An Overview of the Laboratory's Role in the Diagnosis and Treatment of Thrombotic Thrombocytopenic Purpura

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LEARNING OBJECTIVES

1. Describe the role the laboratory has in diagnosis of thrombotic thrombocytopenic purpura (TTP).
2. List the classical diagnostic pentad of TTP and the more modern diagnostic criteria.
3. Describe the treatment method used for congenital and acquired TTP.

ABSTRACT

Thrombotic thrombocytopenic purpura (TTP) is a multifaceted disease for a clinical laboratory with diagnosis data and treatment spread across many different laboratory sections. By encompassing results from hematology, chemistry, molecular, and coagulation sections with treatment from the transfusion medicine/blood bank section of the laboratory, clinicians are able to accurately diagnose and treat TTP.

ABBREVIATIONS: ADAMTS - a disintegrin and metalloprotease with thrombospondin type 1 repeats, ADAMTS13 - a disintegrin and metalloprotease with thrombospondin type 1 repeats, member 13, MAHA - microangiopathic hemolytic anemia, TPE - therapeutic plasma exchange, TTP - thrombotic thrombocytopenic purpura, VWF - von Willebrand factor.

INDEX TERMS: thrombotic thrombocytopenic purpura, ADAMTS13, von Willebrand factor.

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INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP) is a hematologic disorder that results in microthrombi forming in the small capillaries of the circulatory system. Although sometimes confused with other hematologic disorders, TTP is classically seen with thrombocytopenia, microangiopathic hemolytic anemia (MAHA), fragmented erythrocytes, neurological defect, and fever. TTP can be rapidly fatal, requiring quick assessment of symptoms and start of treatment to reduce mortality.

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TTP

TTP was first described in 1924 when a 16-year-old girl presented to the emergency room with fever, anemia, and weakness. Dr Eli Moschcowitz was the first physician to describe the disorder after the girl's death. Autopsy findings showed disseminated hyaline thrombi in arterioles and capillaries of the heart, liver, and kidney. No larger vessels were affected by these observed thrombi.[1,4] In 1966, the pentad of TTP symptoms was described and included fever, hemolytic anemia, thrombocytopenia, neurological symptoms, and kidney involvement; however, over time, the expectation of this classical pentad has decreased. In 1982, the ultra-large von Willebrand factor (VWF) multimers were seen in patients presenting with TTP, and the role of VWF was determined.[3] In 2001, with new techniques in gene cloning, the 13th member of the "a disintegrin and metalloprotease with thrombospondin type 1 repeats" (ADAMTS) protein family was discovered, and it was shown that a decrease in ADAMTS member 13 (ADAMTS13) activity was consistent with TTP.[3] Currently, TTP should be suspected and excluded by laboratory assays and the presence of MAHA with red blood cell fragmentation and thrombocytopenia alone.[2] Additional clinical signs may allow for a faster diagnosis as well. These clinical signs may include petechiae, purpura, epistaxis, and cerebral and retinal hemorrhages. Neurologic symptoms that may appear include headache, confusion, aphasia, and even a coma.[4]

Since the identification of ADAMTS13, TTP can be identified as one of two forms: congenital or acquired deficiency. Clinically, there are many other syndromes, including eclampsia and hemolytic uremic syndrome, that are considered MAHA disorders and that could closely resemble TTP.[5] Most cases of TTP are due to an autoimmune mechanism that interferes with ADAMTS13-acquired TTP.

LABORATORY'S ROLE

Laboratory confirmation of TTP is determined by a profound decrease in ADAMTS13 enzyme activity. The follow-up to a decreased ADAMTS13 activity assay is to

Table 1. Original patient laboratory values for a 40-year-old female who was seen in the emergency department with abdominal pain over 3 days

Hematology	Reference Interval	Original Patient Values
WBC, bil/L	3.3–10.7	4.7
RBC, tril/L	3.87–5.08	3.3
Hemoglobin, g/dl	12.1–15	9.0
Hematocrit, %	34.4–44.2	27.8
MCV, fL	80–100	84
MCH, pg	28–32	27
MCHC, %	32–36	32
RDW, %	11.5–15.5	20
Platelet, bil/L	150–400	32
MPV, fL	8.5–12.5	14
IPF, %	1–11	15
Neutrophils, bil/L	1.6–7.2	3.2
Lymphocytes, bil/L	1.1–4.0	1
Monocytes, bil/L	0.0–0.8	0.4
Eosinophils, bil/L	0.0–0.5	0.0
Basophils, bil/L	0.0–0.1	0.0
Immature granulocytes, bil/L	0.00–0.03	0.01
RBC morphology	<1/hpf	schistocytes 3–5; polychromasia 1–3
Coagulation		
PT, s	9.5–12.3	11.8
aPTT, s	24.3–32.2	29.7
Fibrinogen, mg/dl	180–400	319
ADAMTS13 activity, %	50–160	<5
ADAMTS13 inhibitor, BU	<0.4	2
Chemistry		
LDH, U/L	140–280	362
Creatinine	0.5–1.0	1.2
Bilirubin, mg/dl	0.2–1.2	3.6
Urinalysis—completed day prior to above results		
Test strip results		
Color	Yellow	Dark Yellow
Clarity	Clear	Cloudy
Glucose	Negative	Negative
Bilirubin	Negative	Negative
Ketones	Negative	Negative
Specific gravity	1.003–1.035	1.017
Blood	Negative	3+
pH	5.0–8.0	7.0
Protein, mg/dl	Negative	100
Urobilinogen, mg/dl	0.2–1	2
Nitrates	Negative	Negative
Leukocyte esterase	Negative	Negative
Urinary sediment		
RBC	0–2 (negative)	0–2 (negative)
WBC	0–2 (negative)	3–10
Epithelial, squamous	0–5 (negative)	>50
Casts, hyaline	0–2 (negative)	0–2 negative
Bacteria	0–1+ (negative)	1+

Abbreviations: ADAMTS13, a disintegrin and metalloprotease with thrombospondin type 1 repeats, member 13; aPTT, activated partial thromboplastin time; BU, blood unit; IPF, immature platelet fraction; LDH, lactic acid dehydrogenase; MCH, mean cell hemoglobin; MCHC, mean cell hemoglobin concentration; MCV, mean cell volume; MPV, mean platelet volume; PT, prothrombin time; RBC, red blood cell; RDW, red cell distribution width; WBC, white blood cell.

detect autoantibodies to ADAMTS13, confirming the diagnosis of acquired TTP.[2] Additional laboratory testing includes a complete blood count, clinical chemistry panel, and urinalysis. Specific testing includes lactic acid dehydrogenase, haptoglobin, bilirubin, prothrombin time and activated partial thromboplastin time, and other indicators of hemolysis.[2] The hemolysis in TTP arises from increased shear stress on red blood cells in arterioles and capillaries narrowed by microthrombi.

TTP is still considered a life-threatening disease with a mortality rate of 10%–20%. Even though TTP is a serious hematologic emergency that is almost always fatal in untreated cases, an understanding of its pathophysiology can lead to successful treatment strategies resulting in improved patient management and outcomes.

Aside from routine laboratory findings, TTP is a disease that is classified by abnormal functioning of the ADAMTS13 protease. ADAMTS13 protease impairment can be caused by genetic mutations at the gene level or through autoantibodies that are formed within the circulation. Congenital mutations account for about 5%–10% of the TTP population, whereas the acquired version is more common. The acquired version of TTP is due to inhibitory and noninhibitory autoantibodies that affect the ADAMTS13 protease. Both congenital and acquired TTP are treated through transfusion therapy with therapeutic plasma exchange (TPE). TPE is used to remove the autoantibodies and any mutated ADAMTS13 proteases in the circulation, while providing the addition of normal functioning ADAMTS13 to the circulation. TPE is removal and retention of plasma through an apheresis machine

that allows all cellular products to be returned to the circulation.[6] TPE was first employed in 1952, and by the 1970s, it was a multiuse treatment for many different diseases. The efficiency of TPE depends on the plasma volume that is being removed and pathogenic substrate (immune globulin G and immune globulin M antibodies in TTP). One volume exchange is equivalent to 65% of the initial component removed with 75%–85% substrate removal within two TPE procedures.[6]

CASE STUDY

This Focus Series is designed to provide a comprehensive review of TTP for the laboratory scientist. The following articles will provide in-depth understanding of the etiology, pathogenesis, immunology, laboratory findings, and treatment of TTP. This case study is the review of diagnosis and treatment of a 40-year-old female who presented to the emergency department. The original laboratory findings can be seen in Table 1. The presented results, which are analyzed in the following Focus article, demonstrate why prompt and accurate diagnosis and treatment are needed in cases of TTP.

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