5 pages
Name of anemia
Presentation of symptoms
Treatment

are less consistent presentations. Renal symptoms are more commonly associated with inherited than acquired TTP (Tsai 2007).

Presented symptoms related to hemolytic anemia are pallor, weakness, shortness of breath, darkened or bloody urine, and tachycardia. Thrombocytopenia results in bleeds, producing purpura or petechiae visible under the skin. Cognitive symptoms that may result from intracranial bleeding include headache, stroke, confusion, coma, visual disturbances, or speech changes. Renal symptoms in inherited TTP may very rarely include oliguria, hypertension, fluid overload, acute kidney failure, but most cases of acquired TTP only present mild renal dysfunction and proteinuria (Tsai 2007). Mortality can be as high as 90% if untreated (Crawley 2013).

Laboratory tests and differential diagnosis

As seen in table 1, the typical complete blood count (CBC) in TTP presents with hemolytic anemia, marked thrombocytopenia, and an increased reticulocyte count. The white blood cell (WBC) differential is usually normal and the red blood cell (RBC) morphology may include schistocytes, polychromasia, and nucleated RBCs. Schistocytes are red cell fragments caused by cell injury in circulation. Nucleated RBCs and polychromasia, a bluish tinged anucleated RBC, are seen in reticulocytosis caused by rapid red cell regeneration in hemolytic anemia (Figure 1 , Keohane et al. 2016). Shiga toxin producing Escherichia coli (STEC) HUS, atypical HUS, Drug induced Thrombotic microangiopathy (DITMA), DIC and Immune Thrombocytic Purpura (ITP) may present with similar symptoms to TTP, including low platelets, purpura, or renal impairment. The treatment for each of these various conditions is significantly different, making a differential diagnosis critical to patient survival. Laboratory tests showing thrombocytopenia, increased LDH, negative Coomb's or direct antiglobulin (DAT) test, increased indirect bilirubin,

decreased haptoglobin, schistocytes on blood smear, and elevated reticulocyte counts are results that confirm the general effects of MAHA or TMA, but do not establish the direct underlying cause.

Test	Patient result	Reference Range	L-N-H
WBC	11.9 x 10 ³ /μL	5.0 – 10.0 x 10 ³ /μL	↑
RBC	2.6 x 10 ⁶ /μL	Male: 4.5 – 5.5 x 10 ⁶ /μL Female: 4.0 – 5.0 x 10 ⁶ /μL	↓
HGB	8 g/dL	Male: 14 – 18 g/dL Female: 12 – 16 g/dL	↓
HCT	24 %	Male: 45 – 52 % Female: 36 – 46 %	↓
MCV	92 fL	80 – 100 fL	N
MCH	31 pg	26 – 32 pg	N
MCHC	33 %	32 – 36 %	N
RDW	19 %	11.5 – 14.5 %	↑
PLT	10 x 10 ³ /μL	150 – 450 x 10 ³ /μL	↓
Differential:			
Neutrophils	65%	50 – 75%	N
Lymphocytes	32%	20 – 40%	N
Monocytes	2%	2 – 8%	N
Eosinophils	1%	0 – 5%	N
Reticulocytes	12%	0 – 0.5 %	↑

Table 1. Example CBC report of a typical TTP

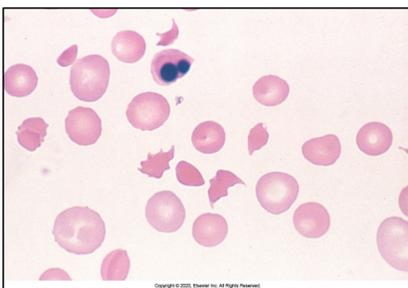


Figure 1. Image from Keohane et al. 2016, p. 366. Note schistocytes and nucleated RBC. (Wright-Giemsa stain, x 1000)

Findings of schistocytes in the differential may vary depending upon the progression of the condition, being variably present in early states, but eventually becoming sine qua non for TTP (Wun 2019).

The hallmark of TTP is severe deficiency of ADAMTS13 activity (<10% normal activity). In practice, ADAMTS13 testing has suffered from long turn-around times, rendering it unavailable during critical decision-making periods in early treatment of suspected TTP (Connell et al. 2016). Because of this, best practice in cases of suspected TTP is to begin plasma exchange treatment, and then conduct additional testing to confirm a diagnosis. New methods have recently been created to address this, yielding turn-around times of 33 minutes (Valsecchi 2019).

However, in some cases of suspected, using ADAMTS13 levels alone would have led to misdiagnosis and treatment. A man with suspected TTP initially presented with ADAMTS13 activity levels of 53% and 60% (via two Swiss assays), yet his condition progressed towards undetectable levels of activity by his 5th and 6th episodes (George 2015). Another woman with suspected TTP was treated with plasma exchange, and later was confirmed to have acute bacterial endocarditis from *Staphylococcus epidermidis*; her ADAMTS13 activity was found to be undetectable by two separate assay methods despite unrelated etiology disconfirming TTP. The physician in these cases concludes that so long as no other etiologies (apart from TTP) are apparent, plasma exchange should be started and continued, and that the overall presentation should be considered rather than relying solely on ADAMTS13.

To rule out other etiologies, a number of diagnostic pathways may be pursued. DIC can be eliminated from consideration by findings of normal fibrinogen, and normal to slightly increased PT-INR/PTT. Negative shiga toxin enzyme immunoassay tests and negative stool cultures for STEC eliminate STEC HUS as a possible cause. Complement assays should be performed to rule

out atypical HUS. ITP can be ruled out by negative platelet autoantibody tests. DITTP should be assessed through discontinuation of suspected medication, since DITTP generally resolves rapidly after removal of the substance.

For inherited TTP, genetic testing of the ADAMTS13 gene is likely sufficient to confirm the diagnosis. In a study of 23 patients with inherited TTP (with documented family history of disease), 33 different mutations in this gene have been found, suggesting that no other mutations are necessary for the condition (Kokame 2004).

In cases of acquired TTP, it is possible to directly detect inhibitory antibodies to ADAMTS13 (Crawley 2013). However, this assay must be performed before plasma exchange treatment is initiated to represent an accurate measure of activity and concentration of inhibitor.

Treatment

As stated earlier, once TTP is suspected, the primary treatment for both acquired and inherited TTP is plasma infusion or exchange therapy (Keohane 2016 p. 397). In inherited TTP cases, it is sufficient to replace the absent ADAMTS13 by plasma infusions to correct symptoms. Acquired TTP is often further treated with corticosteroids and immunosuppressants such as Rituximab to reduce the production of autoantibodies to ADAMTS13. Relapses in acquired TTP are common, effecting up to 20-50% of cases (Crawley 2013). However, in cases where ADAMTS13 activity was improved to greater than 15% activity, relapses were reduced to less than 5% of cases. ADAMTS13 monitoring is critical to preventing relapses.

Works Cited

- Barbour, Thomas, et al. "Thrombotic microangiopathy and associated renal disorders." *Nephrology Dialysis Transplantation* 27.7 (2012): 2673-2685.
- Connell, Nathan T., Tracey Cheves, and Joseph D. Sweeney. "Effect of ADAMTS13 activity turnaround time on plasma utilization for suspected thrombotic thrombocytopenic purpura." *Transfusion* 56.2 (2016): 354-359.
- Crawley, James TB, and Marie A. Scully. "Thrombotic thrombocytopenic purpura: basic pathophysiology and therapeutic strategies." *Hematology 2013, the American Society of Hematology Education Program Book* 2013.1 (2013): 292-299.
- Dervenoulas, J., et al. "Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS): treatment outcome, relapses, prognostic factors. A single-center experience of 48 cases." *Annals of hematology* 79.2 (2000): 66-72.
- George, James N. "Measuring ADAMTS13 activity in patients with suspected thrombotic thrombocytopenic purpura: when, how, and why?" *Transfusion* 55.1 (2015): 11.
- Kakishita, Eizo. "Pathophysiology and treatment of thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS)." *International journal of hematology* 71.4 (2000): 320-327
- Keohane, Elaine M, Larry J. Smith, Jeanine M. Walenga, and Bernadette F. Rodak. Rodak's Hematology: Clinical Principles and Applications. *St. Louis: Elsevier/Saunders* (2016).
- Kokame, Koichi, and Toshiyuki Miyata. "Genetic defects leading to hereditary thrombotic thrombocytopenic purpura." *Seminars in hematology*. Vol. 41. No. 1. *WB Saunders*, 2004.

Tsai, Han-Mou. "The kidney in thrombotic thrombocytopenic purpura." *Minerva medica* 98.6 (2007): 731.

Valsecchi, Carla, et al. "Evaluation of a New, Rapid, Fully Automated Assay for the Measurement of ADAMTS13 Activity." *Thrombosis and haemostasis* 119.11 (2019): 1767-1772.

Wada, Hideo, et al. "Differences and similarities between disseminated intravascular coagulation and thrombotic microangiopathy." *Thrombosis journal* 16.1 (2018): 14

Wun, Theodore. "Thrombotic Thrombocytopenic Purpura (TTP) Workup: Laboratory Studies, Imaging Studies, Histologic Findings." *Medscape*, 15 Nov. 2019, emedicine.medscape.com/article/206598-workup.