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Original article

A multicenter experience of thrombotic microangiopathies in Turkey: The Turkish Hematology Research and Education Group (ThREG)-TMA01 study

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ABSTRACT

Thrombotic microangiopathies (TMAs) are rare, but life-threatening disorders characterized by microangiopathic hemolytic anemia and thrombocytopenia (MAHAT) associated with multiorgan dysfunction as a result of microvascular thrombosis and tissue ischemia. The differentiation of the etiology is of utmost importance as the pathophysiological basis will dictate the choice of appropriate treatment.

We retrospectively evaluated 154 (99 females and 55 males) patients who received therapeutic plasma exchange (TPE) due to a presumptive diagnosis of TMA, who had serum ADAMTS13 activity/anti-ADAMTS13 antibody analysis at the time of hospital admission. The median age of the study cohort was 36 (14-84). 67 (43.5%), 32 (20.8%), 27 (17.5%) and 28 (18.2%) patients were diagnosed as thrombotic thrombocytopenic purpura (TTP), infection/complement-associated hemolytic uremic syndrome (IA/CA-HUS), secondary TMA and TMA-not otherwise specified (TMA-NOS), respectively. Patients received a median of 18 (1-75) plasma volume exchanges for 14 (153) days. 81 (52.6%) patients received concomitant steroid therapy with TPE. Treatment responses could be evaluated in 137 patients. 90 patients (65.7%) achieved clinical remission following TPE, while 47 (34.3%) patients had non-responsive disease. 25 (18.2%) non-responsive patients died during follow-up. Our study present real-life data on the distribution and follow-up of patients with TMAs who were referred to therapeutic apheresis centers for the application of TPE.

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1. Introduction

Thrombotic microangiopathies (TMAs) are rare, but life-threatening disorders characterized by Coombs negative microangiopathic hemolytic anemia and thrombocytopenia (MAHAT) associated with multiorgan dysfunction as a result of microvascular thrombosis and tissue ischemia [1]. Besides thrombotic thrombocytopenic purpura (TTP) and infection/complement-associated hemolytic uremic syndrome (IA-HUS, CA-HUS) there are many systemic disorders and clinical conditions resulting in TMA including, but not restricted to, disseminated intravascular coagulation, autoimmune diseases, neoplasms, infections, solid organ and hematopoietic cell transplantation, pregnancy associated complications, inborn errors of metabolism and medications [2]. Although MAHAT is sine qua non the laboratory feature of all clinical scenarios leading to TMAs, differentiation of the etiology is of utmost importance, as the pathophysiological basis will dictate the physician to initiate appropriate treatment.

While TTP is defined as a disease characterized by an acquired or inherited severe deficiency of the ADAMTS13 enzyme (<10%) (a disintegrin and metalloproteinase with a thrombospondin type I motif, member 13), IA-HUS and CA-HUS result from deregulated activation of the alternative complement pathway [3]. The mainstay of treatment of TTP, CA-HUS, IA-HUS and secondary forms of TMAs is therapeutic plasma exchange (PEX), complement C5 inhibitor therapy (eculizumab), supportive care/hemodialysis and treatment of the underlying disease/condition, respectively.

The differential diagnosis of a patient presenting with a TMA is quite difficult, if not impossible, on the first hospital admission because of overlapping clinical features (renal, gastrointestinal and central nervous system involvement), especially if the TMA is not associated with a known disorder or clinical condition. Outside of specialized centers, the clinician must wait a few days for the results of the ADAMTS13 activity level, which is the most significant parameter for differentiation a TTP from other forms of TMA. As a result of the aforementioned limitations and high mortality of untreated TTP, almost all patients presenting with a TMA are destined to receive TPE at least until exclusion of TTP.

TTP, CA-HUS and IA-HUS are orphan diseases, with a reported incidence rate of $3/10^6$, $2/10^6$ and $2\text{-}6/10^5$, respectively [4]. But the data on the true incidence and distribution of various forms of TMA among patients receiving TPE for MAHAT is still scant due to overlapping symptoms, confusion on terminology, various thresholds and methods used to define severe ADAMTS13 deficiency, a reliable and widely available method indicating increased complement activity, and the availability of genetic testing for complement mutations in only a limited number of research centers [2,5]. In order to shed light on the real-world picture on the distribution and classification of TMAs in Turkey, we retrospectively evaluated adult patients presenting with MAHAT who received TPE.

2. Methods

All consecutive patients who presented with MAHAT and treated with TPE by participating centers during the January 2011-December 2015 period were included in the study. In order to have a more reliable classification of TMAs, patients without available serum ADAMTS13 activity before initiation of TPE were excluded. In all recruited patients serum samples at diagnosis were send for ADAMTS13 activity and anti-ADAMTS13 antibody assays.

In general, the diagnosis, classification of TMA subtypes and hematological response to TPE were done according to recently published consensus reports [5–7]. Due to the retrospective design of our study, we were unable to discriminate refractory patients and other types of non-responsive disease (exacerbation or relapse).

Table 1
Demographic characteristics and TMA subtype.

Demographic characteristics	
Patients who received TPE due to presumptive diagnosis of TMA (Coombs negative MAHAT) with available ADAMTS13 activity/anti-ADAMTS13 antibody levels available before initiation of TPE (n)	154
Age (median; range)	36 (14-84)
Gender (n; %)	Female (99; 64%) Male (55; 36%)
Classification of TMA	
Primary immune TTP (n; %) (ADAMTS13 activity <10%, anti-ADAMTS13 antibody (+), TMA-associated disorder/clinical condition absent) (n; %)	67 (43.5%)
IA/CA-HUS (ADAMTS13 activity ≥10% plus any signs of renal injury) (n; %)	32 (20.8%)
Secondary TMA (ADAMTS13 activity ≥10% plus TMA-associated disorder/clinical condition present) (n; %) Pregnancy (n: 7) SLE (n: 6) Drugs (n: 5) Malignancy (n: 3) Allogeneic HCT (n: 2) Renal transplantation (n: 2) Malignant hypertension (n: 2)	27 (17.5%)
TMA-NOS (ADAMTS13 activity ≥10% plus no signs of renal injury or TMA-associated disorder/clinical condition) (n; %)	28 (18.2%)

Therefore, we evaluated all patients as non-responsive who needed second-line treatment following cessation of TPE. Patients with serum ADAMTS13 activity <10% were diagnosed as TTP. As patients with a presumptive diagnosis of IA-HUS could not be confirmed by serology and/or PCR for Shiga toxin expressing bacteria and mutational analysis for genes associated with regulation of alternative complement pathway were unavailable, patient presenting with MAHAT, any sign of renal injury (serum creatinine >1.5 mg/dL, hematuria, oliguria, proteinuria) and ADAMTS13 activity ≥10% were classified as IA/CU-HUS. Patients with ADAMTS13 activity ≥10% who had disorders or clinical conditions associated with TMAs are categorized as secondary TMA (sTMA). On the other hand, patients with ADAMTS13 activity ≥10%, do not have any TMA-associated disease/condition and signs of renal injury were diagnosed as TMA-not otherwise specified (TMA-NOS).

As a standard practice 1-1.5 volume fresh-frozen plasma was exchanged during each PEX procedure. Response to TPE was evaluated only in patients with the required data on the patient's records. Descriptive statistics for categorical and quantitative variables were presented as frequency (percentage) and median (min-max), respectively.

3. Results

During the study period, 521 consecutive patients from 18 therapeutic apheresis centers were identified who received at least one session of TPE for the presumptive diagnosis of TMAs. 154 (99 females and 55 males) patients had serum ADAMTS13 activity/anti-ADAMTS13 antibody analysis at the time of hospital admission, and constituted the study cohort used for further analysis. The median age of the study cohort was 36 (14-84). 67 (43.5%), 32 (20.8%), 27 (17.5%) and 28 (18.2%) patients were diagnosed as TTP, IA/CA-HUS, sTMA and TMA-NOS, respectively (Table 1).

At presentation 76 (49.4%), 97 (63%) and 77 (50%) patients had fever, neurological abnormalities and renal injury respectively. Thirty-two (20.8%) patients had the classic pentad of the TMA, namely MAHAT, renal failure, neurological abnormalities and fever. Eight (25%) out of 32 patients in the IA/CA-HUS subgroup had a diarrheal prodrome. Patients received a median of 18 (1-75) plasma

Table 2
Response to TPE and long-term follow-up.

Follow-up period (median-range) (months)	22 (1-60)
Treatment response evaluated (n, %)	137 (89%)
Primary immune TTP (n: 59)	
IA/CA-HUS (n: 29)	
Secondary TMA (n: 24)	
TMA-NOS (n: 25)	
Clinical remission[a] (n; %)	90 (65.7%)
Primary immune TTP	44 (75%)
IA/CA-HUS	20 (69%)
Secondary TMA	15 (62.5%)
TMA-NOS	11 (44%)
Patients with non-responsive disease (exacerbation/relapse/refractory) who survived first-line TPE and received second-line therapy (n)	27 (19.7%)
Primary immune TTP (n: 8)	
Increased TPE intensity (n: 1)	
Increased TPE intensity plus addition of steroids and/or immunosuppressive drugs (n: 2)	
Rituximab (n: 2)	
Data unavailable (n: 3)	
IA/CA-HUS (n: 7)	
Eculizumab (n: 5)	
Increased TPE intensity plus addition of steroids and/or immunosuppressive drugs (n: 2)	
Secondary TMA (n: 4)	
Increased TPE intensity (n: 1)	
Increased TPE intensity plus addition of steroids and/or immunosuppressive drugs (n: 1)	
Chemotherapy directed to primary malignancy (n: 1)	
Delivery of the fetus (n: 1)	
TMA-NOS (n: 8)	
Eculizumab (n: 3)	
Increased TPE intensity plus addition of steroids and/or immunosuppressive drugs (n: 3)	
Data unavailable (n: 2)	
Mortality (all had non-responsive disease) (n; %)	25 (18.2%)
Patients died during first-line TPE therapy (n; %)	20 (14.6%)
Primary immune TTP (n: 7)	
IA/CA-HUS (n: 2)	
Secondary TMA (n: 5)	
TMA-NOS (n: 6)	
Patients died in the course of second-line therapy (n; %)	5 (3.6%)
Primary immune TTP (n: 1)	
IA/CA-HUS (n: 1)	
Secondary TMA (n: 2)	
TMA-NOS (n: 1)	

[a] The percentages were calculated according 137 evaluable patients.

volume exchanges for 14 (1-53) days. Eighty-one (52.6%) patients received concomitant steroid therapy with TPE.

Treatment responses could be evaluated in 137 patients. Ninety patients (65.7%) achieved clinical remission following TPE, while 47 (34.3%) patients had non-responsive disease (exacerbation, relapse or refractory). Twenty-five (18.2%) non-responsive patients died during follow-up (20 patients in the course of first-line TPE and 5 patients who received second-line treatment). Data on second-line therapy was available in 22 out of 27 TPE non-responsive patients (Table 2). Second-line treatment was effective in 60% (3 patients had clinical remission, 1 patient died and 1 patient was refractory), 83% (5 patients had clinical remission and 1 patient died), 0% (2 patients died and 1 patient was refractory) and 83% (5 patients had clinical remission and 1 patient died) patients who were diagnosed with primary immune TTP, IA/CA-HUS, sTMA and TMA-NOS, respectively. In a median follow-up of 22 months in 137 evaluable patients, 8 (13.6%), 2 (10.3%), 5 (29%), 6 (28%) patients died who were diagnosed as TTP, IA/CA-HUS, sTMA and TMA-NOS, respectively.

4. Discussion

Registries are the best way to study orphan diseases like the TMAs by providing an adequate number of patients. The relative presentation of the different subtypes of TMAs in published reports may differ as a result of median age and dimension of the study cohort, referral pattern of patients to therapeutic apheresis centers, terminology used for classification of TMAs, and inclusion and exclusion criteria used for enrollment of patients. Even in the largest CA-HUS registry including more than 500 patients, the diagnosis of CA-HUS was not required as part of the protocol [8]. In some of the reports, patients with sTMA [9] and IA-HUS [10] were not included at all. The main objective of the present study was to present real-life data on the distribution and follow-up of patients with TMAs who were referred to therapeutic apheresis centers for application of TPE. According to our registry data on TMAs, 23–71% [9–14], 25–33% [9,13,14] and 6–33% [13–15] of patients were categorized as TTP, sTMA and CA-HUS, respectively. In general, the distribution of TMA subcategories of our study cohort seems to be in line with aforementioned registry data. We were unable to put 28 (18.2%) patients in a defined category of TMA like TTP, IA/CA-HUS or sTMA and used the term TMA-NOS to define this subgroup of patients. Patients in the TMA-NOS subgroup had ADAMTS13 activity >10%, had no signs of renal injury or TMA-associated disease/condition. Although a renal impairment is defining feature of CA-HUS, 20% of patients may present with preserved renal function [16]. Whether some of the patients in the TMA-NOS subcategory had, in fact, CA-HUS, presenting without renal dysfunction is unknown. But irrespective of the proper terminology to be used to define these patients, similar to our study, 22% of patients with TMA could not be assigned to a definite TMA subtype according to the Australian TMA Registry [11].

As we were unable to differentiate IA-HUS from CA-HUS, patients presenting with MAHAT, any sign of renal injury with ADAMTS13 activity ≥10% were classified as IA/CA-HUS, whether or not they had a diarrhea prodrome. In the era of serology and/or PCR analysis for defining IA-HUS due to Shiga toxin-producing bacteria, the older terminology (diarrhea-associated HUS) was abandoned because diarrhea prodrome may also be associated with TTP or CA-HUS in 30% of cases probably as a result of colonic of microinfarcts [5]. IA-HUS is mainly a disease of the pediatric age group, successfully treated with supportive care and/or hemodialysis, and patients are not expected to receive TPE. As the median age of our study cohort was 36 years, we can speculate that most of the patients classified as IA/CA-HUS had, in fact, CA-HUS.

The Canadian Apheresis Study Group showed the superiority of PEX over plasma infusion in the treatment of TTP almost 3 decades ago. The overall survival of patients on the TPE arm at 6 months was 78% compared to 63% of patients who received plasma infusion, despite crossover of some patients to PEX once plasma infusion failed [17]. Although PEX is an effective treatment of TTP, 40% and 18% of patients are expected to relapse and die at long-term follow-up [10]. Harvard TMA Research Collaborative reported higher mortality at 1 year in TTP (7%) compared to non-TTP (52.5%) patients with ADAMTS13 ≥10% at diagnosis [12]. TTP patients in our study cohort had a 75% response rate to PEX and 13.6% mortality at 22 months of follow-up. PEX is frequently used as therapy in CA-HUS as first-line modality. Even in the global atypical HUS registry, only 53% of CA-HUS patients used eculizumab before enrollment and 61% had a history of PEX or plasma infusion [8]. According to the Italian experience, PEX was quite effective in inducing remission in 55-80% of CA-HUS cases, but almost two thirds of adult patients either died or progressed to end-stage renal failure at long-term follow-up [18]. In our study cohort, 69% patients with IA/CA-HUS achieved clinical remission with PEX and only 2 (10.3%) of them died during the study period. We do not have data on the long-term renal outcome of CA-HUS patients. But the relatively low mortality rate in CA-HUS patients may be attributed to the fact, that 5 out of 7 (71%) PEX non-responsive patients received eculizumab as second-line therapy.

Although there has been significant scientific progress in the understanding of the pathophysiology, classification and treatment of TMAs in the last two decades, clinicians still rely on relatively nonspecific signs (MAHAT) and symptoms at initial presentation for decision-making. In most of the situations TPE should be started immediately because TTP cannot be excluded on clinical grounds alone and had an almost 90% mortality in the era before TPE. The French TMA reference center found that patients with TTP frequently have severe thrombocytopenia (<30000/mm^3), non-severe renal failure (creatinine <2.26 mg/dL) and positive antinuclear antibodies (ANA) [9]. Based on this, many study groups and experts suggest using basic laboratory/clinical parameters to predict severe ADAMTS13 deficiency (<10%) at initial diagnosis [4,5,9,19,20]. Another important issue on the differential diagnosis of TMAs is accurate diagnosis of CA-HUS. Although CA-HUS is mainly a genetic disorder (antibodies to factor H detected in 3-6% of cases), which is characterized by dysregulated activation of the alternative complement system, neither evaluation of functional parameters indicating increased complement activation nor genetic mutations frequently encountered in regulatory proteins of the alternative complement system, are required for diagnosis and initiation of anti-complement C5 (eculizumab) therapy [21]. Biomarkers of terminal complement activation (C5a and C5b-9) [22] and a serum-based modified Ham test [23] were suggested to be useful for the diagnosis of CA-HUS. Another problem is that complement activation is not specific for CA-HUS and is frequently seen in various forms of TMA. It is currently unknown whether many clinical conditions or diseases itself result in a TMA or they just trigger a TMA attack in a susceptible individual with inherited or acquired complement activation (CA-HUS) [24]. While there are some encouraging preliminary reports indicating the effectiveness of eculizumab in so-called secondary forms of CA-HUS [25], efforts are being made to define appropriate patients with CA-HUS for discontinuation of eculizumab, in order, probably, to decrease the cost of life-long treatment with this expensive drug [26,27]. As of today, CA-HUS still remains a clinical diagnosis of exclusion and genetic analysis and/or evaluation of the functional status of the complement system are not required for diagnosis. But in order to confirm that the disease is actually related to complement dysregulation, to predict the prognosis, to provide genetic counseling for family members who may have risk for development of CA-HUS in the future, to broaden our knowledge of TMAs in general and CA-HUS in particular, genetic screening for mutations of relevant complement proteins and functional tests for complement activation may be recommended [28].

Conflict of interest statement

All authors declare that they do not have any potential conflict of interest that could inappropriately influence the present study.

References

[1] Shen YM. Clinical evaluation of thrombotic microangiopathy: identification of patients with suspected atypical hemolytic uremic syndrome. Thromb J 2016;14(Suppl. 1):19.

[2] Åkesson A, Zetterberg E, Klintman J. At the cross section of thrombotic microangiopathy and atypical hemolytic uremic syndrome: a narrative review of differential diagnostics and a problematization of nomenclature. Ther Apher Dial 2017;21(4):304–19.

[3] Yenerel MN. Atypical hemolytic uremic syndrome: differential diagnosis from TTP/HUS and management. Turk J Hematol 2014;31:216–25.

[4] Williams LA, Marques MB. Pathology consultation on the diagnosis and treatment of thrombotic microangiopathies (TMAs). Am J Clin Pathol 2016;145(2):158–65.

[5] Laurence J, Haller H, Mannucci PM, Nangaku M, Praga M, de Cordoba SR, et al. Atypical hemolytic uremic syndrome (aHUS): essential aspect of an accurate diagnosis. Clin Adv Hematol Oncol 2016;14(11):2–5.

[6] Sarode R, Bandorenko N, Brecher ME, Kiss JE, Marques MB, Szczepiorkowski ZM, et al. Thrombotic thrombocytopenic purpura: 2012 American Society for Apheresis (ASFA) consensus conference on classification, diagnosis, management, and future research. J Clin Apher 2014;29(3):148–67.

[7] Scully M, Cataland S, Coppo P, de la Rubia J, Friedman KD, Kremer Hovinga J, et al. Consensus on the standardization of terminology in thrombotic thrombocytopenic purpura and related thrombotic microangiopathies. J Thromb Haemost 2017;15(2):312–22.

[8] Licht C, Ardissino G, Ariceta G, Cohen D, Cole JA, Gasteyger C, et al. The global aHUS registry: methodology and initial patient characteristics. BMC Nephrol 2015;91(3):539–51.

[9] Coppo P, Schwarzinger M, Buffet M, Wynckel A, Clabault K, Presne C, et al. Predictive features of severe acquired ADAMTS13 deficiency in idiopathic thrombotic microangiopathies: the French TMA reference center experience. PLoS One 2010;5(4):e10208.

[10] George JN. How I treat patients with thrombotic thrombocytopenic purpura: 2010. Blood 2010;116(20):4060–9.

[11] Blombery P, Kivivali L, Pepperell D, McQuilten Z, Engelbrecht S, Polizzotto MN. Diagnosis and management of thrombotic thrombocytopenic purpura (TTP) in Australia: findings from the first 5 years of the Australian TTP/thrombotic microangiopathy registry. Intern Med J 2016;46(1):71–9.

[12] Bendapudi PK, Li A, Hamdan A, Uhl L, Kaufman R, Stowell C, et al. Impact of severe ADAMTS13 deficiency on clinical presentation and outcome in patients with thrombotic microangiopathies: the experience of the Harvard TMA research collaborative. Brit J Haematol 2015;171:836–44.

[13] Hassan S, Westwood JP, Ellis D, Laing C, Mc Guckin S, Benjamin S, et al. The utility of ADAMTS13 in differentiating TTP from other acute thrombotic microangiopathies: results from the UK TTP Registry. Br J Haematol 2015;171:830–5.

[14] Metjian A, Tanhehco YC, Aqui N, Bhoj VG, Jamensky L, Marques MB, et al. The thrombotic microangiopathy registry of North America: a United States multi-institutional TMA network. J Clin Apher 2016;31(5):448–53.

[15] Sperati CJ, Moliterno AR. Thrombotic microangiopathy: focus on atypical hemolytic uremic syndrome. Hematol Oncol Clin N Am 2015;29(3):541–59.

[16] Azoulay E, Knoebl P, Garnacho-Montero J, Rusinova K, Galstian G, Eggimann P, et al. Expert statements on the standard of care in critically ill adult patients with atypical hemolytic uremic syndrome. Chest 2017;152(2):424–34.

[17] Rock GA, Shumak KH, Buskard NA, Blanchette VS, Kelton JG, Nair RC, et al. N Engl J Med 1991;325:393–7.

[18] Noris M, Caprioli J, Bresin E, Mossali C, Pianetti G, Gamba S, et al. Relative role of genetic complement abnormalities in sporadic and familial aHUS and their impact on clinical phenotype. Clin J Am Soc Nephrol 2010;5:1844–59.

[19] Cataland SR, Wu HM. How I treat: the clinical differentiation and initial treatment of adult patients with atypical hemolytic uremic syndrome. Blood 2014;123:2478–84.

[20] Bendapudi PK, Upadhyay V, Sun L, Marques MB, Makar RS. Clinical scoring systems in thrombotic microangiopathies. Semin Thromb Hemost 2017;43(5):540–8.

[21] Afshar-Kharghan V. Atypical hemolytic uremic syndrome. Hematology Am Soc Hematol Educ Program 2016;2016(1):217–25.

[22] Cataland SR, Holers VM, Geyer S, Yang S, Wu HM. Biomarkers of terminal complement activation confirm the diagnosis of aHUS and differentiate aHUS from TTP. Blood 2014;123(24):3733–8.

[23] Gavriilaki E, Yuan X, Ye Z, Ambinder AJ, Shanbhag SP, Streiff MB. Modified Ham test for atypical hemolytic uremic syndrome. Blood 2015;125(23):3637–46.

[24] Brocklebank V, Kavanagh D. Complement C5-inhibiting therapy for the thrombotic microangiopathies: accumulating evidence, but not a panacea. Clin Kidney J 2017;10(5):600–24.

[25] Cavero T, Rabasco C, López A, Róman A, Ávila A, Sevillano Á, et al. Eculizumab in secondary atypical haemolytic ureamic syndrome. Nephrol Dial Transplant 2017;32:466–74.

[26] Merrill SA, Brittingham ZD, Yuan X, Moliterno AR, Sperati CJ, Brodsky RA. Eculizumab cessation in atypical hemolytic uremic syndrome. Blood 2017;130(3):368–72.

[27] Macia M, de Alvaro Moreno F, Dutt T, Fehrman I, Hadaya K, Gasteyger C, et al. Current evidence on the discontinuation of eculizumab in patients with atypical haemolytic ureamic syndrome. Clin Kidney J 2017;10(3):310–9.

[28] Cheong HI, Jo SK, Yoon SS, Cho H, Kim JS, Kim YO, et al. Clinical practice guidelines for the management of atypical hemolytic uremic syndrome in Korea. J Korean Med Sci 2016;31(10):1516–28.