

Thrombomodulin and Endothelial Dysfunction: A Disease-Modifier Shared between Malignant Hypertension and Atypical Hemolytic Uremic Syndrome

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Keywords

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Abstract

Thrombomodulin (TM) is an endothelial glycoprotein that is present in all blood vessels. Five percent of all patients with atypical hemolytic uremic syndrome (aHUS) have mutations in the gene coding for TM, with a peak presentation in young children. Mutations often translate into quantitative and qualitative abnormalities of this endothelial glycoprotein. Outcome of the TM-associated aHUS is relatively poor with frequent relapses after transplantation despite its membrane-bound character. We observed a woman presenting with malignant hypertension (MHT) and associated kidney, brain, cardiac, and hematological involvement with thrombotic microangiopathy on kidney biopsy. She had a documented mutation of the gene coding for TM, which was associated with both aHUS and an increased risk for venous and arterial thrombosis. As TM has anti-coagulant, anti-in-

flammatory, and cytoprotective properties and also attenuates alternative complement activation, this glycoprotein could play an active role in other diseases with endothelial involvement apart from aHUS. We discuss the potential role of TM in the pathophysiology of various endotheliopathies including MHT. We also provide a framework for future therapeutic options.

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Background

Malignant hypertension (MHT) is a life-threatening condition classically defined by hypertensive retinopathy grade III/IV and/or other end-organ damage, while criteria for blood pressure values are inconsistent but mostly define diastolic blood pressure ≥ 120 mm Hg [1]. Recent guidelines urge to discriminate between hypertensive emergency and hypertensive urgency. Hypertensive emergency is defined by severe hypertension ($>180/120$ mm Hg) and impairment of at least 3 or-

gans even without hypertensive retinopathy. It requires prompt treatment usually by parenteral drugs, while hypertensive urgency is defined as significantly elevated blood pressure without end-organ failure treated by the reinstatement or intensification of antihypertensive drugs [2]. One in four patients with MHT has biochemical signs of micro-angiopathic hemolytic anemia. Although thrombotic microangiopathy (TMA), whether or not in association with underlying atypical hemolytic uremic syndrome (aHUS) can induce severe hypertension [3], the combined retinal findings of cotton-wool spots, flame hemorrhages, retinal arteriolar narrowing, and optic disc swelling are still considered to be pathognomonic for MHT. This should prompt immediate and aggressive blood pressure lowering and should suffice to obtain resolution of TMA and partial or complete recovery of the kidney function without need for additional treatment. Increasing evidence points toward pathophysiological overlap between clinical conditions that share TMA features such as thrombotic thrombocytopenic purpura, aHUS, scleroderma with renal crisis, preeclampsia, and even hypertension [3–5]. Although a potential role of a disturbed complement system in the pathophysiology of hypertension-associated kidney damage is increasingly being considered [6], the exact role of alternative complement dysregulation in the pathophysiology of MHT currently remains ill defined. We describe a patient with TMA and acute kidney injury with tentative diagnosis of aHUS, which was initially treated with plasmapheresis. Ophthalmological examination revealed, however, papilledema with lipoid exudates and choroidal hypoperfusion suggestive of grade IV hypertensive retinopathy. A genetic screening panel for aHUS revealed a very rare pathogenic mutation of the gene coding for thrombomodulin (TM; c.1502C>T), which has been described as a risk factor for aHUS, mainly in children and young adults. We discuss the diagnostic dilemmas, which might arise in similar clinical situations and speculate on a possible pathogenetic and therapeutic role of TM in MHT.

Case Vignette

A 33-year-old woman presented with intermittent headache for 6 weeks, and since 1 week palpitations, fatigue, and exertional dyspnea. She had no visual or neurological complaints. Her medical history was blank apart from biliary pancreatitis 10 years ago and mild obesity without any notion of hypertension. She had 1 pregnancy 10 years ago, which was uneventful apart from severe

postnatal anemia without biochemical signs of TMA and no need for transfusion. She was not taking any drugs apart from intermittent nonsteroidal anti-inflammatory drugs and she smoked 2 cigarettes per day. Her blood pressure at admission was 205/140 mm Hg, but otherwise her clinical examination was unremarkable. She had no clinical signs suggestive of systemic sclerosis. Biochemical evaluation revealed signs of TMA (Table 1). The serum creatinine at admission was 3.2 mg/dL (estimated glomerular filtration rate 18 mL/min/1.73 m²) according to the chronic kidney disease (CKD)-epidemiology collaboration formula with urinalysis showing a blank sediment but moderate proteinuria (2 g/g creatinine) with albuminuria. Coagulation parameters, viral serology, liver tests, antiphospholipid antibodies and antinuclear factor, and a disintegrin and metalloproteinase with a thrombospondin type 1 motif member 13 (ADAMTS13) were unremarkable and ultrasound showed normal-sized kidneys without obstruction. Acceptable blood pressure control was initially realized upon the initiation of calcium antagonists and beta-blockers. A kidney biopsy showed overall 12 glomeruli, some of which were slightly ischemic (Fig. 1a). Expansion of the mesangial matrix was noted with enlargement of the capillary walls by subendothelial expansion. There was scattered mesangiolysis and sequestration of erythrocytes and some neutrophils in some capillaries (Fig. 1b). There were signs of focal segmental fibrinoid necrosis in some glomeruli with presence of fragmented erythrocytes (Fig. 1c, d). There was mild tubular atrophy with interstitial fibrosis and lymphocytic inflammation. Multiple arterial segments had intimal expansion, often with preexistent fibrotic intimal thickening. On Masson staining, there was fibrinoid necrosis in arterial vessel walls (Fig. 1c, d). Immunofluorescence was negative.

Daily plasma exchange was initiated for assumed aHUS with mild signs of TMA. An echocardiography showed left ventricular hypertrophy and signs of grade 3 diastolic dysfunction. Magnetic resonance imaging demonstrated white matter brain lesions. A first ophthalmological examination demonstrated moderate papilledema with peripapillary exudates (Fig. 2a, b). This was interpreted as a sign of MHT and prompted the discontinuation of plasma exchange and optimization of blood pressure control by the initiation of angiotensin-converting enzyme inhibitors next to moxonidine. A repeated fundus examination with additional fluorescein-angiography and ocular coherence tomography confirmed MHT-associated retinopathy with TMA, leakage of the disc, delayed choroidal filling, and macular drusenoid

Table 1. Laboratory values

Test	Value		Reference value
	At presentation	Five months after presentation	
Haptoglobin, g/L	0.23	1.94	0.3–2.0
Hemoglobin, g/dL	9.6	13.8	11.8–14.8
Thrombocytes, $\times 10^3/\mu\text{L}$	137	236	171–374
C3, mg/dL	105	157	72–156
C4, mg/dL	39		15–45
LDH, U/L	527	150	105–233
Schistocytes, %	2	Negative	
Serum creatinine, mg/dL	3.2	1.8	0.5–0.95
Antinuclear factor	Negative		
ADAMTS13, %	94.5		50–160
ANCA	Negative		
C3d, mg/dL		1.4	<1.2
C3d/C3		0.9	<1.4
SC5b-9, ng/mL		136	<314
Factor B, mg/dL		18	8–21
Factor H concentration, mg/dL		82	37–73
Factor H activity, %		91	65–106
Factor I, mg/dL		11.4	4.0–10.7
CD46 (MCP)		99.9% granulocytes	95–100
TM, ng/mL		5.3	1.3–2.5
TAFIa, %		120	40–250

ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif member 13; TAFIa, activated thrombin activatable fibrinolysis inhibitor; TM, thrombomodulin.

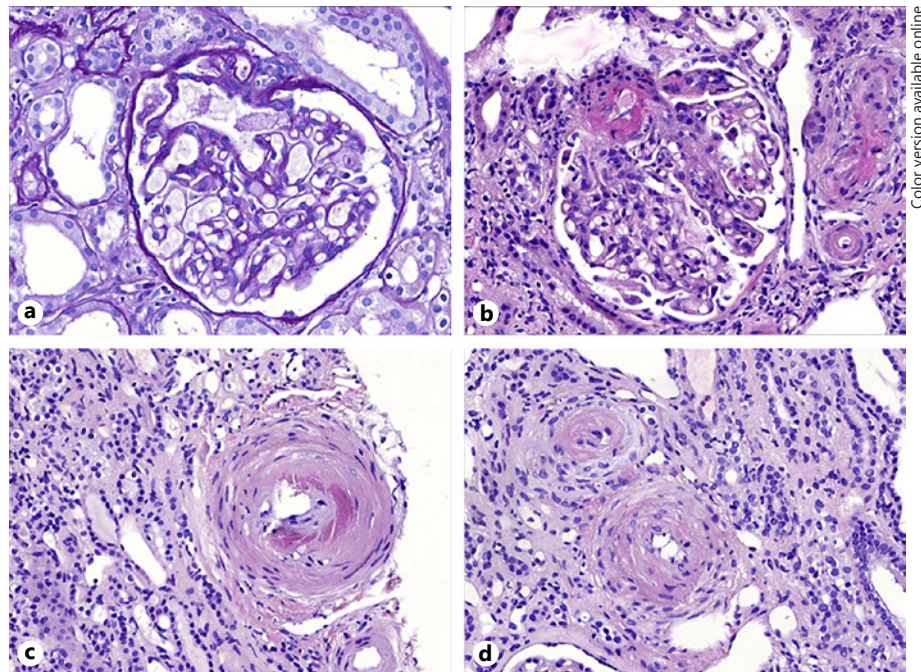


Fig. 1. Histological abnormalities on kidney biopsy. **a** Micro-aneurysm formation and basal membrane remodelling in ischemic glomerulus (periodic acid shiff). **b** Fibrinoid necrosis and mucinous intima expansion with the presence of fragmented red blood cells obliterating the capillary lumen (Masson staining). **c** Fibrinoid necrosis of the vessel wall (Masson staining). **d** Mucinous intima expansion and fibrotic thickening (Masson staining).

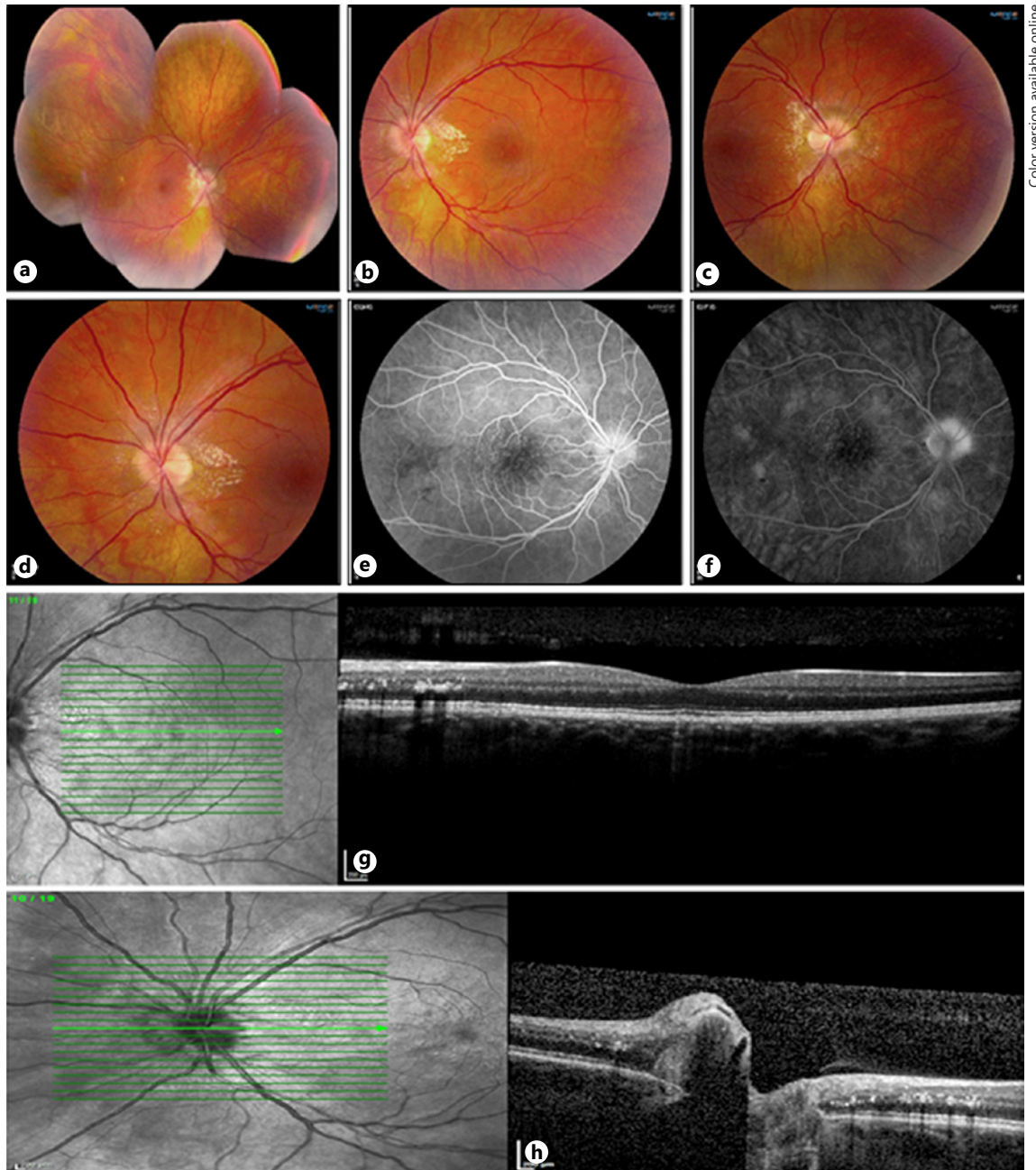


Fig. 2. Eye abnormalities. **a** Right eye composite color fundus photograph (Topcon Fundus Camera): swollen disc with telangiectatic vessels, lipoid exudates surrounding the disc with tendency of star formation toward the macula, mildly engorged and tortuous retinal veins, small drusenoid deposits in the foveal area. **b** Left eye posterior pole color fundus photograph: swollen disc with telangiectatic vessels, lipoid exudates surrounding the disc with tendency of star formation toward the macula, mildly engorged and tortuous retinal veins, small drusenoid deposits in the foveal area. **c** Right eye color fundus photograph right eye centred on the optic disc (after 1 month): decreased edema. **d** Left eye color fundus photograph left eye optic disc detail (after 1 month). **e** Fluorescein angiography (Topcon Fundus Camera): presentation early phase (24 s) fluores-

cein angiography right eye: delayed choroidal filling of temporal macular area and posterior mid-periphery, early hyperfluorescence optic disc with fine telangiectatic vessels, staining of small drusenoid deposits in the foveal area. **f** Fluorescein angiography: presentation late phase (5m17s) fluorescein angiography right eye: hyperfluorescence of the optic disc, patchy leakage choroidal vessels, persistent staining of small drusenoid deposits in the foveal area without leakage. **g** Ocular coherence tomography (OCT-Heidelberg Spectralis OCT). Right eye macula: small drusenoid lesions in the foveal area and lipoid exudates temporal of the fovea within the outer plexiform and inner nuclear layer. **h** OCT. Left eye optic disc: swelling optic disc and lipoid exudates within the outer plexiform and inner nuclear layer on the nasal and temporal side of the disc.

deposits (Fig. 2c–h). TMA and optic disc edema can be secondary to both aHUS and MHT. The small peripheral retinal pigment alterations guided toward underlying MHT. A search for secondary causes of hypertension (renal artery stenosis, adrenal tumor, Cushing syndrome or pheochromocytoma) was negative. A genetic screening panel for aHUS, which was ordered earlier, revealed a pathogenic mutation of the gene coding for TM (c.1502C>T). We assayed TM and thrombin activatable fibrinolysis inhibitor (TAFIa) quantitatively by enzyme-linked immunosorbent assay (respectively IMUBIND from Sekisui Diagnostics, Japan and Asserachrom TAFI from Diagnostica Stago, USA) and evaluated the alternative complement cascade 5 months after presentation considering the initiation of plasmapheresis at presentation, impeding an early assessment of these parameters. Results are summarized in Table 1. Clinical and biochemical signs of TMA resolved 1 week after blood pressure was adequately controlled. Kidney function recovered partially to a serum creatinine of 1.60 mg/dL without proteinuria 20 months after presentation. Blood pressure remains adequately controlled on a combination of 4 different antihypertensive drugs and her headache completely resolved.

TM and Endothelial Dysfunction

TM is a transmembrane type1-glycoprotein, which is uniformly expressed on the vascular endothelium [7]. It binds to the proinflammatory thrombin thereby enhancing the catalytic activation of protein C, which exerts an anticoagulant function by cleaving factors Va and VIIIa and downregulating further thrombin generation. The thrombin-TM complex converts through proteolytic cleavage the zymogen thrombin – TAFI into an activated form (TAFIa), which inhibits fibrinolysis. At the site of vascular injury, thrombin forms the fibrin clot. On the intact endothelium adjacent to the site of injury, thrombin binds to TM. The thrombin/TM complex amplifies the activation of protein C and consequently suppresses the clotting cascade, preventing excessive fibrin clot formation. Simultaneously, the activation of TAFIa will protect the clot already formed from premature lysis. Activated protein C has also anti-inflammatory and cytoprotective properties. TAFIa contributes to the anti-inflammatory potential of TM through cleavage of anafylatoxins C3a and C5a [7–9]. In vitro, TM binds to factor H and C3b and negatively regulates complement by accelerating factor I (CFI)-mediated inactivation of

C3b in the presence of cofactors, thereby attenuating the activation of the alternative complement cascade [7, 8]. Mutant TM is less effective in enhancing CFI-mediated inactivation of C3b [7]. In addition, TM prevents the direct activation of C5 by thrombin. Also, the lectin-like domain of TM binds the proinflammatory cytokine high mobility group box 1 (HMGB1), the ligand of receptor of advanced glycation end-products (RAGE). TM inhibits the proinflammatory HMGB1-RAGE axis by cleaving HMGB1 into an inactive fraction [10].

In healthy people, plasma concentrations of TM remain relatively low. Endothelial damage of whatever origin results in proteolysis and shedding of TM of the endothelial layers resulting in a 1.5–2 fold rise in plasma TM concentration [8]. This phenomenon is observed in variable conditions associated with TMA such as preeclampsia, sepsis, diffuse intravascular coagulation (DIC), Shiga toxin-producing *E. Coli* (STEC)-induced and atypical HUS, thrombotic thrombocytopenic purpura, scleroderma-associated pulmonary hypertension, and arterial hypertension [11–16]. Also, we found an increased plasma concentration of TM as a result of endothelial damage in our hypertensive patient. Paradoxically, higher plasma TM concentrations at inception were associated with a lower incidence of coronary heart disease and diabetes in a cohort of presumed healthy people, implying that its soluble form may be vasculoprotective [17, 18]. Instead, young patients with diabetes have increased plasma TM concentrations compared to patients without diabetes, reflecting endothelial damage [19]. Whether a high plasma TM concentration has to be considered vasculoprotective or as a sign of endothelial damage should be interpreted according to the vascular context and does not reflect the amount of TM present on the endothelium itself [20]. In healthy individuals, relatively higher plasma concentrations of this protective glycoprotein might reflect a higher endothelial production and in this situation, a high concentration of soluble TM reflects a low prothrombotic state with low risk of first-ever coronary events. In disease conditions, a higher or increasing plasma concentration is caused by increased proteolytic activity resulting in the cleavage of endothelial TM. In pathologic conditions, a high soluble TM may reflect the degree of endothelial damage [15, 20]. Impaired kidney or hepatic function can further elevate its concentration [8]. Simultaneously, conditions that cause endothelial stress such as DIC and sepsis, or more specifically exposure to cytokines, endotoxin, human leukocyte antigen antibodies, fibroblast growth factor 23, or Shiga toxin temporarily decrease the endothelial synthesis and ex-

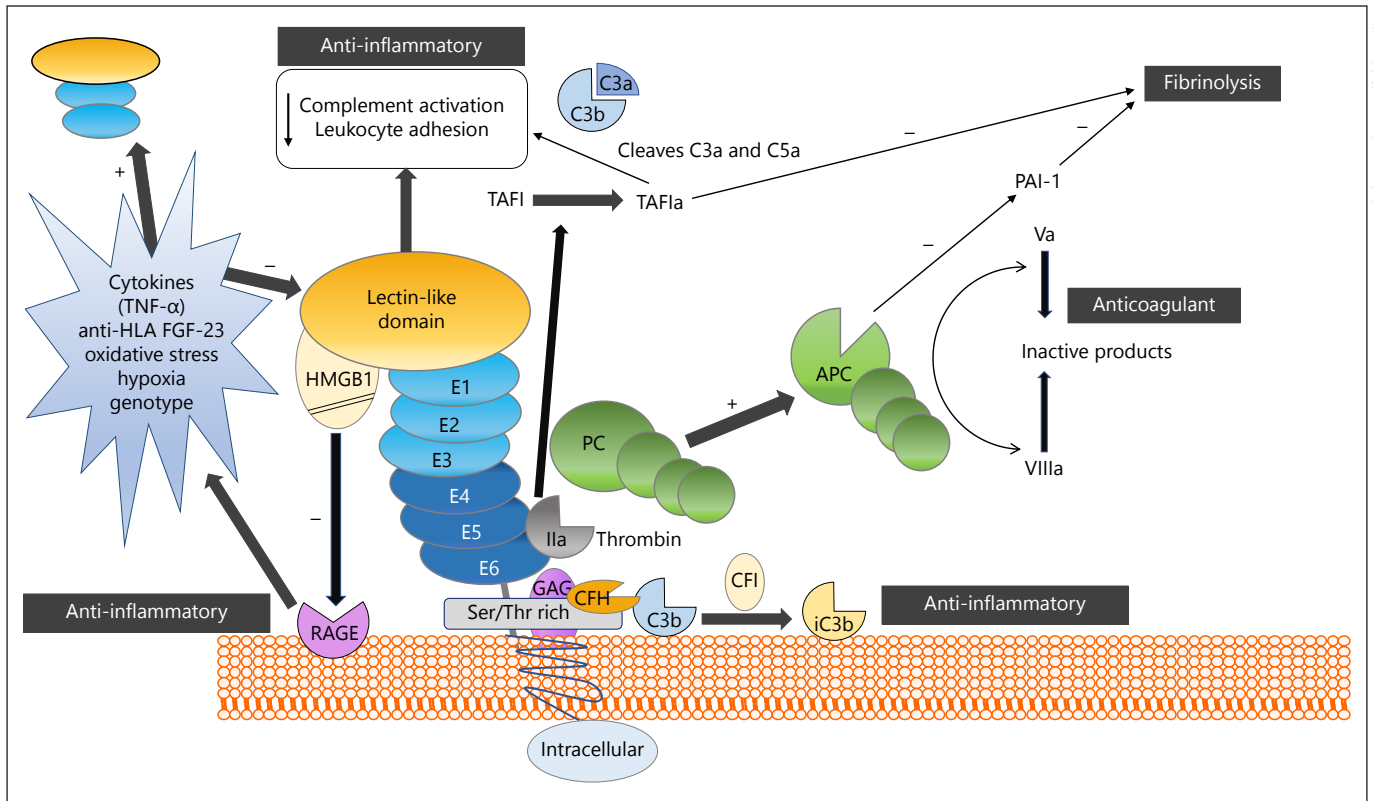


Fig. 3. The potential role of thrombomodulin (TM) in malignant hypertension (MHT) and associated thrombotic micro-angiopathy. TM is an endothelial transmembrane glycoprotein with possible relevance in MHT. It has an intracellular domain, a transmembrane spanning region, a serine/threonine rich domain, 6 epidermal growth factor (EGF)-like repeats and a lectin-like domain. The thrombin (IIa)-binding region has been localized to the fifth and sixth EGF-like domains, while the fourth EGF-like domain is required for protein C binding to the thrombin-TM complex. The serine/threonine-rich spacer region is the site of glycosaminoglycan (GAG) and especially chondroitin sulphate attachment, enabling the interaction between TM and factor H, which is a co-factor for the factor I-mediated cleavage of C3b into inactive fragments (iC3b). TM scavenges thrombin and abrogates all procoagulant activities of thrombin by promoting the activation of protein C with consecutive anticoagulant and anti-inflammatory properties. Activated thrombin activates fibrinolysis inhibitor (TAFIa) stabilizes fibrin clots at intermediate concentrations.

They can cleave the anaphylatoxins C3a and C5a at their COOH-terminal arginine residues. The lectin-like domain binds the proinflammatory cytokine high mobility group box 1 (HMGB1), the ligand of receptor of advanced glycation end-products (RAGE), which is involved in the pathogenesis of hypertension. TM inhibits the proinflammatory HMGB1-RAGE axis by cleaving HMGB1 into an inactive fraction. Environmental triggers that are associated with endothelial dysfunction decrease the expression of TM on endothelial cells. MHT directly or indirectly via oxidative stress and hypoxia (due to microvascular thrombosis and increased concentration of vasoconstrictors endothelin-1 and angiotensin-II) can decrease the expression of TM. Single nucleotide polymorphisms in the gene coding for TM can impair both the concentration and the function of TM by impeding the binding with thrombin and impairment of its activation. HLA, human leukocyte antigen; FGF-23, fibroblast growth factor 23; TNF-alpha, tumor necrosis factor alpha; PAI-1, plasminogen activator inhibitor-1.

pression of membrane-bound TM (Fig. 3, Table 2) [21–25]. A low endothelial concentration of TM contributes to the procoagulant and proinflammatory vascular state of these conditions. Single nucleotide polymorphisms of TM are associated with decreased endothelial expression and/or functional impairment [26]. This condition has previously been associated with an increased risk of coronary disease, venous or arterial thrombosis, and fetal loss

[27–29]. The pleiotropic endothelium-modifying properties of TM are translated into beneficial effects of recombinant human TM in rodent models of endotoxin-induced pulmonary vascular damage, ischemia-reperfusion kidney or liver injury, preeclampsia, STEC-HUS and acute ischemic stroke [30–35]. Of note, statins increase the endothelial expression of TM, possibly contributing to its beneficial cardiovascular properties [36], and acti-

Table 2. TM concentration in different endotheliopathies

	Plasma TM	Endothelial TM	References
Preeclampsia	↑	↓	[11, 23, 24]
Hypertension	↑	↓	[15, 16, 24]
aHUS	↑	↓	[13, 23]
STEC HUS	↑	↓	[13, 23]
Systemic sclerosis	↑	?	[14]
TTP	↑	?	[13]
Sepsis	↑	↓	[12, 25]
DIC	↑	↓	[12, 13, 25]

TM, thrombomodulin; aHUS, atypical hemolytic uremic syndrome; TTP, thrombotic thrombocytopenic purpura; DIC, diffuse intravascular coagulation; STEC, shiga toxin-producing *E. Coli*.

vation of the vitamin D receptor increases soluble TM in CKD patients, which is a possible mechanism whereby improvement in endothelial function may favorably impact vascular health in CKD patients [37].

In humans, recombinant human TM is an approved treatment for DIC in Japan. Pooled data from randomized controlled trials demonstrated that recombinant TM nonsignificantly improves first-month survival by 19% in patients with sepsis-induced DIC without excess bleeding risk [38]. In children, it has been successfully utilized as adjuvant treatment in children with STEC-HUS [39, 40].

TM and aHUS

Missense mutations in the gene coding for TM can lead to a diminished ability to protect against activated complement, a feature of 5% of the mostly infantile aHUS cases [7, 8, 41, 42]. Delvaeye et al. [7] identified 6 amino acid-changing, heterozygous missense mutations of the coding gene in 7 unrelated patients with aHUS. In vitro evaluation demonstrated that mutated TM variants resulted in the dysregulation and suppressed activation of the complement system [7]. A patient with acute TMA was recently demonstrated to have a heterozygous mutation of TM (c.1103C>T) with in vitro decreased generation of TAFIa [43]. In a multicenter, European cohort, mutations of genes coding for TM were associated with a poor prognosis of aHUS, which was far worse than for mutations in the other membrane-bound membrane cofactor protein [44]. Only a few of the reported aHUS patients with TM mutations have undergone transplanta-

tions so far. Relapses after transplantation have been observed and are attributed to circulating mutant soluble TM, which is less effective in enhancing CFI-mediated inactivation of C3b and so activates the complement system rather than providing protection [7, 44]. It has been suggested that endothelial TM is downregulated in kidney allografts, with loss of the anti-complement activity, thus resulting in a greater dependence on the soluble plasma forms of TM for kidney protection. The mutant forms of soluble TM may be quantitative or qualitative, inadequate to provide sufficient protection or may even contribute to disease [45]. The protective role of soluble TM so far is unestablished. Also, taking into account that about 50% of all aHUS patients have no proven mutation in proteins involved in the complement pathway [45], possibly some of the patients with aHUS and TM mutation have another unidentified genetic abnormality, which promotes the development of aHUS and potential relapses after transplantation [46].

TM in MHT

A potential role of TM in MHT has so far not been considered. There are however arguments for such a hypothesis. Endothelial dysfunction is a prime mechanism leading to hypertension. As TM is a key player in endothelial homeostasis, it is well conceivable that a dysfunctional TM can mediate hypertension. Simultaneously, TM is a biomarker of endothelial dysfunction, and hypertension can induce itself endothelial damage. As a hallmark of these links, plasma TM concentrations are significantly higher in people with hypertension or pregnant women with preeclampsia than in control subjects [6].

The placental expression of TM was lowest in those preeclamptic women with the highest diastolic blood pressure [23]. Patients with MHT have abnormalities of microvascular function including increased circulating endothelial cells and endothelial progenitor cells [47].

The missense mutation with C/T substitution at position 1,502, which predicts an amino acid change (Pro⁴⁸³Leu) in the Ser/Thr rich region of TM as observed in our patient was both associated with aHUS and an increased propensity toward arterial and venous thrombosis and fetal loss [48]. This mutation is associated with a decreased expression and impaired functionality of TM [26]. The serine/threonine domain is the site of chondroitin sulfate attachment, whose presence not only enhances the TM interaction with thrombin, procuring anticoagulant properties, but also binds factor H, while the

lectin-like domains have an anti-inflammatory potential. Alterations of complement activation are mainly caused by mutations in the lectin-like domain, whereas mutations in the epidermal growth-factor repeats interfere with thrombin-mediated activation of protein C, which has anticoagulant and cytoprotective properties, and the generation of activated TAFI, which has C3a- and C5a-degrading properties [8]. Decreased anticoagulant properties could aggravate microvascular thrombosis in MHT.

In retinal endothelial cells, continuous laminar shear stress upregulates the expression of TM in a time- and dose-dependent manner [49]. Some studies have non-consistently shown decreased endothelial TM expression upon cyclic strain [8]. In conditions of exaggerated shear stress, such as in MHT, it is conceivable that retinal damage is more pronounced because endothelial upregulation of TM becomes exhausted, which will manifest more rapidly when TM function is impaired due to a genetic mutation. Of note, hypertensive retinal endothelial damage (sclerosis) has been associated with increased concentrations of plasma TM [15].

MHT is characterized by increased concentrations of potent vasoconstrictors endothelin-1 and angiotensin-II, which together with ongoing platelet aggregation and microvascular thrombosis can contribute to ischemia and hypoxia [50]. Hypoxia has been previously demonstrated to downregulate the expression of TM on endothelial cells with stable soluble TM concentrations [51]. TM also inactivates the proinflammatory cytokine HMGB1, the ligand of RAGE, which is involved in the pathophysiology of hypertension [52].

Finally, in humans with high blood pressure, the pro-inflammatory anaphylatoxin C5a plasma concentrations are increased [6]. TM inhibits the activation of C5a [8]. In animal models of hypertensive kidney damage, C5a exerts negative effects on the kidney by binding to C5aR₁ receptors [6]. A dysfunctional TM will be less able of attenuating the damaging effects of C5 on the kidney. It is thus plausible that a dysfunctional or decreased concentration of the ubiquitous TM in many different ways contributes to the phenotype of MHT with TMA, renal disease, retinopathy, myocardial involvement, and white matter brain lesions.

Considering the omnipresence of TM across the vasculature, its role in endothelial homeostasis, and its association with different clinical entities that share vascular thrombosis, it seems likely that abnormalities in this glycoprotein might also translate into many diseases apart from aHUS [53].

The aHUS-MHT Conundrum

In practice it is often difficult to distinguish MHT-associated TMA from complement-mediated TMA with associated severe hypertension, as the latter may well represent aHUS [3]. Moreover, in most algorithms of the approach of aHUS, the differentiation with MHT is poorly delineated and guidelines are lacking as to how to diagnose and treat patients presenting with MHT-associated TMA. A kidney biopsy should be performed only upon achievement of adequate blood pressure control. It has a rather poor discriminatory capacity to disclose the primary etiology of renal TMA. Whereas HUS predominantly affects the glomeruli, MHT more typically affects arterioles and interlobular arteries. Renal TMA is characterized by arteriolar and/or glomerular intra-capillary thrombosis, often with accumulation of fragmented erythrocytes, and focally ischemic or congested glomerular tufts [54]. A kidney biopsy may be informative by distinguishing between low versus high probability of aHUS in patients with severe hypertension [3, 55]. Glomerular involvement and identifiable fibrin thrombi might increase the likelihood of aHUS following 2 recent observational studies [3, 55]. Unfortunately, the included patients mostly had neither MHT nor hematological abnormalities suggestive of TMA. If patients with severe hypertension without evidence of retinopathy grade III/IV have signs of TMA on kidney biopsy including glomerular involvement, this increases the odds of complement-mediated injury. Screening for complement abnormalities or TM mutations in all patients with severe hypertension presenting with renal TMA might however lead to diagnostic overuse of expensive complement assays, genetic analyses, and unneeded or undirected treatments such as plasmapheresis or eculizumab.

In our opinion, an eye fundus examination at presentation remains warranted for patients who present with TMA and severe hypertension with or without visual disturbances. However, if the fundoscopy reveals a grade III/IV retinopathy, then we suggest that treatment with anti-hypertensive medication instead of immediate plasmapheresis be started. While previously ophthalmologic findings suggestive of severe hypertensive retinopathy precluded further investigations, nowadays, much attention is paid to masked aHUS presenting with severe hypertension [3]. Most clinical guidelines propose to start treatment with plasmapheresis awaiting the results of a genetic screening [56–58]. But if antihypertensive treatment results in a complete remission of TMA with recovery of kidney function, genetic screening for aHUS might not be indicated. However, in young patients, relapse

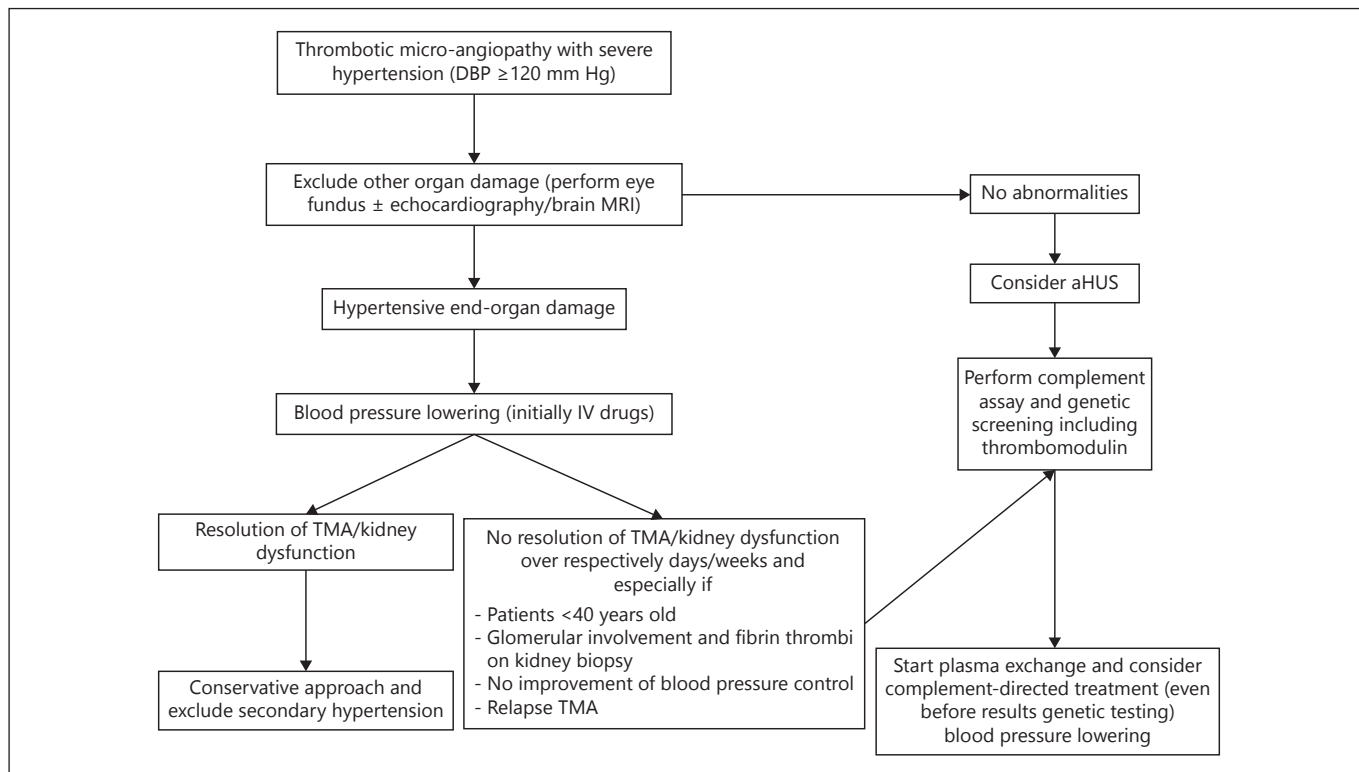


Fig. 4. Algorithm thrombotic microangiopathy (TMA)-Hypertension. When patients present with signs of TMA and severe hypertension (DBP ≥ 120 mm Hg), end-organ damage has to be excluded by an eye fundus, brain MRI, and/or echocardiography. If fundoscopy reveals grade III/IV retinopathy or in case of other end-organ damage, IV antihypertensive treatment has to be started. If antihypertensive treatment results in a complete remission of TMA with recovery of kidney function, genetic screening for atypical hemolytic uremic syndrome (aHUS) might not be indi-

cated. However, if recovery is absent and especially in young patients, relapsing TMA, inadequate response upon antihypertensive drugs, or signs of glomerular involvement and fibrin thrombi on renal biopsy, complement and genetic screening including genotyping of thrombomodulin (TM) is warranted. If end-organ damage is excluded, then aHUS has to be considered and genetic screening for aHUS including TM has to be performed. DBP, diastolic blood pressure; MRI, magnetic resonance imaging.

TMA, inadequate response upon antihypertensive drugs or signs of glomerular involvement, and fibrin thrombi on renal biopsy, complement and genetic screening including genotyping of TM have to be performed (Fig. 4).

Our patient presented with signs of TMA and a hypertensive emergency. An immediate fundoscopy at admission could have prevented the initiation of plasma exchange with its ensuing risks and costs. Considering the tentative diagnosis of aHUS, we performed a genetic analysis in our patient, which revealed a TM mutation. Aggressive management of the blood pressure nevertheless easily resolved the biochemical signs of TMA with partial restoration of kidney function.

The recognition of the TM mutation in our patient did not alter therapy. It is however likely that qualitative defects of TM decrease the ability of the endothelium to recover from complement-driven damage from whatever

origin, rather than being the prime culprit. A further exploration of the contribution of a dysfunctional TM in the pathophysiology of MHT-related TMA is desirable.

Is There a Therapeutic Role for TM?

A potential therapeutic role of recombinant thrombomodulin in the management of MHT-associated TMA can be speculated. As the prevalence of TMA associated with MHT is 10 times more frequent than that of aHUS, this question deserves further attention [1]. TM has shown promising results in the treatment approach of DIC, with a good safety profile with less bleeding complications in comparison with recombinant human activated protein C [38, 53]. Possibly, the presented case history can set the stage for designing not only the diagnostic but also the therapeutic

exploration of TM in MHT-related end-organ damage and especially kidney injury. It is likely that TM often is one of the players in the complex interplay of genetic and acquired factors. Possibly its functional capacities and selective loss can contribute to various conditions, which share a propensity to exaggerated thrombosis. As the administration of recombinant TM has already demonstrated beneficial effects on the endothelium in both mice and humans, this hypothesis possibly is amenable for exploration in particular patient populations including subjects with MHT.

Conclusion

We present the case history of an adult woman with MHT and a TM mutation that has been associated with the development of aHUS, be it mostly in juvenile patients. Considering the crucial role of TM in endothe-

lial homeostasis and protection, we speculate that mutations resulting in dysfunctional TM are associated with other diseases as well. It is likely that an aberrant TM could be a disease-modifier rather than a primary cause in most cases. Finally, use of recombinant TM should possibly be explored beyond the field of sepsis and DIC.

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Disclosure Statement

The authors have no conflicts of interest to declare.

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