THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP)

TERM DEFINITION

Thrombotic microangiopathy (TMA) associated with severe deficiency (< 10%) of ADAMTS13 activity.

TMA - a group of syndromes with different etiologies (including ADAMTS13 deficient and nondeficient states) that share *clinical features* of thrombocytopenia, microangiopathic hemolytic anemia (MAHA), and organ injury + *pathological features* of occlusive microvascular or macrovascular disease.

Microangiopathic hemolytic anemia (MAHA) - hemolytic anemia (median hemoglobin 8-10 g/dL) in which erythrocytes are fragmented in high-shear environment caused by partially occluded microvessel.

CLASSIFICATION

CONGENITAL

- Mutations in ADAMTS13.
- Also called Upshaw-Schulman syndrome.
- < 5% all TTP cases.

IMMUNE

- Antibodies against ADAMTS13.
- Also called acquired TTP.
- > 95% of all TTP cases.
- May be primary or secondary depending on whether underlying disease (e.g., SLE) present; almost always primary.

CLINICAL PEARLS

When suspect TMA, critical to rule out TTP as soon as possible since the latter requires urgent treatment.

Ruling out TTP means testing for ADAMTS13 activity levels; these can take a few days to come back.

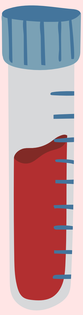
If in doubt about the diagnosis, initiate plasma exchange as soon as possible with plan to stop if/when ADAMTS levels return >10%.

Patients rarely present with historical pentad of fever, hemolytic anemia, thrombocytopenia, and renal and neurologic dysfunction. More common is MAHA + neurological symptoms.

Suspect diagnosis of immune TTP in adults with isolated MAHA, thrombocytopenia, new focal neurological symptoms, seizure, or acute myocardial infarction with unexplained microangiopathic hemolytic anemia.

Strictly speaking, the term TTP refers to those patients with low ADAMTS13 levels. These patients almost always fall in the "**primary**" category of TMA because they have no underlying causative disease. However, some continue to use the term TTP to describe patients with **secondary** TMA and a TTP-like clinical phenotype (especially neurological findings), despite normal ADAMTS13 levels. This should be discouraged.

DIAGNOSIS



CBC
- Anemia
- Thrombocytopenia

Peripheral smear
- Schistocytes

Hemolytic indices
- Elevated LDH
- Low haptoglobin
- Elevated AST
- Elevated indirect bilirubin

Establishing diagnosis of TTP
- PLASMIC score*
- ADAMTS13 activity <5-10%
- Mixing studies or anti-ADAMTS13 immunoglobulin G (IgG) antibodies shows functional inhibitor in acquired (immune) ITP

Evidence of organ impairment

Troponin

BUN, creatinine

Brain imaging

*Clinical prediction score, see https://harvardtma.partners.org/PLASMIC/

CLINICAL PREDICTION RULE - THE PLASMIC SCORE

		NO	YES
P	**Platelet count < 30**	0	1
L	Combined **hemolysis** parameter: Indirect bilirubin > 2mg/dL, OR Reticulocyte count > 2.5%, OR Haptoglobin undetectable	0	1
A	Patient has **active cancer**, defined as treatment for any non-superficial skin cancer within the last 12 months.	1	0
S	Patient has a history of **solid-organ** or **stem-cell transplant**	1	0
M	**Mean Cell Volume (MCV) < 90 fL**	0	1
I	**INR < 1.5**	0	1
C	**Creatinine < 2.0 mg/dL**	0	1

LOW RISK SCORE 0-4 / **INTERMEDIATE RISK SCORE 5** / **HIGH RISK SCORE 6-7**

Use of plasmic score restricted to patients with a platelet count <150,000 per microliter and schistocytes visible on the peripheral blood smear.

THERAPEUTIC PRINCIPLES

- TTP is a medical emergency.
- If TTP suspected, start therapeutic plasma exchange (TPE) within 4-8 hours of presentation; TPE removes autoantibodies and replenishes ADAMTS13 levels.
- TPE can be stopped if ADAMTS13 levels are > 10%.
- Administer corticosteroids.
- Consider addition of rituximab and/or caplacizumab in those with immune (acquired) TTP.

EVOLUTIONARY CONSIDERATIONS

Von Willebrand factor (vWF) and ADAMTS13 are present in all vertebrates, indicating they arose in the ancestral vertebrate 500-600 million years ago...

Ancestral vertebrate

Appearance of:
- PLATELETS
- CLOSED CIRCULATION

Appearance of:
- VWF
- ADAMTS13

...at the same time that the circulation became closed and platelets (thrombocytes) appeared. Thus, the substrates for TTP have been around half a billion years!

PROXIMATE MECHANISMS

von Willebrand factor (VWF) is a multimeric protein that tethers platelets to the endothelium and subendothelial surface, initiating blood vessel repair. During hemostasis, the metalloprotease ADAMTS13 prevents excessive platelet adhesion by cutting high molecular weight multimers into smaller pieces. Genetic or autoimmune deficiency of ADAMTS13 impairs this adaptive mechanism and causes thrombotic thrombocytopenic purpura (TTP), which is characterized by life-threatening microvascular thrombosis.

HISTORY OF MEDICINE

TTPwas first described by Eli Moschcowitz in 1924 who described a case of acute febrile hemolytic anemia with petechiae and the development of neurological signs shortly before death. No further case was described until 1936, when a composite clinico-pathological study of four cases was published. Only then did interest in TMA (which are that time was synonymous with TTP) begin to pick up. Jump ahead to 1991 when a seminal paper was published in the New England Journal of Medicine showing that therapeutic plasma exchange increased survival in TTP from **10% to 90% - a true game changer!** ADAMTS13 was first purified in 2001.

NOTES

ATTRIBUTIONS

Written by: Dr. William Aird

Input from: Dr. Stephen Stearns (*Evolutionary Medicine*)
Dr. John Harvey (*Comparative Physiology*)
Dr. Jane Maenschein & Dr. Kara McCord (*History of Medicine*)

The Blood Project
ENCYCLOPEDIA OF BLOOD