When to suspect thrombotic microangiopathy (TMA) ?

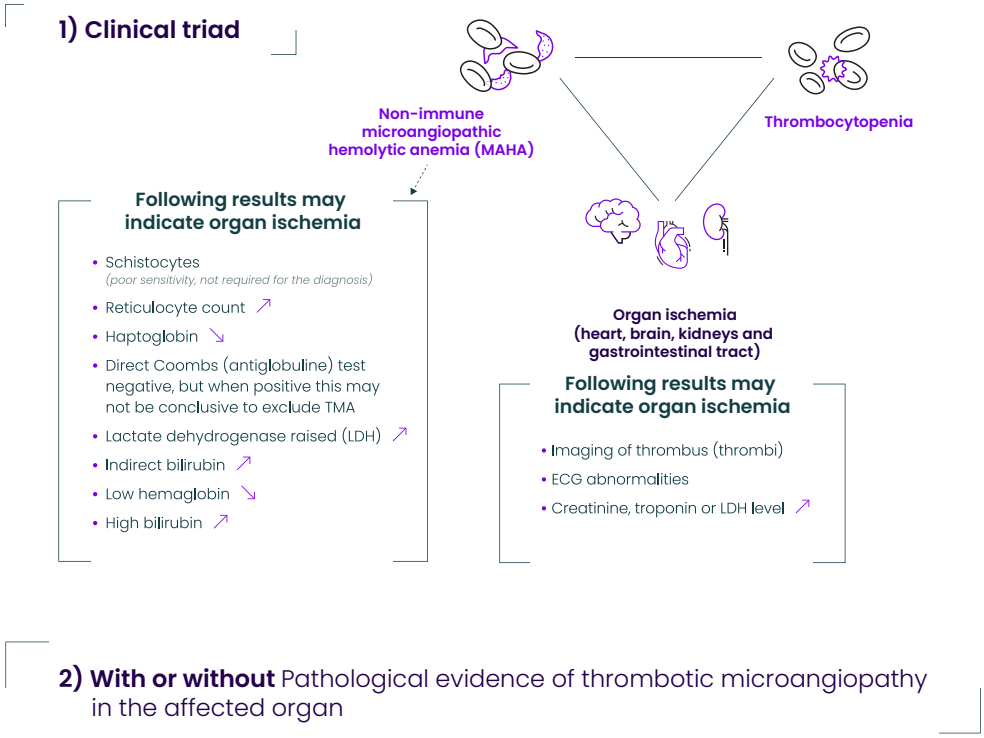

Figure 1: When to suspect Thrombotic Microangiopathy (TMA). From Scully M et al., Br J Haematol. 2012; 158(3):323–35 &. Joly B et al., Blood 2017;129(21):2836–46.

TMA is characterized by the clinical triad of thrombocytopenia, non-immune microangiopathic hemolytic anemia, and ischemic end-organ injury with or without pathological evidence of TMA in an affected organ. Thrombocytopenia may be missing in a low proportion (~15%) of cases and the sensitivity of schistocytes on blood smear is variable. Early recognition of these conditions is important, as TMA are rare and life-threatening disorders requiring specific management.[1-2]

Other conditions may also cause anemia, thrombocytopenia and organ damage and mimic TMA, such as e.g., disseminated intravascular coagulation (altered coagulation tests, low fibrinogen levels), severe sepsis, hematological diseases, vitamin deficiency and liver disease.[3]

Once a positive diagnosis of TMA is made, a thorough workup is needed to identify the underlying mechanism and define the appropriate treatment. **Etiologies of TMA** include: congenital or acquired thrombotic **thrombocytopenic purpura** (defined by an ADAMTS13 activity <10%), **HUS associated with shigatoxin secreting enterobacteriae, TMA associated with various triggers and conditions** (i.e. systemic lupus erythematosus, systemic sclerosis, pregnancy, drugs, cancer, malignant hypertension, human immunodeficiency virus infection, hematopoietic stem cell or solid organ transplantation) and **primary atypical HUS**.[4]

Etiology of Thrombotic Microangiopathy (TMA)

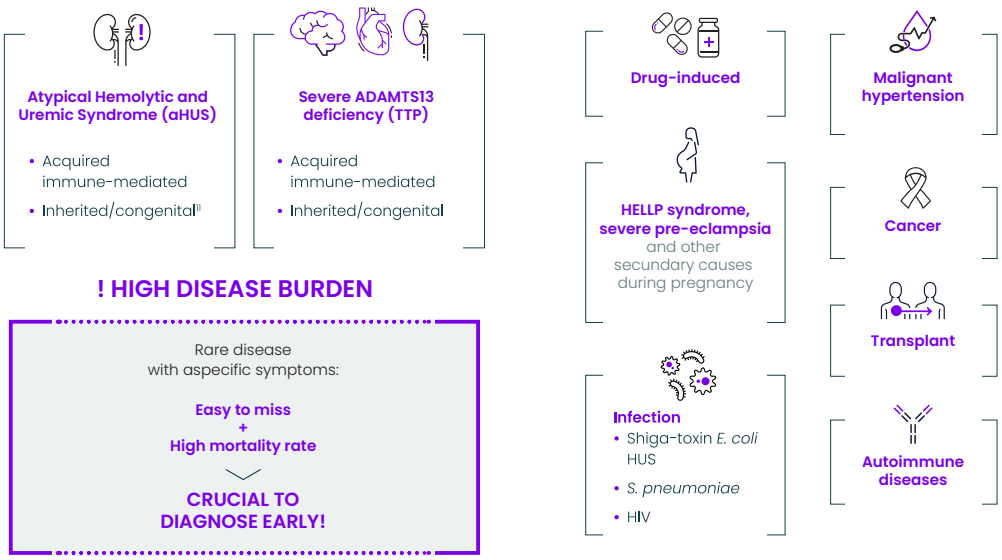

Figure 2: Etiology of Thrombotic Microangiopathy (TMA). From Bayer G. et al., Clin J Am Soc Nephrol 14: 557–566, 2019

Thrombotic thrombocytopenic purpura (TTP) **is an ultra-rare & life-threatening disease classified in the group of thrombotic microangiopathies (TMA)** and is defined as an acquired or congenital deficiency in ADAMTS13 activity, the von Willebrand factor-cleaving protease. Loss of activity of this protease stimulates the formation of microthrombi. In acquired TTP (aTTP) the activity of ADAMTS13 is inhibited by autoantibodies, whereas in congenital TTP mutations in the ADAMTS13 gene lead to loss of ADAMTS13 function.[1]

ADAMTS13 activity should be evaluated as soon as possible (ideally <24h) in any patient with a diagnosis or suspicion of TMA. **The definitive diagnosis of TTP relies on the demonstration of a severely decreased ADAMTS13 activity, <10%.**[5]

While awaiting the results of ADAMTS13 activity, **treatment should be initiated when clinical suspicion is high.** To provide guidance in predicting likelihood of ADAMTS13 deficiency the **PLASMIC & French score** were developed.[6] A platelet count <30.103/µL and a serum creatinine <2.26 mg/dL are features suggestive of TTP rather than HUS.

PLASMIC or French score predicts the likelihood of severe ADAMTS13 deficiency in case of suspected TTP

Parameters	French score	PLASMIC score
Platelet count	<30x10^9/L(+1)	<30 x 10^9/L (+1)
Serum creatinine level	<2.26 mg/dL (+1)	<2.0 mg/dL (+1)
Hemolysis Indirect bilirubin >2 mg/dL or Reticulocyte count >2.5% or Undetectable haptoglobin	-*	+1
No active cancer in previous year	-*	+1
No history of solid organ or SCT	-*	+1
INR <1.5	-*	+1
MCV <90 fL	NA	+1
Likelihood of severe deficiency of ADAMTS13 activity (10%)	0: 2% 1: 70% 2: 94%	0-4 : 0-4% 5: 5-24% 6-7: 62-82%

ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; TTP, thrombotic thrombocytopenic purpura; INR, international normalized ratio; MCV, mean corpuscular volume; NA, not available; SCT, stem cell transplantation.

* French score considered patients with TMA that included hemolysis and schistocytes in their definition and assumed that there was no history or clinical evidence for associated cancer, transplantation or disseminated coagulation. Therefore, these items were intrinsic to the scoring system. NA and MCV were not incorporated in the French score. Table adapted from Joly BS, et al.

Figure 3: PLASMIC or French score. From Coppo P et al., PLoS One. 2010;5:e10208. 6. Bendapudi PK et al., Lancet Haematol. 2017;4:e157-64.

Treatment of aTTP: aTTP is a medical emergency and treatment should be initiated early to prevent death and severe, debilitating complications. Urgent management of aTTP relies on three cornerstones: (i) drugs that inhibit the interaction between von Willebrand factor multimers and platelets (ii) repletion of ADAMTS13 and removal of anti-ADAMTS13 autoantibodies by therapeutic plasma exchanges, and (iii) immunosuppression.[6]

References

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