Pancreatitis preceding acute episodes of thrombotic thrombocytopenic purpura-hemolytic uremic syndrome: report of five patients with a systematic review of published reports

Karen K. Swisher, John T. Doan, Sara K. Vesely, Hau C. Kwaan, Benjamin Kim, Bernhard Lämmle, Johanna A. Kremer Hovinga, James N. George

Hematology-Oncology Section, Department of Medicine, College of Medicine (KKS, JTD, JNG); Department of Biostatistics and Epidemiology, College of Public Health, The University of Oklahoma Health Science Center Oklahoma City, OK, USA (SKV, JNG); Division of Hematology/Oncology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA (HCK, BK); Department of Hematology and Central Hematology Laboratory, University Hospital, Berne, Switzerland (BL, JAKH).

Funding: supported by grants from the Swiss National Foundation for Scientific Research (3200B0-108261) and the Mach-Gaensslen Foundation, Switzerland.

Manuscript received October 24, 2006.
Accepted May 7, 2007.

Correspondence:
James N. George, M.D., The University of Oklahoma Health Sciences Center, Hematology-Oncology Section, P.O. Box 26901, Oklahoma City, OK 73190 USA.
E-mail: james-george@ouhsc.edu

ABSTRACT

Background and Objectives

The thrombotic thrombocytopenic purpura-hemolytic uremic syndromes (TTP-HUS) have diverse etiologies, clinical manifestations, and risk factors, but the events that may trigger acute episodes are often unclear. We describe the occurrence of TTP-HUS following pancreatitis and consider whether pancreatitis may be a triggering event for acute episodes of TTP-HUS.

Design and Methods

We report on three patients from the Oklahoma Registry and two patients from Northwestern University who had an acute episode of TTP-HUS following pancreatitis. A systematic review of published case reports was performed to identify additional patients who had TTP-HUS following pancreatitis.

Results

In each of our five patients there was an apparent etiology of alcoholism or common bile duct obstruction for the pancreatitis and no evidence of TTP-HUS when the pancreatitis was diagnosed. Two patients had severe ADAMTS13 deficiency with an inhibitor; in one of these patients TTP-HUS recurred following a subsequent recurrent episode of pancreatitis. The systematic review identified 16 additional patients who had TTP-HUS following pancreatitis; recurrent TTP-HUS occurred in three of these patients following a subsequent episode of recurrent pancreatitis. In all 21 patients, the interval between the diagnosis of pancreatitis and TTP-HUS was short (1-13 days; median, 3 days). The three Oklahoma patients represent approximately 1% of the 356 patients in the Registry.

Interpretation and Conclusions

These observations suggest that in some patients pancreatitis, a disorder that results in an intense systemic inflammatory response, may be a triggering event for acute episodes of TTP-HUS.

Key words: pancreatitis, thrombotic thrombocytopenic purpura, TTP, hemolytic uremic syndrome, HUS.

Haematologica 2007; 92:936-943

The thrombotic thrombocytopenic purpura-hemolytic uremic syndromes (TTP-HUS) have multiple diverse recognized etiologies, clinical manifestations, associated conditions, and risk factors.[1] Although the pathogenesis in many patients may involve deficiency of ADAMTS13[2-4] or disorders of complement regulation,[5;6] the events that actually trigger acute episodes of TTP-HUS are often unclear. Patients may have undetectable ADAMTS13 activity or disorders of complement regulation, on either a congenital or acquired basis, without evidence of TTP-HUS until a precipitating condition, such as pregnancy, infection, or surgery, occurs.[5;7-12] These clinical observations are similar to experimental observations on transgenic mice.[13;14] In some strains of mice complete ADAMTS13 deficiency was well tolerated, demonstrating that although ADAMTS13 deficiency caused a prothrombotic state, other genetic modifying factors or environmental triggers were necessary to induce abnormalities similar to TTP-HUS syndromes.[13,14] In the conditions that have been reported to trigger acute episodes of TTP-HUS,[5,7-12] inflammatory cytokines may stimulate endothelial cell release of ultralarge and hyperreactive von Willebrand factor multimers and inhibit the cleavage of these multimers by ADAMTS13.[15]

The pancreas is an organ frequently and severely involved in patients with TTP-HUS,[16,17] and pancreatic ischemia caused by TTP-HUS may contribute to the common symptom of abdominal pain.[16] Our clinical experience suggests that the reverse of this sequence may also occur, that pancreatitis may immediately precede an acute episode of TTP-HUS. We report on five patients who were diagnosed with acute pancreatitis and then subsequently, 1-13 days after the diagnosis of pancreatitis, developed an acute episode of TTP-HUS. In these patients there was evidence that the pancreatitis preceded the acute episode of TTP-HUS and was not caused by TTP-HUS. (i) Each patient had a documented etiology for her/his pancreatitis, either alcoholism or common bile duct obstruction. (ii) When the pancreatitis was diagnosed, there was no microangiopathic hemolysis or thrombocytopenia. (iii) In three of the patients the pancreatitis was resolving when the signs of TTP-HUS first appeared. To supplement our experience we conducted a systematic literature review to identify all previously reported patients in whom acute pancreatitis preceded TTP-HUS.

Design and Methods

Oklahoma patients

The Oklahoma TTP-HUS Registry includes all consecutive patients for whom the Oklahoma Blood Institute (OBI) is requested to provide plasma exchange treatment for clinically diagnosed TTP-HUS,[18;19] based on the presence of microangiopathic hemolytic anemia and thrombocytopenia without an apparent alternative etiology.[1] Since the OBI is the sole provider of plasma exchange services for all hospitals in central, western, and southeastern Oklahoma, the Registry is an inception cohort of all patients in our region. The standard practice in our region is to treat all adult patients who are diagnosed as having TTP or HUS, as well as children with TTP or atypical HUS, with plasma exchange. Therefore, the only patients systematically excluded from the Registry are children with typical (diarrhea-associated) HUS, who are not treated with plasma exchange. The Registry has enrolled and prospectively followed all 356 consecutive patients with clinically diagnosed TTP or HUS from January 1, 1989 to December 31, 2006. All data from the hospital course and continuing follow-up are complete to the present time for 354 of the 356 patients and recorded in a Microsoft Access® database. The Oklahoma TTP-HUS Registry is approved by the institutional review boards of each participating hospital.

Northwestern University patients

Following a presentation of the Oklahoma data at Northwestern University in 2005 describing pancreatitis preceding TTP-HUS, two additional patients from the Northwestern University were identified.

ADAMTS13 activity and inhibitor

ADAMTS13 activity and inhibitors in serum samples (Oklahoma patients) or plasma samples (Northwestern University patients) obtained immediately before beginning the first plasma exchange treatment were measured in Berne, Switzerland, using an immunoblotting method.[20,21] Previously published data documented that there is no significant difference in ADAMTS13 activity measured in either citrated platelet-poor plasma or serum obtained from unanticoagulated blood[20] and that the activity of ADAMTS13 is stable in both serum and plasma.[22] In the two patients with ADAMTS13 deficiency and an inhibitor, IgG antibodies to ADAMTS13 were also measured by the Technozym® ADAMTS13-INH ELISA assay (Technoclone GmbH, Vienna, Austria). Results are given in arbitrary antibody units/mL (AU/mL) and titers <15.1 AU/mL were considered to be negative, according to the manufacturer's instructions.

Systematic review

Ovid software was used to search the Medline database of published reports to identify additional patients who had TTP-HUS following pancreatitis. Key words and MeSH terms searched for TTP-HUS were: *thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, thrombotic thrombocytopenic purpura-hemolytic uremic syndrome, TTP-HUS, thrombotic microangiopathy, microangiopathic hemolytic anemia, thrombocytopenia, renal failure, kidney failure, hemolysis, hemolytic anemia,* and *thrombosis*. Keywords and MeSH terms searched for pancreatitis were: *pancreatitis, pancreatitis-acute necrotizing, pancreatitis-alcoholic, pan-*

creatitis-severe, and *pancreatitis-gallstone*. All articles identified by both one of the TTP-HUS terms and by one of the pancreatitis terms were reviewed and their bibliographies searched for additional articles. All reviewed articles were searched to identify patients who had TTP-HUS diagnosed following the onset of pancreatitis.

Levels of evidence

Levels of evidence for pancreatitis as a potential triggering event for an acute episode of TTP-HUS were assessed according to criteria presented in Table 1. Pancreatitis preceding TTP-HUS was the criterion for identifying all patients. The presence of a recognized etiology for the pancreatitis and evidence that the pancreatitis was resolving when the TTP-HUS was diagnosed supported the interpretation that pancreatitis preceded the TTP-HUS and was not caused by TTP-HUS. Recurrent TTP-HUS following a subsequent episode of recurrent pancreatitis also supported the interpretation that pancreatitis may be a triggering event for TTP-HUS. The levels of evidence derived from these criteria describe pancreatitis as a possible or probable precipitating event.

Table 1. Levels of evidence for pancreatitis as a potential triggering event for an acute episode of TTP-HUS.

Required criterion
Pancreatitis preceded the presence of diagnostic criteria for TTP-HUS
Additional criteria
Recognized etiology for pancreatitis present
Pancreatitis resolving when diagnostic criteria of TTP-HUS occurred
Recurrent episode of pancreatitis associated with recurrent TTP-HUS
Levels of evidence that pancreatitis was a triggering event for TTP-HUS
Possible relation: inclusion criterion, no additional criteria
Probable relation: inclusion criterion + additional criteria 1 and 2 or additional criterion 3

Design and Methods

Three patients (patients #1, #2, and #5) from the Oklahoma TTP-HUS- Registry and two patients from Northwestern University (patients #3 and #4) who developed acute episodes of TTP-HUS following pancreatitis are reported. Their data are summarized in Table 2.

Patient #1. A 38-year old white woman was evaluated for obstructive jaundice 4 months after a cholecystectomy in early 1992; endoscopic retrograde cholangiopancreatography (ERCP) documented a common bile duct stricture. Several hours following the procedure she developed severe abdominal pain with nausea and vomiting. Acute pancreatitis was diagnosed by elevated amylase and lipase and an abnormal abdominal ultrasound. Hemoglobin, platelet count, creatinine, and coagulation tests were normal; lactate dehydrogenase (LDH) was slightly increased. On day 3 she was less symptomatic but developed anemia, thrombocytopenia and increased creatinine and LDH. On day 7, TTP-HUS was diagnosed, based on a new onset of diplopia with intermittent confusion, more severe anemia with red cell fragmentation, and thrombocytopenia. Amylase and lipase levels were normal. She recovered with plasma exchange treatment and has had no further illness during the following 14 years.

Patient #2. A 48-year old white woman had a previous episode of pancreatitis related to gallstones and was treated by cholecystectomy in 2002. In early 2003 she was diagnosed with recurrent pancreatitis attributed to excessive alcohol. During the first 3 days in hospital she developed anemia, thrombocytopenia, acute renal failure requiring dialysis, and became confused while her serum amylase was improving. Coagulation tests were normal. On day 5 schistocytes were noted and TTP-HUS was diagnosed. Serum amylase was normal; ADAMTS13 activity was 90%. She had a grand mal seizure on day 7 requiring intubation. She recovered with plasma exchange treatment and hemodialysis and has had no further illness during the following 4 years.

Patient #3. A 43-year old white alcoholic man was admitted to the hospital in late 2005 with severe epigastric pain and was diagnosed with pancreatitis. The following day he developed delirium tremens. On day 3, TTP-HUS was diagnosed when he became more anemic and thrombocytopenic, schistocytes were noted, and his creatinine increased. Coagulation tests were normal. ADAMTS13 was <3% with a strong inhibitor (defined as >2 Bethesda Units). The anti-ADAMTS13 IgG antibody titer by immunoassay was 18 AU/mL. He recovered with plasma exchange and prednisone treatment and has had no further illness over the following 15 months.

Patient #4. A 37-year old black woman presented in late 2005 with the onset of severe epigastric pain, nausea and vomiting. The previous day, she had undergone a mediastinoscopy and lymph node biopsy resulting in the diagnosis of sarcoidosis. Computed tomography scans were consistent with pancreatitis and also demonstrated large peri-pancreatic and porta-hepatis lymph nodes. The diagnosis was pancreatitis due to bile duct obstruction by sarcoid lymphadenopathy[23] or granulomatous infiltration of the pancreas.[24] On day 2, the woman was confused and developed anemia with schistocytes and thrombocytopenia. Coagulation tests were normal except for a slightly prolonged prothrombin time. TTP-HUS was diagnosed; ADAMTS13 activity was 80%. She recovered with plasma exchange and prednisone and has had no further illness over the following 12 months.

Patient #5. A 35-year old white woman was first diagnosed with TTP-HUS in 1999. Following recovery she had enterobacter sepsis related to her central venous catheter that was complicated by acute pancreatitis with pseudocyst and abscess formation requiring surgical drainage. Later in 1999 she had an elective splenectomy, described as definitive therapy for her TTP-HUS. In 2003

Table 2. Clinical course of Oklahoma and Northwestern patients with pancreatitis preceding an acute episode of TTP-HUS.

Day	*Hb (g/dL)*	*Plt (10^3/μL)*	*Cr (mg/dL)*	*LDH (U/L)*	*Amylase (U/L)*	*Lipase (U/L*	*Comments*
Patient 1							
1	12.7	346	0.9	272	1077	40	ERCP-pancreatitis diagnose
3	9.7	80	2.7	1679	1101	–	
6	8.0	40	2.1	1526	154	20	
7	7.3	52	2.1	–	90	18	TTP-HUS diagnosed (ADAMTS13 not measured), first PE
11	9.3	289	1.9	271	–	–	Last PE
Patient 2							
1	14.3	291	0.7	345	1704	–	Pancreatitis diagnosed
2	12.7	93	4.6	–	1169	–	
3	10.0	51	7.7	–	501	–	Dialysis started
4	9.7	37	6.3	–	249	–	
5	9.0	24	4.9	1668	140	–	TTP-HUS diagnosed (ADAMTS13 90%), first PE
7	9.7	90	3.5	362	–	–	Seizure
10	9.7	267	3.1	287	–	–	Last PE
Patient 3							
1	15.4	301	1.2	–	140	648	Pancreatitis diagnosed
2	12.4	115	1.4	–	–	–	
3	10.1	53	2.0	1093	–	–	TTP-HUS diagnosed (ADAMTS13 <3%), first PE
4	10.4	40	1.9	–	–	553	
8	8.9	172	–	–	–	228	
12	8.3	287	1.5	–	–	136	
16	–	–	–	–	–	–	Last PE
Patient 4							
1	12.5	359	1.5	–	–	907	Pancreatitis diagnosed
2	9.6	74	4.1	1195	–	1284	TTP-HUS diagnosed (ADAMTS13 80%), first PE
4	6.2	53	5.2	870	–	–	
10	8.6	109	2.2	749	–	–	
12	7.1	174	1.8	488	–	–	
24	–	–	–	–	–	–	Last PE
Patient 5							
1	10.3	588	0.8	–	627	1457	Pancreatitis diagnosed
5	7.7	445	0.5	–	205	357	
7	9.3	193	1.0	–	100	151	
8	7.7	37	0.9	–	–	–	
13	9.3	58	1.9	703	–	–	Laparotomy, drainage of pancreatic abscesses
14	8.0	35	2.1	997	433	1743	TTP-HUS diagnosed (ADAMTS13 <3%), first PE
20	8.7	32	2.3	672	355	244	Laparotomy
25	9.0	255	2.3	337	53	37	PE stopped
31	9.0	324	1.5	483	107	116	
32	8.7	29	1.5	1573	227	369	Cardiac arrest. PE resumed for exacerbated TTP-HUS
38	8.7	237	2.3	273	111	67	Intermittent PE started
61	9.3	392	1.5	–	–	226	Sepsis, last PE
83	9.7	359	1.2	–	–	90	Discharge
101	13.8	340	1.3	–	1584	6658	Re-admission, pancreatitis
105	11.7	187	0.9	174	536	385	Laparotomy, enterococcal
107	10.0	75	1.1	376	88	34	abscess/sepsis
108	10.0	45	1.1	541	40	24	TTP-HUS diagnosed (ADAMTS13 <3%), first PE
113	9.7	280	1.3	184	129	302	
117	9.7	468	1.0	182	108	264	Last PE

Data are presented for each of the 5 reported patients from Oklahoma and Northwestern University. Day 1 is the day of diagnosis of pancreatitis. ERCP: endoscopic retrograde cholangiopancreatography; PE: plasma exchange; Hgb: hemoglobin; Plt: platelet count; Cr: creatinine; LDH: lactate dehydrogenase.

TTP-HUS recurred following surgery to repair an incisional hernia at the splenectomy site. In 2006 she was admitted to the hospital for acute pancreatitis. Ultrasound demonstrated bile sludge. Computed tomography scan documented multiple pancreatic abscesses that required surgical drainage on day 13. TTP-HUS was diagnosed and plasma exchange begun on day 14 because of hemolytic anemia with schistocytes, thrombocytopenia, and renal failure. ADAMTS13 activity was <3% with a strong inhibitor. The immunoassay for anti-ADAMTS13 IgG antibody was also positive (>88.3 AU/mL). Coagulation tests were normal. On day 32 she had ventricular fibrillation and cardiac arrest that was attributed to an acute exacerbation of TTP-HUS. Again she responded promptly to plasma exchange. The pancreatitis apparently resolved and she was discharged on day 83. Pancreatitis

Table 3. Clinical characteristics of the 16 previously reported patients and the five Oklahoma/Northwestern University patients in whom pancreatitis preceded an acute episode of TTP-HUS.

No.	Year, ref	Age, race, sex	Etiology of pancreatitis	Days from diagnosis of pancreatitis to diagnosis of TTP-HUS	Pancreatitis resolving when TTP-HUS diagnosed	ADAMTS13	Laboratory data on days of diagnoses of pancreatitis and of TTP-HUS										Level of evidence that pancreatitis triggered TTP-HUS
							Hb (g/dL)		Pit (10^3/μL)		Cr (m/dL)		LDH (U/L)		Amylase (U/L)		
							Pancr	TTP-HUS	Pancr	TTP-HUS	Pancr	TTP-HUS	Pancr	TTP-HUS	Panc	TTP-HUS	
Oklahoma/Northwestern patients																	
1		38 WF	ERCP	6	Yes	–	12.7	8.0	346	40	0.9	2.1	272	1526	1077	154	probable
2		48 WF	Alcohol	4	Yes	90%	14.3	9.0	291	24	0.7	7.7	345	1668	1704	140	probable
3		43 BM	Alcohol	2	No	<3%	15.4	10.1	301	53	1.2	2	–	1093	140	-	possible
4		37 BF	Sarcoidosis	1	No	80%	12.5	9.6	359	74	1.5	4.1	–	1195	-	-	possible
5a		35 WF	GB	13	No	<3%	10.3	8.0	588	35	0.8	2.1	–	997	627	433	probable
5b			GB	7	Yes	<3%	13.8	10.0	340	45	1.3	1.1	–	541	1584	40	–
Previously reported patients																	
1	1978[27]	18 BM	Idiopathic	4	NR	–	13.4	10.6	NI	2	–	2.3	–	–	1441	–	possible
2	1989[28]	55 F	Idiopathic	2	Yes	–	14.7	8.0	240	24	1.7	1.7	–	–	1131	127	possible
3	1991[29]	36 M	Alcohol	3	NR	–	16.3	9.2	265	45	–	–	–	–	2235	–	possible
4	1992[30]	55 M	GB	3	Yes	–	16.0	10.0	235	20	1.1	7.9	–	1045	760	–	probable
5	1995[31]	18 M	Alcohol	3	Yes	–	14.8	6.0	327	30	1.1	15.0	NI	2024	840	341	probable
6	1997[32]	25 M	Alcohol	3	NR	–	NI	5.0	NI	53	NI	5.3	NI	-	-	-	possible
7a	1998[33]	28 F	Idiopathic	2	Yes	–	11.5	9.2	167	9	–	1.3	–	4250	2000	619	probable
7b		30 F	Idiopathic	2	NR	–	–	7.0	–	32	–	–	–	–	–	–	
8	1998[34]	65 M	GB	3	Yes	–	18.0	10.3	145	32	1.5	2.2	499	647	5215	230	probable
9a	1998[35]	37 M	Alcohol	2	NR	–	16	11.7	186	22	1.36	4.8	–	–	1010	–	probable
9b		38 M	Alcohol	3	NR	–	15.7	9.7	280	18	NI	7.8	–	–	–	–	
10	2000[36]	70 M	Idiopathic	15	Yes	–	9.7	7.7	352	22	1	2.4	115	1111	200	190	possible
11	2002[37]	38 M	Alcohol	2	NR	–	NI	NI	259	28	NI	?	NI	–	291	–	probable
12	2002[38]	35 WM	ERCP	2	NR	–	NI	5.3	NI	15	NI	2.2	–	1434	1494	–	possible
13	2002[39]	58 M	Alcohol	2	Yes	–	15.5	8.3	145	14	1	3.2	896	1701	1313	824	probable
14	2004[40]	33 WM	Alcohol	3	Yes	–	NI	5.8	353	90	NI	7.0	-	1657	1900	1900	probable
15	2005[41]	55 F	ERCP	2	NR	53%	13.8	12.1	403	50	–	–	295	350	1800	–	possible
16	2005[42]	19 M	GB	3	NR	–	14.9	8.8	NI	32	NI	6.7	–	–	1426	–	possible

Summary data are presented for the five Oklahoma and Northwestern University patients and the 16 previously reported patients. The etiology of the pancreatitis was reported to be (1) chronic severe alcoholism, (2) GB, gallbladder disease, either gallstones or bile sludge, (3) common bile duct obstruction resulting from endoscopic retrograde cholangiopancreatography (ERCP) or lymphadenopathy caused by sarcoidosis, or (4) idiopathic. Laboratory data are listed for the day of diagnosis of pancreatitis (Pancr) and day of diagnosis of TTP-HUS. Hgb: hemoglobin; Plt: platelet count; Cr: creatinine; LDH: lactate dehydrogenase; NR: not reported; Nl: reported as normal. The levels of evidence for a relation between the pancreatitis and the subsequent TTP-HUS were derived according to the criteria in Table 1. Although the occurrence of repeated episodes of TTP-HUS following pancreatitis in patient 11 are not described in this Table, the original report described that over the next 3 years the patient had several episodes of acute pancreatitis and during each of these episodes, despite normal blood counts and renal function at the time of diagnosis of his pancreatitis, he developed clinical and laboratory evidence for TTP-HUS within 48 hours.

recurred on day 101 with no signs of TTP-HUS. Four days later she became septic and required another laparotomy for pancreatic necrosis and multiple abscesses. Three days after her laparotomy TTP-HUS was diagnosed because of thrombocytopenia and the appearance of schistocytes on her blood smear. ADAMTS13 activity was again <3%. Prothrombin time (PT) and activated partial thromboplastin time (aPTT) were slightly prolonged; fibrinogen was increased. She recovered with plasma exchange, her pancreatitis resolved, and she has had no further illness for the following 6 months. She did not receive glucocorticoids or other immunosuppressives agenst because of her recurrent pancreatic abscesses.

Results

Oklahoma and Northwestern University patients

Data for these five patients are summarized in Table 3. The three patients from the Oklahoma Registry represent 1% of the 356 patients treated for TTP-HUS from January 1, 1989 to December 31, 2006.

All five patients had apparent etiologies for their pancreatitis: ERCP for bile duct stricture in patient 1, alcoholism in patients 2 and 3, bile duct obstruction by sarcoidosis lymphadenopathy in patient 4, and by bile sludge in patient 5. Patients 2 and 5 had had previous episodes of pancreatitis without associated TTP-HUS. None of the patients had evidence of TTP-HUS when the pancreatitis was diagnosed. TTP-HUS was diagnosed 1-13 days (median, 5 days) after the diagnosis of pancreatitis. The pancreatitis was resolving when TTP-HUS was diagnosed in patients 1 and 2, and in the second episode of patient 5. Patient 1 had focal neurologic abnormalities; patient 2 had a grand mal seizure; in patient 3 delirium was attributed to alcohol withdrawal; patient 4 had episodes of confusion; patient 5 had no neurologic abnormalities. The comprehensive term, TTP-HUS, has been used to describe the condition in these patients because all five patients had renal involvement documented by increased serum creatinine levels and patients 2 and 4 had acute renal failure as previously defined[18]; patient 2 required dialysis. None of the patients had evidence of possible disseminated intravascular coagulation, except for a prolonged PT and aPTT at the time of the second episode of pancreatitis-associated TTP-HUS in patient 5. All patients were treated with plasma exchange; patients 3 and 4 were also treated with steroids. Using the criteria

in Table 1, pancreatitis probably triggered the acute episode of TTP-HUS in patients 1, 2 and 5; in patients 3 and 4 there was a possible relation between the pancreatitis and the subsequent TTP-HUS since it was unclear whether the pancreatitis was resolving when TTP-HUS was diagnosed.

The demographics of these patients are characteristic of patients with TTP-HUS:[18,25] four were women; three of the women (patients 1, 4, and 5) were obese (body mass index 30.1-62.1); the one man was not obese. ADAMTS13 activity was measured in patients 2-5; patients 2 and 4 had normal activity; patients 3 and 5 had severe deficiency and strong inhibitors of ADAMTS13 activity were demonstrated. Patient 5 had had two previous episodes of TTP-HUS; her first episode had no apparent triggering event; her second followed abdominal surgery. It was considered that spuriously low levels of ADAMTS13 activity could have resulted from circulating pancreatic proteases, since ADAMTS13 can be proteolytically inactivated.[26] However the normal ADAMTS13 activity in two of the four patients supports the validity of the measurements demonstrating absent ADAMTS13 activity in the other two patients. The identification of the ADAMTS13 inhibitor in patients 3 and 5 as an IgG immunoglobulin further supports the clinical relevance of the ADAMTS13 deficiency No tests for disorders of complement regulation[5,6] were performed in these patients.

Previously reported patients

The literature review identified 16 articles, each describing one patient in whom pancreatitis preceded TTP-HUS (Table 3).[27-42] Among these 16 patients, 13 were men, opposite to the gender disparity of TTP-HUS[25] but consistent with the greater frequency of acute pancreatitis among men.[43] The etiologies of the pancreatitis in these 16 patients were typical for acute pancreatitis among adults:[43,44] seven cases were related to chronic severe alcohol use, five to gallbladder disease, and four were idiopathic. The diagnosis of acute pancreatitis was made by clinical signs and elevated serum amylase and/or lipase levels in all patients. The diagnosis was supported by computed tomography scan or ultrasound demonstrating pancreatic abnormalities in eight patients; two patients required laparotomy for pancreatic necrosis and abscess formation.[29,36]

TTP-HUS was diagnosed 2-15 days (median, 3 days) after the diagnosis of pancreatitis. In only two patients was the onset of TTP-HUS accompanied by neurologic abnormalities: patient 1 had slurred speech and patient 10 had right hemiparesis. Coagulation test results were reported in 12 patients and all were normal. Eight patients had acute renal failure and seven required dialysis. ADAMTS13 activity was reported only for patient 15; her activity was slightly low (53%, normal range 67-177%) without a demonstrable inhibitor.[41] Ten patients were treated with plasma exchange, four with plasma infusion, one with splenectomy,[27] and one with only supportive care including hemodialysis.[32] Using the criteria in Table 1, there was a possible relation between the pancreatitis and the subsequent development of TTP-HUS in eight patients (Table 3). In these patients, either there was no apparent etiology for their pancreatitis or it was not reported that the pancreatitis was resolving at the time TTP-HUS was diagnosed. In the other eight patients, pancreatitis probably triggered the acute episode of TTP-HUS. Recurrent TTP-HUS occurred in three of these patients following a subsequent episode of recurrent pancreatitis. The recurrent episodes of TTP-HUS of patient 11 are not presented in Table 3 because the case report only describes that the patient had several episodes of acute pancreatitis over the following 3 years and that following each of these episodes he developed clinical and laboratory evidence of TTP-HUS within 48 hours.

Discussion

Our experience and previously published case reports suggest that the acute inflammatory response to pancreatitis may trigger the onset of TTP-HUS. The short interval between the diagnosis of pancreatitis and the diagnosis of TTP-HUS, a median of 3 days, raises the hypothesis that the inflammatory consequence of pancreatitis has a direct impact on the pathogenesis of TTP-HUS. The clinical course of these patients suggests that pancreatitis actually preceded the onset of TTP-HUS and was not caused by TTP-HUS: (i) None of the patients were anemic or thrombocytopenic when the pancreatitis was diagnosed. (ii) In 17 of 21 patients, there was a clear etiology for the pancreatitis: excessive alcohol use, gall bladder/biliary disease, or common bile duct obstruction. In the other four (19%) patients without an apparent etiology it may be considered that pancreatitis could have been caused by TTP-HUS that was not yet overt, but this frequency is comparable to the expected 20% frequency of idiopathic pancreatitis in adults.[44] (iii) In 13 patients, the pancreatitis was resolving when the TTP-HUS was diagnosed. Although the diagnosis of TTP-HUS may be uncertain in patients already ill with pancreatitis, all 21 patients developed diagnostic criteria for TTP-HUS, including severe ADAMTS13 deficiency in two of the five patients in whom ADAMTS13 activity was measured. In both patients with severe ADAMTS13 deficiency, strong inhibitors of ADAMTS13 activity were identified and the positive results in the anti-ADAMTS13-ELISA provided evidence that the inhibitors were IgG immunoglobulins. The three Oklahoma patients in whom pancreatitis immediately preceded TTP-HUS represent 0.84% of patients in the Oklahoma TTP-HUS Registry (3 of 356 patients).

The possibility of coincidental occurrence of pancreatitis and TTP-HUS can be estimated from the annual incidence of TTP-HUS (5 per 10^6 population, the mean value of four estimates determined in the US)[25,45-47]and

the annual incidence of new and recurrent episodes of pancreatitis in the US population (750 per 10^6 population).[48] Based on these data, the expected incidence of coincidental occurrence of both disorders within the same year is 3.75 per 10^9 population), indicating that the percentage of patients with TTP-HUS who would also have pancreatitis would be 0.000000375%, 2.24×10^6-fold less than our observed percent.

Since this assessment is based on annual incidence rates for TTP-HUS and pancreatitis, it would be much less likely for TTP-HUS to occur by chance just a few days after pancreatitis. Therefore, our observed cases of pancreatitis preceding acute episodes of TTP-HUS are unlikely to be the result of coincidence.

The hypothesis that pancreatitis may trigger an acute episode of TTP-HUS is consistent with observations that multiple factors may be involved in the onset of TTP-HUS. In Upshaw's initial patient with congenital TTP-HUS, infections and pancreatitis were noted to trigger her acute episodes.[7] Women with congenital ADAMTS13 deficiency may have no signs of TTP-HUS until near the end of their first pregnancy.[8,9] Pregnancy, infections, and surgery may also trigger acute episodes of acquired TTP-HUS associated with ADAMTS13 deficiency.[8-10;12,18]

The former conditions may result in an inflammatory response that could augment the risk of ADAMTS13 deficiency by enhancing the release of ultralarge von Willebrand factor (VWF) multimers from endothelial cells and inhibiting their cleavage by ADAMTS13.[15] This has been demonstrated in *in vitro* studies in which the inflammatory cytokines, interleukin (IL)-8 and tumor necrosis factor (TNF)-α, stimulated endothelial cell release of ultralarge VWF multimers in a dose-dependent manner and IL-6 inhibited the cleavage of ultralarge VWF by ADAMTS13.[15] Similar conditions may trigger acute episodes of TTP-HUS not associated with ADAMTS13 deficiency[18] and acute episodes in patients with congenital HUS due to abnormal complement regulation.[5]

The systemic inflammatory response of pancreatitis, mediated by IL-6, IL-8, TNF-α, and other cytokines,[49] may also contribute to the onset of an acute episode of TTP-HUS.[15] Furthermore, pancreatitis is associated with endothelial cell damage, which may contribute to the development of TTP-HUS as well as lead to disseminated intravascular coagulation.[50] Since TTP-HUS is a rare complication of pancreatitis, patients who develop TTP-HUS following pancreatitis may have a predisposing risk. Acquired ADAMTS13 deficiency was the apparent risk factor present in two of the four patients in whom ADAMTS13 activity was measured.

Authors' Contributions

KKS, JTD, SKV, HCK, BK, BL, JAKH, JNG: substantial contributions to conception and design of the study revising the article critically for important intellectual content; final approval of the version to be published.

Conflict of Interest

The authors reported no potential conflicts of interest.

References

1. George JN. Thrombotic thrombocytopenic purpura. N Engl J Med 2006; 354:1927-35.
2. Moake JL. Thrombotic microangiopathies. N Engl J Med 2002; 347: 589-600.
3. Lammle B, Kremer Hovinga JA, Alberio L. Thrombotic thrombocytopenic purpura. J Thromb Haemost 2005;3:1663-1675.
4. Veyradier A, Meyer D. Thrombotic thrombocytopenic purpura and its diagnosis. J Thromb Haemost 2005;3: 2420-7.
5. Caprioli J, Noris M, Brioschi S, Pianetti G, Castelletti F, Bettinaglio P, et al. Genetics of HUS: the impact of MCP, CFH and IF mutations on clinical presentation, response to treatment, and outcome. International Registry of Recurrent and Familial HUS/TTP. Blood 2006;108:1267-79.
6. Besbas N, Karpman D, Landau D, Loirat C, Proesmans W, Remuzzi G, et al. A classification of hemolytic uremic syndrome and thrombotic thrombocytopenic purpura and related disorders. European Paediatric Research Group for HUS. Kidney Int 2006;70:423-31.
7. Upshaw JD Jr. Congenital deficiency of a factor in normal plasma that reverses microangiopathic hemolysis and thrombocytopenia. N Engl J Med 1978; 298:1350-2.
8. Furlan M, Lammle B. Aetiology and pathogenesis of thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome: the role of von Willebrand factor-cleaving protease. Best Pract Res Clin Haematol 2001; 14:437-54.
9. George JN. The association of pregnancy with thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. Curr Opin Hematol 2003;10:339-44.
10. Niv E, Segev A, Ellis MH. Staphylococcus aureus bacteremia as a cause of early relapse of thrombotic thrombocytopenic purpura. Transfusion 2000; 40:1067-70.
11. Naqvi TA, Baumann MA, Chang JC. Post-operative thrombotic thrombocytopenic purpura: a review. Int J Clin Pract 2004;58:169-72.
12. Cataland SR, Jin M, Smith E, Stanek M, Wu HM. Full evaluation of an acquired case of thrombotic thrombocytopenic purpura following the surgical resection of glioblastoma multiforme. J Thromb Haemost 2006;4:2733-7.
13. Motto DG, Chauhan AK, Zhu G, Homeister J, Lamb CB, Desch KC, et al. Shigatoxin triggers thrombotic thrombocytopenic purpura in genetically susceptible ADAMTS13-deficient mice. J Clin Invest 2005;115:2752-61.
14. Banno F, Kokame K, Okuda T, Honda S, Miyata S, Kato H, et al. Complete deficiency in ADAMTS13 is prothrombotic, but it alone is not sufficient to cause thrombotic thrombocytopenic purpura. Blood 2006;107:3161-6.
15. Bernardo A, Ball C, Nolasco L, Moake J, Dong JF. Effects of inflammatory cytokines on the release and cleavage of the endothelial cell-derived ultralarge von Willebrand factor multimers under flow. Blood 2004;104:100-6.
16. Ridolfi RL, Bell WR. Thrombotic thrombocytopenic purpura. Report of 25 cases and review of the literature. Medicine 1981;60:413-28.
17. Hosler GA, Cusumano AM, Hutchins GM. Thrombotic thrombocytopenic purpura and hemolytic uremic syndrome are distinct pathologic entities. A review of 56 autopsy cases. Arch Pathol Lab Med 2003;127:834-9.
18. Vesely SK, George JN, Lammle B, Studt JD, Alberio L, El-Harake MA, et al. ADAMTS13 activity in thrombotic thrombocytopenic purpura-hemolytic uremic syndrome: relation to presenting features and clinical outcomes in a prospective cohort of 142 patients. Blood 2003;101:60-8.
19. George JN, Vesely SK, Terrell DR. The Oklahoma thrombotic thrombocytopenic purpura-hemolytic uremic syndrome (TTP-HUS) registry: a community perspective of patients with clinically diagnosed TTP-HUS. Semin Hematol 2004;41:60-7.

20. Furlan M, Robles R, Lammle B. Partial purification and characterization of a protease from human plasma cleaving von Willebrand factor to fragments produced by in vivo proteolysis. Blood 1996;87:4223-34.
21. Furlan M, Robles R, Galbusera M, Remuzzi G, Kyrle PA, Brenner B, et al. Von Willebrand factor-cleaving protease in thrombotic thrombocytopenic purpura and the hemolytic-uremic syndrome. N Engl J Med 1998; 339:1578-84.
22. Gerritsen HE, Robles R, Lämmle B, Furlan M. Partial amino acid sequence of purified von Willebrand factor-cleaving protease. Blood 2001; 98: 1654-61.
23. Peyre C, Wakim M, Mateo R, Genyk Y, Singh G, Selby RR, et al. Unusual cases of jaundice secondary to non-neoplastic bile duct obstruction. Am Surg 2004;70:620-4.
24. Boruchowicz A, Wallaert B, Cortot A, Bouault JM, Paris JC, Colombel JF. Idiopathic acute pancreatitis and sarcoidosis. Gastroenterol Clin Biol 1995; 19:439-41.
25. Terrell DR, Williams LA, Vesely SK, Lämmle B, Hovinga JA, George JN. The incidence of thrombotic thrombocytopenic purpura-hemolytic uremic syndrome: all patients, idiopathic patients, and patients with severe ADAMTS13 deficiency. J Thromb Haemost 2005;3:1432-6.
26. Crawley JTB, Lam JK, Rance JB, Mollica LR, O'Donnell JS, Lane DA, et al. Proteolytic inactivation of ADAMTS13 by thrombin and plasmin. Blood 2005;105:1085-93.
27. Bone RC, Henry JE, Petterson J, Amare M. Respiratory dysfunction in thrombotic thrombocytopenic purpura. Amer J Med 1978;65:262-70.
28. Jackson B, Files JC, Morrison FS, Scott-Conner CEH. Thrombotic thrombocytopenic purpura and pancreatitis. Amer J Gastroenterol 1989;84:667-9.
29. Alvarez MA, Rojas R, Velasco F, Torres A. Resolution of hemolytic-uremic syndrome complicating acute pancreatitis after surgery. J Clin Gastroenterol 1991;13:118-9.
30. Garcia-Cano J, Vazquez Rodriguez de Alba J, Garcia Cabezas J, Diaz-Rubio M. Pancreatitis aguda en el seno de la purpura thrombocitopenica thrombotica. A proposito de dos casos. An Med Interna 1992; 9:551-3.
31. Silva VA. Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome secondary to pancreatitis. Amer J Hematol 1995;50:53-6.
32. Aaron L, Bellaiche G, Coulon A, Lusina D, Nouts A, Ley G, et al. Pancréatite aiguë bilaire compliquee d'un syndrome hémolytique et urémique. Gastroenterol Clin Biol 1997;21:1003-4.
33. Daryanani S, Wilde JT. Relapsing thrombotic thrombocytopenic purpura in association with recurrent pancreatitis. Clin Lab Haematol 1998; 20:317-8.
34. Holt A, Cochran M, Thomas T. Haemolytic uraemic syndrome with acute oedematous pancreatitis. Australian N Z J Med 1998;28:69.
35. Vergara M, Modolell I, Puig-Divi V, Guarner L, Malagelada JR. Acute pancreatitis as a triggering factor for thrombotic thrombocytopenic purpura. Am J Gastroenterol 1998; 93: 2215-8.
36. Varadarajula S, Ramsey WH, Israel RH. Thrombotic thrombocytopenic purpura in acute pancreatitis. J Clin Gastroenterol 2000;31:243-5.
37. Talawalkar JA, Ruymann FW, Marcoux P, Farraye FA. Recurrent thrombotic thrombocytopenic purpura (TTP) as a complication of acute relapsing pancreatitis. Dig Dis Sci 2002; 47:1096-9.
38. Bong JJ, Ammori BJ, McMahon MJ, Kumar A, Turney JH, Norfolk DR. Thrombotic microangiopathy in acute pancreatitis. Pancreas 2002;25:107-9.
39. Minami T, Saito M, Yamamoto T, Kondo S, Ohmori O, Kanayama S. A case of hemolytic uremic syndrome and whole splenic infarction secondary to acute pancreatitis. J Gastroenterol Hepatol 2002;17:1040-1.
40. Boyer A, Chadda K, Salah A, Bonmarchand G. Thrombotic microangiopathy: an atypical cause of acute renal failure in patients with acute pancreatitis. Intensive Care Med 2004;30:1235-9.
41. Ruiz J, Koduri PR, Valdivieso M, Shah PC. Refractory post-pancreatitis thrombotic thrombocytopenic purpura: response to rituximab. Ann Hematol 2005;84:267-8.
42. Sinha A, Rai R. Haemolytic uraemic syndrome following acute pancreatitis. J Pancreas 2005;6:365-8.
43. Swaroop VS, Chari ST, Clain JE. Severe acute pancreatitis. JAMA 2004; 291:2865-8.
44. Whitcomb DC. Acute pancreatitis. N Engl J Med 2006;354:2142-50.
45. Török TJ, Holman RC, Chorba TL. Increasing mortality from thrombotic thrombocytopenic purpura in the United States. Analysis of national mortality data, 1968-1991. Am J Hematol 1995;50:84-90.
46. Miller DP, Kaye JA, Shea K, Ziyadeh N, Cali C, Black C, et al. Incidence of thrombotic thrombocytopenic purpura/hemolytic uremic syndrome. Epidemiology 2004; 15:208-15.
47. Schech SD, Brinker AD, Shatin D, Burgess M. New-onset and idiopathic thrombotic thrombocytopenic purpura: incidence, diagnostic validity, and potential risk factors. Am J Hematol 2006;81:657-63.
48. Banks PA. Epidemiology, natural history, and predictors of disease outcome in acute and chronic pancreatitis. Gastro Endosc 2002;56 Suppl 6: S226-S230.
49. Bhatia M, Wong FL, Cao Y, Lau HY, Huang J, Puneet P, et al. Pathophysiology of acute pancreatitis. Pancreatology 2005;5:5132-44.
50. Kwaan HC, Anderson MC, Gramatica L. A study of pancreatic enzymes as a factor in the pathogenesis of disseminated intravascular coagulation during acute pancreatitis. Surgery 1971;69: 663-72.