Thrombotic thrombocytopenic purpura-hemolytic uremic syndrome following allogeneic HPC transplantation: a diagnostic dilemma

James N. George, Xiaoning Li, Jay R. McMinn, Deirdra R. Terrell, Sara K. Vesely, and George B. Selby

BACKGROUND: Thrombotic thrombocytopenic purpura-hemolytic uremic syndrome (TTP-HUS) has been described as a specific sequela of allogeneic HPC transplantation (HPCT). Nevertheless, because multiple transplant-related sequela can cause the characteristic clinical features of TTP-HUS, the diagnosis is difficult.
STUDY DESIGN AND METHODS: All English-language articles describing patients with TTP-HUS following HPCT were identified. Articles reporting five or more total patients, including at least one patient diagnosed with TTP-HUS following allogeneic HPCT, were reviewed. All articles describing autopsies of patients diagnosed with TTP-HUS following allogeneic HPCT were also reviewed.
RESULTS: Thirty-five articles reporting 5 or more total patients described 447 patients diagnosed with TTP-HUS following allogeneic HPCT. The frequency of diagnosis of TTP-HUS following allogeneic HPCT varied by 125-fold (0.5%-63.6%). Twenty-eight different sets of diagnostic criteria were described in the 35 articles; 25 articles included both RBC fragmentation and increased serum LDH. Many risk factors described as correlating with the diagnosis of TTP-HUS also predict greater risk for multiple transplant-related complications. Benefit of plasma exchange treatment could not be documented. Survival information was reported for 379 patients, 232 (61%) died, and reported mortality rates varied from 0 to 100 percent. Autopsies have been reported for 35 patients who were diagnosed with TTP-HUS following allogeneic HPCT; none had systemic thrombotic microangiopathy, the diagnostic abnormality of TTP-HUS; and infection (19 patients) was the most commonly reported cause of death.
CONCLUSIONS: The clinical features of TTP-HUS following allogeneic HPCT may be caused by common transplant-related complications; the benefit from plasma exchange treatment is uncertain.

The syndromes of thrombotic thrombocytopenic purpura and hemolytic uremic syndrome (TTP and HUS) were first reported to be associated with HPC transplantation (HPCT) more than 20 years ago.[1] During the succeeding years, TTP-HUS has been described as a specific sequela of allogeneic HPCT.[1-4] Nevertheless, the diagnosis of TTP-HUS, often uncertain in previously well patients,[5] is always more uncertain in patients following HPCT, who may be critically ill with opportunistic infections, acute GVHD, and radiation-related and chemotherapy-related toxicity. Consideration of TTP-HUS is an important clinical issue because the diagnosis can never be confidently excluded and because it requires a decision regarding plasma exchange treatment, a procedure that can be life-saving for patients with TTP-HUS[6] but that has high risk for major complications.[7,8] Therefore, the possible diagnosis of TTP-HUS in a patient following allogeneic HPCT creates a diagnostic and management dilemma.

To better understand appropriate evaluation and management of these critically ill patients, we performed a systematic review[9] of reports describing patients with TTP-HUS following allogeneic HPCT. The strength of systematic reviews is their explicit and reproducible method, including a defined literature search strategy, objective criteria for article and patient selection, and independent

ABBREVIATIONS: HPCT = HPC transplantation; TTP-HUS, thrombotic thrombocytopenic purpura-hemolytic uremic syndrome.

From the Hematology-Oncology Section, Department of Medicine, College of Medicine, and the Department of Biostatistics and Epidemiology, College of Public Health, The University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma.

Address reprint requests to: James N. George, MD, Hematology-Oncology Section, The University of Oklahoma Health Sciences Center, P.O. Box 26901, Oklahoma City, OK 73190; e-mail: James-George@OUHSC.edu.

TRANSFUSION 2004;44:294-304.

assessments by multiple reviewers.[9] This review is limited to patients with allogeneic HPCT because TTP-HUS is not frequently reported following procedures with autologous PBPC support.

METHODS

Literature search

Ovid software was used to search the Medline database from January 1, 1966, to October 16, 2003. The key words and MeSH terms searched for HPCT were "bone marrow transplantation," 'bone marrow transplant," "hematopoietic stem cell transplantation," or "stem cell transplant." The key words and MeSH terms searched to identify patients diagnosed with TTP-HUS were "thrombotic thrombocytopenic purpura," "hemolytic-uremic syndrome," "thrombotic thrombocytopenic purpura-hemolytic uremic syndrome," "TTP," "HUS," "TTP-HUS," "thrombotic microangiopathic," "TMA," "microangiopath," "intravascular hemolysis," "plasma exchange," and "plasmapheresis." The search was limited to English language. All articles identified by both one of the HPCT terms and one of the TTP-HUS terms were retrieved. For publications from 1989 to 2003, alternative literature search software (Reference Update) was also used. The bibliographies of all retrieved articles, including articles not selected for further review, were searched to identify additional articles.

Criteria for article selection

Articles were selected for further review if they reported five or more total patients, to avoid reports of exceptional patients. Articles that did not report primary patient data, abstracts with incomplete data, and articles that described only autologous HPCT were not reviewed. Articles reporting five or more total patients were reviewed to determine whether they described patients diagnosed with TTP-HUS following allogeneic HPCT. As we reviewed these data, we determined that few autopsy examinations of patients who were diagnosed with TTP-HUS following allogeneic HPCT have been reported. Therefore, for analysis of autopsy data, we searched all articles describing patients diagnosed with TTP-HUS following allogeneic HPCT, including abstracts and case reports of less than five total patients, to identify all reports of autopsy examinations.

Criteria for patient selection

Patients were selected for review if they were diagnosed with TTP-HUS following allogeneic HPCT, regardless of the terms used to describe these syndromes. A variety of diagnostic terms was used in the 35 case series reporting five or more total patients identified by our systematic review: thrombotic microangiopathy, 14; TTP, 7; HUS, 5; TTP-HUS, 3; microangiopathic hemolytic anemia, 3; nephrotoxicity, 2 (both articles reporting patients as nephrotoxicity also described their disorder as resembling TTP[10] or HUS[11]); and intravascular hemolysis with renal insufficiency, 1. Although some of these terms may not imply the diagnosis of TTP-HUS, patients were included because the descriptions included microangiopathic hemolysis, the hallmark diagnostic sign of TTP-HUS, and the management with plasma therapy indicated that the authors considered these syndromes to be comparable to TTP-HUS. The diagnosis of TTP-HUS in these articles was accepted; no reassessment of the diagnosis was attempted. The same criteria were used to select patients in the additional articles reporting autopsies. The term TTP-HUS, rather than thrombotic microangiopathy,[1,3] is used in this report because these syndromes have been described as TTP in recent reviews,[2,4] because both TTP and HUS have been commonly used to describe these patients in case reports and because neither current diagnostic criteria[5] nor pathologic features[12] distinguish TTP from HUS. Furthermore, it is the diagnosis of TTP that requires a decision regarding plasma exchange treatment[6] and therefore creates the diagnostic and management dilemma.

Article assessment

Each article was reviewed independently by two of the authors to determine patient eligibility. Each article reporting five or more total patients that described at least one patient diagnosed with TTP-HUS following allogeneic HPCT was further reviewed by two of the authors using a standard form and a priori criteria for analysis of the individual patients. The additional articles reporting autopsies were also reviewed by two of the authors. Disagreements were resolved by consensus among the authors.

RESULTS

Figure 1 describes the results of the literature search and the selection of articles and patients for review. The literature search identified 99 articles; 35 articles reported 5 or more patients and also included at least 1 patient diagnosed with TTP-HUS following allogeneic HPCT. These articles described 5423 patients who had had allogeneic HPCT; 447 (8.2%) patients were diagnosed with TTP-HUS. Ten additional articles reported autopsy information on 11 patients diagnosed with TTP-HUS following allogeneic HPCT.

Table 1 describes each of the 35 articles with 5 or more total patients that reported at least one patient diagnosed with TTP-HUS following allogeneic HPCT. Thirty (86%) reports are from single institutions; 18 (51%) reports are

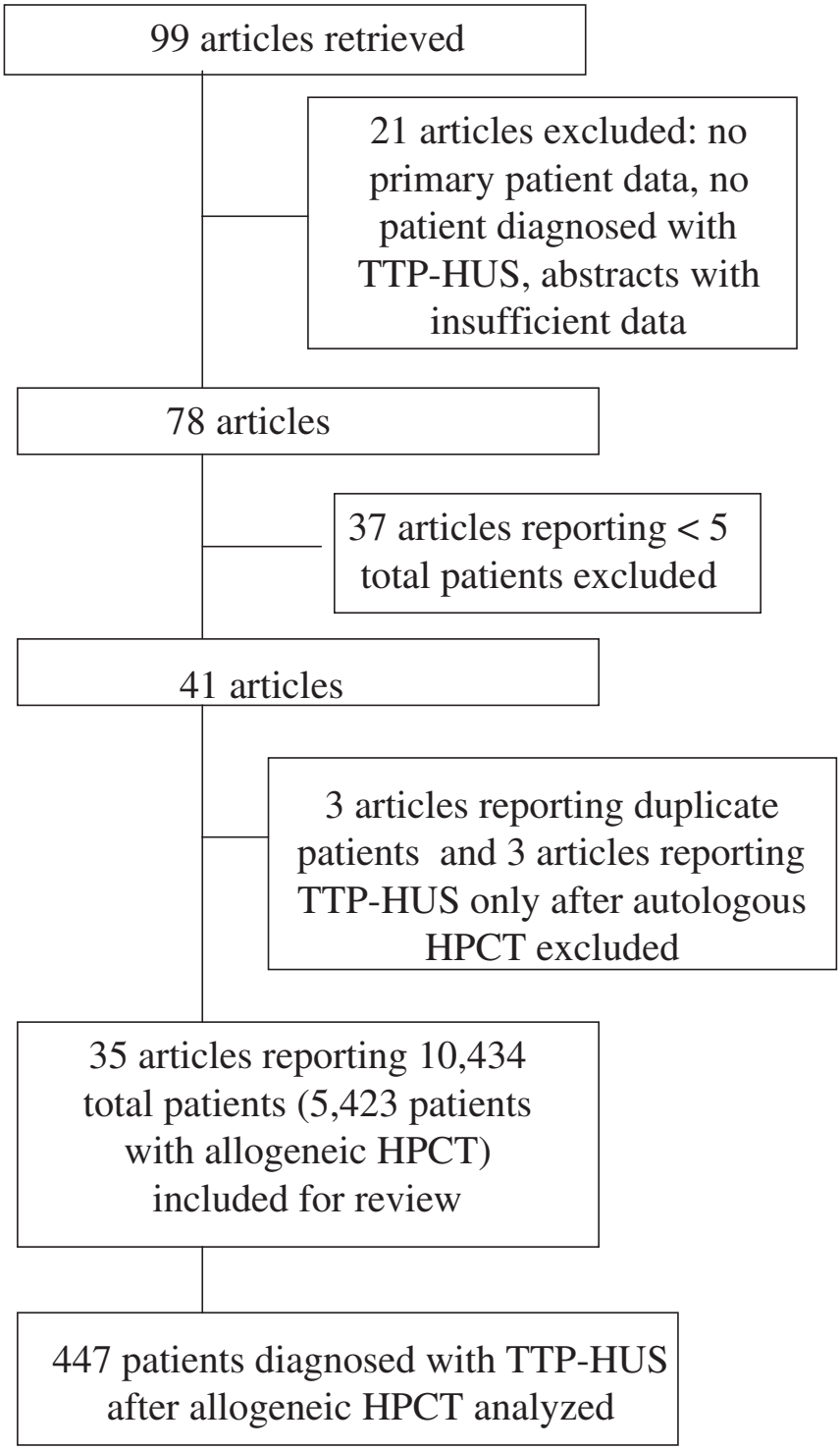

Fig. 1. Results of the systematic literature search and article selection. This diagram only includes the results of article and patient selection for case series of five or more patients reporting at least one patient with TTP-HUS following allogeneic HPCT.

from the United States; and 20 countries contributed to these studies, including 17 countries participating in the one international study.[13] The largest number of patients with TTP-HUS following allogeneic HPCT, 102 (23%) of all 447 patients, were reported from Munich, Germany.[14,15] The frequency of diagnosis of TTP-HUS among all patients with allogeneic HPCT was reported in 24 articles; it varied by 125-fold from 0.5 percent[16] to 63.6 percent;[15] the median frequency of diagnosis was 7.9 percent (Table 1). Twenty-nine articles reported the interval between HPCT and the diagnosis of TTP-HUS; the range was 3 to 890 days following transplantation; the reported median (or mean, when the median was not reported) intervals were 19 to 210 days.

Twenty-eight different sets of diagnostic criteria for TTP-HUS were used in these 35 articles (Table 2). Although we describe 19 different diagnostic criteria, some are merely different ways to interpret the course of anemia and thrombocytopenia (Table 2). RBC fragmentation and an increased serum LDH, evidence for microangiopathic hemolysis, were the most frequently cited criteria, in 31 and 25 articles, respectively. In 6 articles, these were the only criteria required to make the diagnosis of TTP-HUS;[14,17-21] 3 of these 6 articles were from one institution (Pittsburgh, PA).[17-19]

Potential risk factors for the diagnosis of TTP-HUS were assessed in 14 articles (Table 3). Twenty-three different demographic, primary disease, or transplant-related criteria were reported to correlate or not correlate with the risk for the diagnosis of TTP-HUS.

Transplant-related complications were reported in many of the patients diagnosed with TTP-HUS. Acute GVHD (Grades II-IV) was described in 185 (42%) patients. Systemic viral infections were described in 79 (18%) patients; 24 (30%) of these patients had cytomegalovirus infections. Systemic bacterial infections were described in 47 (11%) patients and systemic fungal infections in 30 (7%) patients.

Treatment was either explicitly reported or determined from a summary of the clinical course for 334 (75%) of the 447 patients (Table 4); plasma exchange was described for 184 (55%) of these 334 patients. Many patients were managed only by withdrawing or decreasing the dose of cyclosporine. In some patients there was no

TABLE 1. Articles reporting the occurrence of TTP-HUS following allogeneic HPCT*

Country (city)	Publication date	Accrual dates	Reference number(s)	All allogeneic HPCT patients	Patients diagnosed with TTP-HUS (% of all HPCT patients)	TTP-HUS patients treated with PE†		Mortality of all patients diagnosed with TTP-HUS (% of all TTP-HUS patients)
						Number (% of TTP-HUS patients)	Number who died (% of patients treated with PE)	
US (Seattle, WA)	1981	NA	11	16	3 (19)	0 (0)		3 (100)
Australia (Sydney)	1983	1975-1980	10	34	2 (6)	0 (0)		2 (100)
UK (London)	1988	1978-1987	30	215	6 (3)	1 (17)	1 (100)	4 (67)
US (Boston, MA)	1988	1980-1987	22	NA	3	0 (0)		0 (0)
US (Milwaukee, WI)	1988	NA	33	NA	5	0 (0)		2 (40)
Germany (Munich)	1989	NA	15	77	49 (64)	3 (6)	NA	7 (14)
France (Paris)	1989	NA	23	3	1 (33)	0 (0)		0 (0)
US (Minneapolis, MN)	1991	1974-1990	29	NA	5	3 (60)	2 (67)	4 (80)
US (Boston, MA)	1991	1983-1989	24	56	5 (9)	2 (40)	0	0 (0)
US (Columbus, OH)	1991	1983-1990	32	182	3 (2)	0 (0)		1 (33)
US (Missouri)	1991	1985-1988	75	112	7 (6)	7 (100)	6 (86)	6 (86)
Australia (Westmead)	1995	1981-1993	31, 74	115	5 (4)	4 (80)	3 (75)	4 (80)
US (Milwaukee, WI)	1995	1988-1993	76	NA	9	8 (89)	6 (75)	7 (78)
US (Pittsburgh, PA)	1995	1992-1993	17	52	22 (43)	7 (32)	6 (86)	8 (36)
US (Pittsburgh, PA)	1996	1992-1995	18	86	15 (17)	15 (100)	12 (80)	12 (80)
US (Pittsburgh, PA)	1996	1993-1994	19	NA	5	5 (100)	NA	NA
US (multiple)	1996	NA	20	NA	52	NA		NA
Spain (Madrid)	1997	1984-1996	34	NA	10	10 (100)	7 (70)	7 (70)
Japan (Nagoya)	1998	1982-1995	25	122	5 (4)	0 (100)		0 (0)
US (Los Angeles, CA)	1998	1983-1996	26	NA	7	7 (100)	7 (100)	7 (100)
Japan (Shimane)	1998	1993-1995	77	24	4 (17)	0 (0)		3 (75)
Italy (multiple)	1999	1985-1995	16	1759	9 (0.5)	6 (67)	5 (83)	5 (56)
Japan (multiple)	1999	1997-1998	78	12	3 (25)	0 (0)		NA
Netherlands (Utrecht)	1999	NA	63	NA	4	1 (25)	1 (100)	4 (100)
Italy (Padova)	2000	1994-1997	79	131	28 (21)	16 (57)	7 (44)	12 (43)
US (Oklahoma City, OK)	2001	1989-1998	46	262	17 (7)	17 (100)	16 (94)	16 (94)
US (multiple)	2001	1989-1999	27	NA	7	6 (86)	6 (100)	7 (100)
UK (Bristol)	2001	1993-1999	80	456	22 (5)	17 (77)	16 (94)	19 (86)
US (Baltimore, MD)	2001	1999	28	NA	6	0 (0)		6 (100)
Germany (Munich)	2002	1990-1996	14	364	53 (15)	NA		31 (58)
Canada (Toronto)	2002	1992-1999	81	603	25 (4)	25 (100)	24 (96)	24 (96)
International (multiple)	2002	1996	13	406	23 (6)	5 (22)	4 (80)	16 (70)
Japan (Yokohama)	2003	1994-2001	47	50	8 (16)	NA		NA
US (Baltimore, MD)	2003	1995-1999	21	55	11 (20)	11 (100)	10 (91)	10 (91)
US (Rochester, NY)	2003	1999-2001	4	118	8 (7)	8 (100)	5 (63)	5 (63)

* Each of the 35 articles reporting five or more total patients and at least one patient diagnosed with TTP-HUS following allogeneic HPCT is listed, with the country and city of the study, in the order of the publication year and patient accrual dates. The total number of patients with allogeneic HPCT is presented; in some articles either the total number of patients with HPCT was not reported or the patients with allogeneic and autologous transplants were not distinguished. Two citations are listed as the references for the report from Australia (Westmead)[31,74] because one of the patients from this case series who was diagnosed with TTP-HUS was described in detail in a separate single-patient case report.[74] Some of the patients described in the 3 articles from Pittsburgh[17-19] were reported in more than one article.

† PE = plasma exchange.

treatment intervention either because of critical illness and rapid death or because the TTP-HUS was diagnosed with only minimal laboratory abnormalities, without clinical illness. Table 4 compares the mortality of patients treated with plasma exchange, 82 percent, to patients not treated with plasma exchange, 50 percent.

Mortality rates, reported in 31 articles, varied from 0[22-25] to 100 percent;[10,11,23,26-28] the median mortality rate was 75 percent (Table 1). Overall mortality for the 379 patients for whom survival information was reported was 61 percent. The time of death was reported for 123 patients; 101 (82%) patients died within 3 months of the diagnosis of TTP-HUS.

Complete postmortem examinations were reported for 35 patients, 24 from the articles reporting 5 or more patients that were included in our systematic review[10,21,27-34] and 11 from articles reporting fewer than 5 patients.[35-44] Most autopsy descriptions were very brief, only one or two sentences per patient for 18 of the 35 patients. The cause of death was attributed to HUS in 3 patients, related to the observation of renal thrombotic microangiopathy. In the other 32 patients, the cause of death was attributed to infection in 19 patients, diffuse alveolar hemorrhage in 7 patients, venoocclusive disease in 3 patients, and acute GVHD, central nervous system hemorrhage, and relapsed acute lymphocytic leukemia in

TABLE 2. Criteria used for the diagnosis of TTP-HUS following allogeneic hematopoietic stem cell transplantation in 35 case series*

	Reference number																																		
Diagnostic criteria	11	10	30	22	33	15	23	29	24	32	75	31,74	76	17	18	19	20	34	25	26	77	16†	78	63	79‡	46	27	80§	28	14	81	13	47	21	4	Total
RBC fragmentation	X		X		X	X	X	X		X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	31
LDH increase						X			X		X		X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	25
PLT decrease	X					X		X	X			X	X					X		X		X	X	X	X	X		X	X		X	X			X	18
Renal failure	X	X	X	X	X		X	X	X		X	X	X					X				X						X	X		X		X			17
Neurologic abnormality		X								X	X		X									X						X	X				X			8
Hb decrease				X		X			X			X													X				X							6
No DIC											X									X							X					X			X	5
Negative DAT									X		X								X	X					X											5
Increased PLT transfusion requirement				X	X						X							X																		4
Requirement for RBC transfusion				X																												X				2
Increased RBC transfusion requirement					X																															1
Reticulocyte increase																							X													1
Refractoriness to PLT transfusion												X																								1
Sudden and persistent increase in LDH and BUN or Cr																			X																	1
Sudden and persistent decrease in Hb and PLTs																			X																	1
New-onset thrombocytopenia																					X															1
Renal pathology demonstrating TMA		X																																		1
Fever																						X														1
Arterial hypertension	X																																			1

* The diagnostic criteria reported in each of the 35 case series are presented in chronological order, from left to right. Diagnostic criteria are listed from top to bottom in the order of the frequency of their descriptions. Twenty-eight different sets of diagnostic criteria were described.
† Diagnosis required an increased LDH and at least two of the other five criteria.
‡ Diagnosis required the presence of either a decreased PLT count or Hb concentration.
§ Diagnosis required three of the five criteria.
Abbreviations: DIC = disseminated intravascular coagulation; BUN = blood urea nitrogen; Cr = creatinine; TMA = thrombotic microangiopathy.

TABLE 3. Risk factors in patients having BMT that predict for TTP*

	Number of articles reported			
Risk factors	Correlated	Reference number(s)	Not correlated	Reference number(s)
Age (older)	1	80	9	4, 13, 15, 25, 26, 46, 63, 78, 79
Sex				7, 4, 15, 25, 26, 63, 78, 79
Male	1	20		
Female	3	13, 46, 80		
Status of primary disease			5	13, 15, 26, 63, 78
Advanced disease	2	25, 46	1	80
Neuroblastoma vs. other disease	1	25		
Interval from diagnosis to HPCT			1	26
Marrow remission at time of HPCT			1	79
Transplant				
URD†	4	13, 26, 46, 79	3	63, 78, 81
URD and NMA‡	1	4		
Marrow vs. peripheral blood	1	4		
HLA mismatch	1	46	1	80
Number of previous transplants			3	4, 46, 80
Conditioning regimen			3	13, 15, 26
TBI§	1	25	9	4, 13, 24, 26, 46, 63, 78-80
Cytoxan			2	63, 78
Busulfan			1	46
GVHD prophylaxis	1	26	6	13, 17, 46, 63, 80
Cyclosporine	1	15		
Complications				
Acute GVHD	4	15, 46, 80, 81	6	13, 24, 26, 63, 78, 79
Infection	2	46, 81	3	15, 63, 78
CMV			1	80
VOD‖	1	81	3	46, 63, 78
Day +180 mortality	1	46		

* Risk factors that correlate with increased frequency of diagnosis of TTP-HUS in patients following allogeneic HPCT. Fourteen of the 35 articles described the correlation or lack of correlation of demographic factors, disease, or transplant-related conditions with the diagnosis of TTP-HUS.
† URD = unrelated donor.
‡ NMA = nonmyeloablative conditioning regimen.
§ TBI = total body irradiation.
‖ VOD = venoocclusive disease.

TABLE 4. Mortality and treatment with plasma exchange in patients diagnosed with thrombotic TTP-HUS following allogeneic HPCT*

Total number of patients reported	447
Number of patients evaluable for mortality	379
Death	232/379 (61)
Number of patients evaluable for treatment	334
Number of patients treated with plasma exchange	184/334 (55)
Evaluable for mortality	176
Death	144/176 (82)
Number of patients not treated with plasma exchange	150/334 (45)
Evaluable for mortality	101
Death	50/101 (50)

* Data are reported as number (%). Mortality and treatment with plasma exchange in patients diagnosed with TTP-HUS following allogeneic HPCT. Mortality rates are presented for all patients and separately for patients treated, or not treated, with plasma exchange.

one patient each. Among the 19 patients in whom death was attributed to infection, the most common etiologies were *Aspergillus* species (7 patients) and cytomegalovirus (6 patients). In 19 patients, arteriolar or capillary thrombi were described in the kidneys; fibrin thrombi were described in one lobe of the lungs in one patient and in the liver of another patient. Reports of 11 autopsies explicitly stated that there was no evidence for TTP-HUS. In no patients were systemic microthrombi described.

DISCUSSION

Case series describing TTP-HUS following allogeneic HPCT are characterized by extraordinary variability. Among the 35 reports assessed in this systematic review, 28 different sets of diagnostic criteria were used to establish the diagnosis of TTP-HUS; the frequency of the diagnosis of TTP-HUS among these reports varied by 125-fold, from 0.5[16] to 63.6 percent.[15] The frequency actually extends to 0, but articles that did not describe patients with the diagnosis of TTP-HUS were not included in our systematic review. For example, one analysis of 58 patients with allogeneic HPCT described RBC fragmentation in nearly all patients but did not diagnose TTP-HUS in any patient.[45] In addition to the variation of diagnostic frequency across transplant centers, variation among individual physicians within a single transplant center has

also been described.[46] These extreme variations document the difficulty of diagnosis and emphasize that TTP-HUS following allogeneic HPCT is not a well-defined syndrome.

The difficult diagnosis of TTP-HUS following allogeneic HPCT is understandable. These patients frequently are critically ill with multiple transplant-related complications, and many are rapidly deteriorating. Anemia and thrombocytopenia, the principal presenting features in previously well patients,[5,6] are not reliable diagnostic criteria. The difficulty assessing anemia and thrombocytopenia is reflected in the many different diagnostic criteria that have been described for their evaluation (Table 2). Impaired renal function and mental status abnormalities may also have multiple different etiologies after allogeneic HPCT and are also of limited value as diagnostic criteria. Therefore, the diagnosis of TTP-HUS, often difficult in previously well patients,[5] is always uncertain in patients who are critically ill with multiple concurrent systemic complications of allogeneic HPCT.

TABLE 5. Systemic infections that may mimic TTP-HUS*

Infection	Reported clinical features	Reference number(s)
Aspergillus species	Microangiopathic hemolytic anemia, (schistocytes, ↑ LDH), thrombocytopenia, focal neurologic abnormalities, renal failure, fever	51, 52
CMV	Microangiopathic hemolytic anemia, (schistocytes, ↑ LDH), thrombocytopenia, focal neurologic abnormalities, renal failure, fever	53-55
Adenovirus	Microangiopathic hemolytic anemia, (schistocytes, ↑ LDH), thrombocytopenia, confusion, renal failure, fever	56
Human herpesvirus-6	Microangiopathic hemolytic anemia, (schistocytes, ↑ LDH), thrombocytopenia, renal failure, fever	57
Human parvovirus B19	Microangiopathic hemolytic anemia, (schistocytes, ↑ LDH), thrombocytopenia, confusion, renal failure, fever	58

* Systemic infections that can mimic the clinical features of TTP-HUS and that may occur after allogeneic HPCT. Selected references are listed that describe patients with these infections who presented with clinical features suggesting the diagnosis of TTP-HUS.

The most commonly used diagnostic criteria (Table 2), and those thought to be most specific for TTP-HUS following allogeneic HPCT,[1] are the signs of microangiopathic hemolysis: RBC fragmentation and an increased serum LDH concentration. Nevertheless, RBC fragmentation occurs in almost all patients after allogeneic HPCT and therefore may also be an unreliable diagnostic criterion for TTP-HUS.[45,47] RBC fragmentation is more severe after allogeneic HPCT compared to autologous HPCT, similar to the more frequent diagnosis of TTP-HUS following allogeneic HPCT compared to autologous HPCT.[45]

Common transplant-related complications can cause all of the diagnostic clinical features of TTP-HUS (Table 5). *Aspergillus* species and cytomegalovirus,[48-50] the most common causes of posttransplant infections among the patients in this review, can cause systemic vascular damage resulting in microangiopathic hemolysis with severe RBC fragmentation and increased LDH levels.[51-55] Other viruses that may cause posttransplant infections, adenovirus,[56] human herpesvirus-6,[57] and human parvovirus B19,[58] can also cause severe microangiopathic hemolytic anemia and clinical features resembling TTP-HUS. Other transplant-related complications, such as acute GVHD[15,47] and cyclosporine toxicity,[15,45,59] have also been associated with RBC fragmentation, increased serum LDH levels, thrombocytopenia, and renal failure.

Patients diagnosed with TTP-HUS following allogeneic HPCT may be expected to have complicated courses with multiple transplant-related complications because many of the risk factors that have been reported to correlate with the diagnosis of TTP-HUS (Table 3), such as older age, more advanced primary disease, and an unrelated or HLA-mismatched donor, are also risk factors for poor outcomes following allogeneic HPCT. Other risk factors reported to correlate with the diagnosis of TTP-HUS, such as acute GVHD, infection, hepatic venoocclusive disease, and mortality 180 days after HPCT, describe the actual occurrence of transplant-related complications.

Because a severe deficiency of the VWF-cleaving protease, termed ADAMTS13 (a disintegrin-like and metalloprotease with thrombospondin type 1 repeats), has been described as a specific abnormality for TTP,[60-62] ADAMTS13 activity has been measured in patients who were diagnosed with TTP-HUS following allogeneic HPCT. Five studies[2,4,28,63,64] have reported ADAMTS13 activity levels in 40 patients diagnosed with TTP-HUS following allogeneic HPCT; none had a severe deficiency. In one report, the ADAMTS13 activity levels were normal in all 10 patients.[4] In two reports the ADAMTS13 activity levels were normal in 7 of 8[63] and 5 of 6[28] patients and minimally decreased in 1 patient in each report. In one report, the ADAMTS13 activity levels were described as less than normal but greater than the severe deficiency reported for patients in whom TTP was diagnosed without any preceding condition.[2] In the Oklahoma TTP-HUS Registry,[64] ADAMTS13 activity levels in 7 patients diagnosed with TTP-HUS following allogeneic HPCT were 25 to 100 percent (median, 70%). The moderate deficiencies of ADAMTS13 activity reported in some patients diagnosed

with TTP-HUS following allogeneic HPCT are consistent with reports of moderate deficiencies in a variety of critical illnesses, including severe systemic infections.[64,65] For example, in the Oklahoma TTP-HUS Registry ADAMTS13 activity was measured in 16 patients who were initially diagnosed with TTP-HUS but in whom systemic infections or systemic malignancies were subsequently discovered to be the cause of their acute illness; the ADAMTS13 activity levels in these 16 patients were 8 to 100 percent (median, 35%).[64]

Plasma exchange, the principal treatment for TTP-HUS in adults,[6] cannot be documented to benefit patients diagnosed with TTP-HUS following allogeneic HPCT because of the limited data available to assess the effectiveness of plasma exchange treatment. Insufficient data were available to assess the response to plasma exchange by the conventional parameters used to assess the response of previously well patients who develop TTP-HUS:[5,64] recovery from thrombocytopenia, achievement of a normal or near normal serum LDH concentration, beginning recovery of anemia, and survival for more than 30 days following completion of treatment. The time of death following the diagnosis of TTP-HUS was often not reported. Because recovery from anemia and thrombocytopenia cannot always be expected in patients following allogeneic HPCT, we attempted to document response to plasma exchange by the criteria of no further requirement for RBC or PLT transfusions; however, data were insufficient to evaluate transfusion requirements. The only available comparison between patients treated or not treated with plasma exchange was mortality, which was greater in patients treated with plasma exchange (Tables 1 and 4). Nevertheless, interpretation of these data is limited because the mortality varied from 0 to 100 percent among reported case series (Table 1) and because patients who were more critically ill were more likely to have been treated with plasma exchange. For example, in some patients the diagnosis of TTP-HUS was based only on abnormal laboratory observations, such as RBC fragmentation, rather than clinical features; in these patients who may not have been seriously ill, there was often no treatment intervention, or the only treatment was discontinuation or decreased dosage of cyclosporine.

The apparent ineffectiveness of plasma exchange treatment has been attributed to the absence of ADAMTS13 deficiency;[63] however, we have previously demonstrated that severe ADAMTS13 deficiency does not identify all patients who are appropriately diagnosed with TTP-HUS and who may respond to plasma exchange treatment.[64] The ineffectiveness of plasma exchange treatment may more likely be due to unrecognized alternative etiologies as the cause of the clinical features suggesting TTP-HUS. Clinical features characteristic of TTP-HUS may be the result of repeated exposure of the vascular endothelium to toxic agents both during the preparative radiation therapy or chemotherapy for HPCT and during the infections or other transplant-related complications that can occur during the first several months following HPCT[66] (Table 5).

Although the reported mortality of patients diagnosed with TTP-HUS following allogeneic HPCT varied from 0[22-25] to 100 percent,[10,11,23,26-28] the median mortality was high, 79 percent (Table 1). Autopsies have been reported in only 35 patients who have been diagnosed with TTP-HUS following allogeneic HPCT. The most commonly reported causes of death were infections caused by *Aspergillus* species or cytomegalovirus, consistent with the ability of these organisms to cause severe microangiopathic hemolytic anemia (Table 5) and therefore cause consideration of the diagnosis of TTP-HUS. No autopsy has been reported that demonstrated the systemic microthrombi that are the diagnostic abnormality of TTP-HUS.[67,68] The importance of the absence of autopsy confirmation is that TTP-HUS was originally described as a unique pathologic entity[69] and remained primarily a pathologic diagnosis for 50 years.[67,68] In the current era of effective plasma exchange treatment, rapid diagnosis of TTP-HUS based on clinical features has become imperative, and the frequency of the diagnosis has increased sevenfold.[70,71] Nevertheless, autopsy examination remains the "gold standard" diagnostic definition of TTP-HUS; if microvascular thrombi are not present in multiple organs, the diagnosis of TTP-HUS is excluded.

It has been suggested that earlier diagnosis and initiation of treatment may be beneficial for patients with suspected TTP-HUS following allogeneic HPCT.[2] Nevertheless, accurate earlier diagnosis may be impossible to achieve, because there are no consistent diagnostic criteria and even at autopsy the diagnosis of TTP-HUS following allogeneic HPCT has not been confirmed. It has also been suggested that randomized clinical trials may be necessary to learn the appropriate management of patients diagnosed with TTP-HUS after allogeneic HPCT.[1,2] Nevertheless, clinical trials may be impossible to design, because of the inevitably imprecise patient inclusion and exclusion criteria and the difficulty excluding transplant-related complications as the cause for the signs suggesting TTP-HUS.

Our opinion is that TTP-HUS is not a specific sequela of HPCT. Although TTP-HUS may occur in patients following allogeneic HPCT, the incidence may be no greater than that of the general population. Reasons to support this opinion are 1) the extreme variability of reported incidence and mortality, 2) the uncertainty of the diagnosis in these critically ill patients, 3) the potential for common transplant-related complications to cause the characteristic clinical features of TTP-HUS, and 4) the absence of autopsy documentation of systemic microthrombi, the characteristic pathologic feature of TTP-HUS. Rather than concern for earlier diagnosis, perhaps more appropriate

management for patients with suspected TTP-HUS following allogeneic HPCT is a more deliberate assessment, to exclude, as carefully as possible, systemic infections or GVHD as the cause of the clinical signs suggesting TTP-HUS. Because plasma exchange treatment may provide minimal or no benefit (Table 4), but does have risk for major complications,[7,8] it may be prudent to defer plasma exchange treatment until alternative etiologies for the signs suggesting TTP-HUS can be more confidently excluded. With continuing improvements in the prevention and management of transplant-related complications, such as the decreased risk for *Aspergillus*[72] and cytomegalovirus[72,73] infections, concern for TTP-HUS as a post-HPCT sequela may diminish.

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