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Infection Frequently Triggers Thrombotic Microangiopathy in Patients with Preexisting Risk Factors: A Single-Institution Experience

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Thrombotic microangiopathies are rare conditions characterized by microangiopathic hemolytic anemia, micro thrombi, and multiorgan insult. The disorders, which include hemolytic uremic syndrome and thrombotic throm bocytopenic purpura, are often acute and life threatening. We report a retrospective analysis of 65 patients pre senting to our institution from 1997 to 2008 with all forms of thrombotic microangiopathy. Therapeutic plasma exchange was a requirement for analysis and 65 patients were referred to our institution; 66% of patients were female and median age at presentation was 52 years. Bacterial infection was the most commonly identified etiol ogic factor and in the multivariate model was the only significant variable associated with survival outcome (odds ratio 5.1, 95% confidence interval, 1.2 21.7). As infection can be considered a common trigger event for thrombotic microangiopathy, patients with hepatobiliary sepsis may benefit from elective cholecystectomy. We conclude that bacterial infection frequently triggers TTP and other thrombotic microangiopathies in patients with preexisting risk factors and propose a model for the development of these syndromes.

Key words: infection; thrombotic thrombocytopenic purpura; thrombotic microangiopathy; hemolytic uremic syndrome; bacterial sepsis; cholelithiasis

INTRODUCTION

The thrombotic microangiopathies (TMA), mainly comprising thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) as well as some rarer syndromes, are infrequent disorders characterized by microangiopathic hemolytic anemia, microthrombi, and multiorgan injury. Although the etiology of HUS is multifactorial, infection with verotoxin-producing *Escherichia coli* (VTEC), particularly *E. coli* O157, has been clearly established as the predominant cause of diarrhea-positive (D+) HUS, with childhood HUS most often following bloody diarrhea caused by VTEC [1,2]. In contrast, TTP frequently occurs in adults with a number of identifiable precipitants. Studies have implicated the von Willebrand factor (VWF) cleaving metalloprotease, ADAMTS13 (a disintegrin and metalloprotease with thrombospondin Type 1 motif, number 13), as being important in the pathogenesis of TTP [3–5]. Deficiency of ADAMTS13 can be genetic (Upshaw-Schulman syndrome) or acquired through autoimmune production of antibodies to the metalloprotease [6]. In the last decade, the syndrome of atypical HUS (aHUS or D(-)HUS) has become recognized as one with predominantly renal involvement, no diarrheal prodrome, and mutations in complement factor genes *CFH*, *CFI*, or *MCP* in approximately 50% of cases [7–9]. In both HUS and TTP, although initial endothelial damage is believed to arise by different mechanisms, the end result is extensive microvascular platelet deposition with resultant thrombocytopenia and occlusion of small vessels. Several rarer TMA syndromes, including HELLP syndrome of pregnancy [10] posttransplant TTP associated with calcineurin inhibitors, and cancer-associated thrombotic microangiopathy can also lead to a similar clinical picture [11].

However, ADAMTS13 deficiency or complement gene abnormalities alone cannot explain all the variable manifestations of TTP and aHUS, which range from minimal symptoms to multiorgan failure [12,13]. Disease pathogenesis may also involve additional unknown genetic factors and/or environmental triggers. Recently,

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it was demonstrated that verotoxin was able to induce a TTP-like syndrome in ADAMTS13-knockout mice, suggesting a role for this toxin as a potential trigger for TTP [14], although the same group found that lipopolysaccharide (LPS)-induced mortality was not affected by ADAMTS13 or VWF deficiency [15]. We previously reported population-based epidemiologic surveillance of TMAs and noted severe sepsis as one of the most frequent precipitants of TTP [2].

LPS, a component of the cell walls of Gram-negative bacteria is a potent mediator of inflammation [16] and evokes powerful responses, leading to activation of acute phase proteins including interleukin-6, a cytokine which contributes to the body's defense by inducing fever, a common presentation of TTP. Furthermore, LPS has been postulated to activate platelets and/or damage endothelium and, therefore, precipitate platelet consumption during HUS, which may contribute to TMA [17]. Previous evidence has shown that the onset of TTP can be triggered by pancreatitis [18] or abdominal surgery for conditions such as cholelithiasis, where presumably Gram-negative bacteria may cause systemic infection and the subsequent thrombotic process [19].

The Clinical Apheresis Unit (CAU) at Gartnavel Hospital in Glasgow is a referral center for treatment of patients with TMA. We retrospectively reviewed cases with all forms of TMA at our institution from 1997 to 2008 and determined that bacterial infection frequently triggers TTP and other TMAs in patients with preexisting risk factors, which may include autoimmune disease, antihypertensive therapy, antiplatelet agents, pregnancy, and/or genetic determinants.

PATIENTS AND METHODS

All cases of TMA (TTP, HUS, or rarer syndromes) were identified at a single apheresis unit on referral for therapeutic plasma exchange (TPE), as a consecutive-patient series from October 1997 to September 2008 inclusive. Information on presenting symptomatology, medical history (including any recent infections), medications used in the month before diagnosis, family history, health behavior, and demographics were obtained by questionnaire. Medical records were reviewed for laboratory and clinical data. Patients were consented for HIV testing before plasma exchange; all were HIV negative. We included all patients who fulfilled the following minimum criteria: microangiopathic hemolytic anemia (low hemoglobin with evidence of red cell fragmentation on blood film), thrombocytopenia (platelets $< 150 \times 10^9$/L), and elevated lactate dehydrogenase (LDH; at least 150% of upper end of normal LDH range of referring hospital at diagnosis). Additionally, a coagulation screen and fibrinogen assay was carried out at the time of referral to exclude other causes of thrombocytopenia such as disseminated intravascular coagulation (DIC).

Assays for ADAMTS13, anti-ADAMTS13 antibody and genetic abnormalities in Complement Factors H and I are increasingly used worldwide to help differentiate TTP (low ADAMTS13 levels +/− anti-ADAMTS13 antibody) from aHUS (frequently associated with complement factor gene mutations); however, such assays have not until very recently been available routinely in Scotland. We therefore defined TTP, HUS or other TMA syndromes on clinical grounds as described below.

Patients were considered to have typical HUS if they had developed TMA following culture-confirmed infection with *E. coli* O157 or pneumococcus (in children), or if there was a well documented pro-dromal episode of bloody diarrhea in the absence of positive cultures. For the remaining patients, clinical distinction between aHUS and TTP was on the basis of predominantly renal involvement (aHUS) or predominantly hematological/neurologic involvement (TTP). Thirteen patients were considered to have typical HUS (nine patients with documented *E. coli* O157 infection, two children with documented prodromal pneumococcal septicaemia, and two adults with well-documented prodromal bloody diarrhea). Of the remaining 52 patients, 12 were considered to have atypical HUS on clinical grounds and 38 were considered to have TTP (of whom two had postpartum TTP and two had posttransplant TTP). Two patients had cancer-associated thrombotic microangiopathy, with metastatic malignancy being diagnosed after plasma exchange had been commenced.

Statistical Methods

Associations between categorical variables were investigated using Chi-squared tests or Fisher's exact test, and odds ratios and 95% confidence intervals are presented. Quantitative variables were analyzed using *t*-tests or Mann-Whitney tests as appropriate for the distribution of the data. Variables which were significant at the 5% level were then used in a logistic regression model to determine the independent predictors of survival. Spearman's correlation coefficient (two-tailed) was also used to measure hematological variables. All analyses were done using Minitab (version 15).

RESULTS

Between January 1, 1997 and December 31, 2008, 65 patients fulfilled the case definition of TMA and were subsequently treated at our institution. This figure corresponds to an annualized incidence of 0.4 cases per 100,000. The median age of cases was 52 (range 1–81); 43 cases were female (66%). Of the cases for whom discharge outcome data were available (n = 54), 28 fully recovered (52%), 14 (26%) had residual renal impairment (of which seven were dialysis de-

pendent) and 10 patients died (19%). One patient experienced a cerebrovascular accident and another patient suffered residual neurologic complications.

Preexisting Risk Factors for Development of Thrombotic Microangiopathy

From our institutional experience, we report that development of TMA is preceded by a number of preexisting risk factors including infection, malignant hypertension and immunomodulating drugs (Table I). Laboratory-confirmed or clinically suspected infection was the predominant identified risk factor (69% of cases, Table II) although only 14% were attributed to infection with *E. coli* O157. Thirty-nine of 65 (60%) cases reported gastrointestinal symptoms ranging from transient diarrhea and/or vomiting to acute bloody diarrhea and abdominal pain. Of the 39 patients, nine cases had positive stool cultures for *E. coli* O157, two cases had acute bloody diarrhea considered to be infectious despite negative cultures, and a further 14 had a prodromal history of gastro-intestinal symptoms, which were microbiologically negative for gastro-intestinal pathogens including *E. coli* O157. For the remaining 14 patients with gastrointestinal symptoms, these could be explained by other infections (*e.g.,* pancreatitis) or noninfectious causes (Table II).

TABLE I. Preexisting Factors in Development of Thrombotic Microangiopathy

Variable	*n*	Cases	(%)
Infection	65	45	69.2
E. coli O157 cultured		9	13.8
Gastro intestinal symptoms	65	39	60.0
Diarrhea		30	46.9
Bloody diarrhea		10	15.6
Vomiting		19	29.7
Antihypertensive drugs	50	17	34.0
Systemic lupus erythematosus or other autoimmune condition	64	9	14.1
Aspirin or other anti platelet agents	50	8	16.0
Cyclosporin/tacrolimus	65	8	12.3
Previous TMA	65	6	9.2
Cholelithiasis	65	4	6.1

Factors Associated with Survival Outcome

In the multivariate model, infection (OR 5.1, 95%CI, 1.2–21.7) was the only variable which remained using backwards selection and was significantly associated with survival outcome (Table III). Table III shows odds ratios, *P*-values and 95% confidence intervals for categorical variables in relation to survival. Patients presenting with gastrointestinal symptoms were significantly associated with an improved survival outcome (OR 5.0, 95%CI, 1.1–22.3).

Factors Associated with Residual Renal Impairment

In the multivariate model, there was evidence to suggest that higher serum creatinine levels at referral were associated with residual renal impairment ($P < 0.03$) and that higher peak serum creatinine levels were significantly associated with residual renal impairment ($P < 0.02$; Table IV). We also observed a positive cor-

TABLE II. Details of Laboratory Confirmed and Suspected Infections Observed in TMA Cohort

Infection type	Clinical sub group of TMA ($n = 45$)	Clinical details
Gram positive bacterial infection (confirmed)	HUS (2)	Pneumococcal septicemia
	aHUS (2)	Staphylococcus aureus (infected sebaceous cyst; elbow abscess)
	TTP (2)	Streptococcus pyogenes (throat infection; post partum endometritis with beta hemolytic Streptococcus)
Gram negative bacterial infection other than *E. coli* O157 (confirmed)	aHUS (2)	*E. coli* bacteremia ($n = 4$: presumed sources infected pancreatic pseudocyst post pancreatitis; suspected ischaemic bowel post cardiogenic shock; soft tissue abscess; no obvious source in one patient)
	TTP (3)	*Klebsiella* urinary tract infection
E. coli O157	HUS (9)	*E. coli* O157 cultured from stool
Viral infection	TTP (5)	Hepatitis C infection ($n = 2$)
		CMV re activation post HSC transplant
		Recent HSV encephalitis
		MMR vaccine (live attenuated vaccine) 18 days prior to presentation with TTP
Clinically suspected infection no organism identified	HUS (2)	Gastro intestinal upset considered likely to be infectious, without bloody diarrhoea ($n = 14$)
	aHUS (4)	Bloody diarrhea but negative cultures ($n = 2$)
	TTP (14)	Pancreatitis ($n = 2$)
		Suspected cholelithiasis (transiently abnormal LFTs and suggestive clinical picture)
		Severe upper respiratory infection treated with antibiotics

relation between referral platelet count and serum creatinine levels ($r = 0.38$, $P = 0.002$).

Patients with More Than One Potential Risk Factor

Several patients appeared to have more than one premorbid risk factor (examples given in Table V). The common pattern involved infection as an acute trigger in a patient with a preexisting predisposition to TMA in the form of multisystem autoimmune disease, administration of calcineurin inhibitors, or presumed genetic predisposition to TMA on the basis of several previous episodes.

DISCUSSION

This retrospective 12-year review of our institution's experience with TMA patients undergoing plasma exchange was aimed at elucidating etiologic variables associated with disease development. One potential strength of this study is that we present data on a large number of consecutive patients from a single institution with inclusion criteria of referral for plasma exchange and a blood picture consistent with thrombotic microangiopathy (regardless of presumed underlying cause). Our patient population of 65 cases was comparable with that of other series published in the literature [20–22]. Our consistent approach over the years has previously allowed us to aid identification of significant predisposing factors to TMA [2].

This study provides a range of data including epidemiology, demography, clinical parameters, and outcomes, and it suggests that in the West of Scotland, bacterial infection is one of the most common precipitants of TMA in those with preexisting risk factors. Infection with VTEC such as *E. coli* O157 is recognized to be the predominating risk factor for D+HUS, with serotype O157 being the most common [1]. Pneumococcal-HUS is also a well-recognized etiologic factor in pediatric patients [23]. However, other studies have previously shown that there may be a role for other pathogens as potential triggers of TMA [24,25] and studies with animal models of TTP have also suggested this [14]. Our current findings support a significant role for infections other than *E. coli* O157 as common precipitants of TMA, including both clinically defined TTP and aHUS. However, in the absence of routine ADAMTS13 assays the assignment of patients to either TTP or aHUS on clinical grounds may be somewhat imprecise.

Few previous studies have investigated potential premorbid risk factors or trigger factors for TTP and aHUS. A multicenter prospective epidemiologic study of TTP is underway in North America, with preliminary findings having been published [26]. Although the main aim of the SERF project was to elucidate the role of anti-platelet agents as potential risk factors for TMA, other risk factors identified included recent antibiotic use, history of connective tissue disease, and a family history of thrombocytopenia or stroke. It seems

TABLE III. Comparisons for Quantitative Variables Associated with Survival ($n = 54$)

Variable	Comparison	OR	*P* value	95% CI
Gender	male vs. female	2.3	0.33	0.4, 12.1
Fever	yes vs. no	2.7	0.37	0.3, 24.2
CNS symptoms	yes vs. no	0.4	0.24	0.1, 1.8
Abnormal LFTs	yes vs. no	1.1	0.91	0.2, 4.4
Gastro intestinal symptoms	yes vs. no	5.0	0.035	1.1, 22.3
Diarrhea	yes vs. no	2.3	0.26	0.5, 10.2
Bloody diarrhea	yes vs. no	0.6	0.61	0.1, 3.7
Vomiting[a]			0.02	
SLE or ''other''	yes vs. no	1.5	0.74	0.2, 13.7
Cholelithiasis[a]			1.00	
Cyclosporin/tacrolimus	yes vs. no	0.5	0.47	0.1, 3.1
Previous TMA[a]			0.57	
Anti platelet drugs	yes vs. no	0.4	0.31	0.1, 2.5
Antihypertensive drugs	yes vs. no	0.2	0.12	0.04, 1.4
Infection	yes vs. no	5.1	0.03	1.2, 21.7
E. coli O157 cultured	yes vs. no	0.6	0.61	0.1, 3.7

[a]All with yes survived.

TABLE IV. Comparisons for Quantitative Variables Associated with Residual Renal Impairment

Variable	Renal impairment	*n*	Minimum	Median	Maximum	*P* value
Age (years)	Yes	49	1	45	79	
	No	7	26	54	72	0.69
Platelet count first referral	Yes	49	6	38	151	
	No	7	27	63	88	0.26
LDH first referral	Yes	46	252	1537	5678	
	No	7	942	1918	3702	0.63
Creatinine first referral	Yes	47	80	230	2480	
	No	7	243	450	1050	0.03
Peak creatinine	Yes	47	78	296	2480	
	No	7	390	628	1050	0.02
Discharge creatinine	Yes	38	50	129	800	
	No	7	96	220	325	0.41
No. of plasma exchanges	Yes	48	1	9	62	
	No	7	8	11	27	0.15

TABLE V. Five Patients with a Clear History Suggesting an Infective Trigger for TMA in an Individual with a Preexisting Risk Factor

Age & Gender	Clinical summary	Eventual outcome	Presumed biological mechanism of TMA
54, F	On tacrolimus after previous single lung transplant. Presented in acute renal failure with TMA (HUS) after confirmed *E. coli* O157 gastroenteritis	Full recovery (including renal recovery) after 11 plasma exchanges	*E. coli* O157 infection in patient taking calcineurin inhibitor
38, F	Preexisting severe longstanding SLE. Developed TMA after episode of confirmed cholelithiasis	Full recovery after 13 plasma exchanges	Probable Gram negative bacteraemia in patient with preexisting multisystem autoimmune disease
45, M	Two previous episodes of TMA 15 and 32 years earlier. Developed TMA after episode of cholecystitis	Full recovery after 10 plasma exchanges	Probable Gram negative bacteraemia in patient with presumed genetic susceptibility to TMA
70, F	Known Wegener's granulomatosis, in remission on immunosuppressive therapy. Developed TMA after confirmed coliform bacteraemia (not *E. coli*) in association with gastroenteritis	TMA resolved after 36 plasma exchanges, but remains dialysis dependent	Proven Gram negative bacteraemia in patient with preexisting multisystem autoimmune disease
44, F	Known SLE; developed TMA after episode of pancreatitis (which appeared related to underlying cholelithiasis)	Full recovery after 11 plasma exchanges	Probable Gram negative bacteraemia in patient with preexisting multisystem autoimmune disease

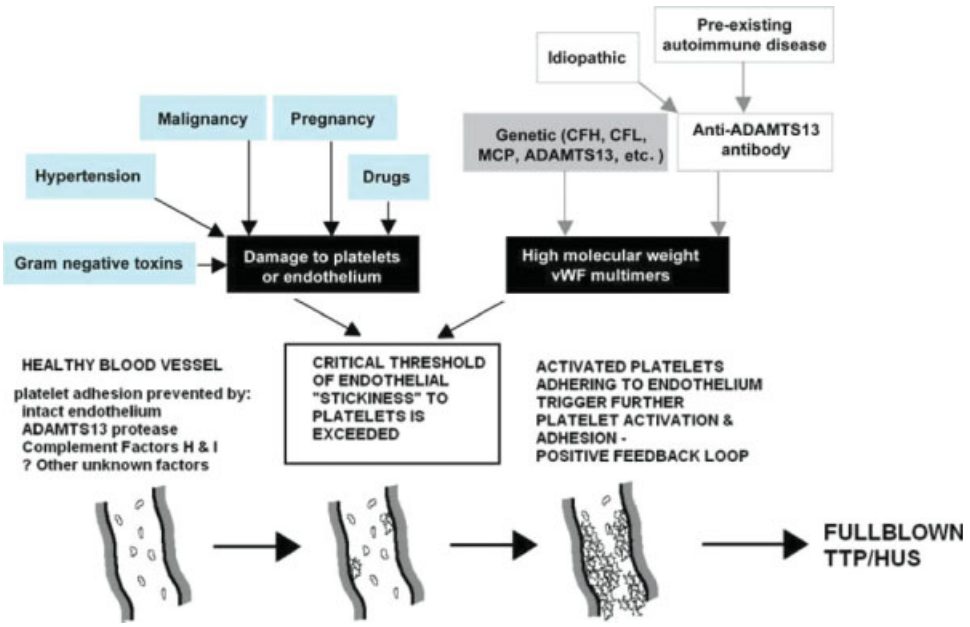

Fig. 1. Hypothesis of thrombotic microangiopathy as a multifactorial process. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

probable that recent antibiotic use in the SERF study group is a surrogate marker for acute infection immediately preceding presentation with TMA. There are two extant TTP registries that have published findings: the Oklahoma TTP-HUS Registry [27] and the South East England TTP Registry [5]. The former registry is relevant in that, like our own patient group, this is a clinically defined group of all patients with TMA referred for plasma exchange. However, despite a number of valuable lessons (particularly regarding what subgroups of patients are more likely to respond to plasma exchange), the focus of the Oklahoma registry is on the correlation of clinical and laboratory features with treatment outcome, rather than with potential premorbid or prodromal risk factors. The South East England Registry did consider potential precipitating causes and found defined infection (Mycoplasma) in only a single patient, although 2% of patients had pancreatitis and/or hepatobiliary sepsis. However, these patients were not specifically questioned about premorbid infections or

recent antibiotic usage, compared with our patient group so the incidence of premorbid infection may have been underestimated. It is interesting that pancreatitis or hepatobiliary sepsis was also a common premorbid factor in our study [18] and pancreatitis has also been reported as a potential precipitant for TMA in a series of patients from the Oklahoma Registry [28].

One potential confounding factor may be misdiagnosis of DIC associated with acute sepsis as TMA. However, as has been reported by other groups [24], the clinical picture observed in our cohort was almost always the development of TMA during the apparent recovery phase and not in the acute infectious phase. Excepting two of our patients, all had an entirely normal coagulation screen and fibrinogen at the time of referral for plasma exchange making DIC unlikely.

In the past few years, efforts have been made to correlate plasma levels of ADAMTS13 activity and severity of TTP [5]. The largest series to date was published from the Oklahoma registry and demonstrated that severe ADAMTS13 deficiency was not sensitive to detect all patients with thrombotic microangiopathy who benefitted from plasma exchange [12]. In our study, we were unable to assess the role of ADAMTS13 due to the assay not being available within Scotland and the associated financial constraints of performing the assay elsewhere in the United Kingdom. We are hopeful of addressing this in the near future by participating in a proposed national UK TTP registry (Dr. M. Scully, personal communication).

In our experience, there is some overlap between the three syndromes of TTP, aHUS, and D+HUS, and we suggest infection (other than with *E. coli* O157) as being a plausible common trigger for TTP and aHUS. We have frequently observed more than one potential premorbid risk factor for TMA in the same patient. We, therefore, propose a model for the development of TMA, where TMA can be considered a final common outcome of increased adhesion between platelets and microvascular endothelium (Fig. 1). TMAs can arise by a variety of mechanisms, although one or two tend to predominate in an individual patient. Once a critical level of adhesion between platelets and microvascular endothelium is exceeded, the presence of activated platelet microthrombi in the microvasculature induces ongoing platelet activation and adhesion *via* a positive feedback loop, resulting in a thrombotic microangiopathic cascade.

Our results have potential implications for patients who have recovered from an episode of TMA, given that both TTP and aHUS have a significant risk of relapse. If infection is considered a common trigger event, then the risk of recurrence in patients with a history of TMA might be reduced by prompt treatment of any bacterial infections, coupled with careful monitoring of platelet counts and LDH following any infectious episode. There may also be an argument for elective cholecystectomy in patients where hepatobiliary sepsis appears to be a premorbid trigger event. The anti-CD20 monoclonal antibody, Rituximab, is increasingly used in the treatment of TTP [5]. Although systemic immunosuppression associated with this drug is generally mild and the short-term relapse risk of TTP is reduced [29], there is the theoretical potential that patients may become increasingly susceptible to bacterial infections which may in turn, increase the long-term relapse risk of TMA. This should be investigated in large-scale prospective studies such as the UK TTP registry.

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