JOP. J Pancreas (Online) 2012 Jan 10; 13(1):80-82.

CASE REPORT

Acute Pancreatitis-Induced Thrombotic Thrombocytopenic Purpura

Mohan Gurjar[1], Saurabh Saigal[1], Afzal Azim[1], Samir Mohindra[2], Narayan Prasad[3], Gaurav Srivastava[4]

Departments of [1]Critical Care Medicine, [2]Gastroenterology, [3]Nephrology, and [4]Hematology; Sanjay Gandhi Post Graduate Institute of Medical Sciences. Lucknow, India

ABSTRACT

Context Acute pancreatitis due to thrombotic thrombocytopenic purpura is a well recognized condition. Here, we are reporting a rare converse phenomenon, in which thrombocytopenic purpura occurred secondary to acute pancreatitis. **Case report** A 19-year-old male referred to our intensive care unit with diagnosis of acute pancreatitis with multi-organ dysfunction. He had history of severe abdominal pain and recurrent vomiting about one month ago, requiring hospital admission. There, on diagnostic work-up at admission, abdominal ultrasonography was suggestive of pancreatitis. His serum amylase and lipase were 1,900 and 1,582 U/L, respectively. Other laboratory parameters were within normal limits. He was managed conservatively with intravenous fluids, antibiotics and analgesics; and discharged after about 2 weeks One week after discharge he was readmitted in same hospital with abdominal pain, multiple episodes of bilious vomiting and abdominal distention. Later on he was referred to our intensive care unit; having classical pentad of thrombocytopenic purpura, i.e., thrombocytopenia, micro-angiopathic hemolytic anemia, renal failure, encephalopathy, and fever. His condition improved with plasma exchange therapy and transferred out from our ICU to ward after 10 days of stay. **Conclusion** Thrombocytopenic purpura may be precipitate by acute pancreatitis due to multiple mechanisms. A high clinical suspicion is required to make an early diagnosis and allow early initiation of plasma exchange therapy, resulting in a good prognosis.

INTRODUCTION

Thrombotic thrombocytopenic purpura is a rare prothrombotic disorder classically presented by the pentad of fever, thrombocytopenia, microangiopathic hemolytic anemia, renal failure and neurological manifestations [1]. In thrombocytopenic purpura, there is lack of ADAMTS-13 protease enzyme, either due to the deficiency of this enzyme (congenital) or presence of antibodies against this enzyme (acquired). The ADAMTS-13 enzyme (also known as von Willebrand factor-cleaving protease), cleaves the ultra-large, von Willebrand factor (VWF) multimers which releases from the sub endothelium after endothelial activation or damage [2, 3]. Due to accumulation of ultra-large VWF multimers, extensive platelet aggregation occurs in vasculature of different organ that may manifest clinically as neurological problems, renal dysfunction, and myocardial ischemia [2, 3]. Also, acute pancreatitis due to thrombocytopenic purpura is a well recognized condition because of the same pathogenesis, described in the literature [4]. Here, we are reporting a rare converse phenomenon, in which thrombocytopenic purpura occurred secondary to acute pancreatitis.

Received October 14th, 2011 - Accepted November 14th, 2011

Key words Pancreatitis; Plasmapheresis; Purpura, Thrombotic Thrombocytopenic

Abbreviations VWF: von Willebrand factor

Correspondence Mohan Gurjar
Department of Critical Care Medicine; Sanjay Gandhi Post Graduate Institute of Medical Sciences; Rae Bareli Road; Lucknow (UP) 226014; India
Phone : +91-522-249.5403; Fax: +91-522-266.8017
Email: m.gurjar@rediffmail.com

CASE REPORT

A 19-year-old male referred to our intensive care unit with diagnosis of acute pancreatitis with multi-organ dysfunction. He had history of severe abdominal pain and recurrent vomiting about one month ago, requiring hospital admission. There, on diagnostic work-up at admission, abdominal ultrasonography was suggestive of pancreatitis. His serum amylase and lipase were 1,900 (reference range: 16-108 U/L) and 1,582 U/L (reference range: 0-160 U/L), respectively. Other laboratory parameters were: hemoglobin 12.8 g/dL (reference range: 14-18 U/L), total leukocyte count 18,000 mm^{-3} (reference range: 4,000-10,000 U/L), platelets 230,000 mm^{-3} (reference range: 150,000-400,000 U/L), total bilirubin 0.46 mg/dL (reference range: 0.1-1.3 U/L), blood urea nitrogen 20 mg/dL (reference range: 8-25 U/L), and creatinine 0.8 mg/dL (reference range: 0.5-1.6 U/L). Computer tomography (CT) of abdomen was done on day 4 of illness, which revealed necrosis of body with mild fluid collections. Diagnosis of acute necrotizing pancreatitis was made and managed conservatively with intravenous fluids,

antibiotics and analgesics. He was discharged after about two weeks with advice of tablet pantoprazole 40 mg once a day till follow-up; and his blood investigations before discharge from the hospital were: hemoglobin 13.3 g/dL, total leukocyte count 8,000 mm^{-3}, platelets 264,000 mm^{-3}, total bilirubin 0.26 mg/dl, blood urea nitrogen 16 mg/dL, and creatinine 0.65 mg/dL.

One week after discharge he was readmitted in same hospital with abdominal pain, multiple episodes of bilious vomiting and abdominal distention. During this admission, his laboratory parameters were: hemoglobin 10.5 g/dL, total leukocyte count 9,200 mm^{-3}, platelets 63,000 mm^{-3}, total bilirubin 1.93 mg/dL, blood urea nitrogen 58 mg/dL, creatinine 3.19 mg/dL, SGOT 55 U/L, SGPT 29 U/L, prothrombin time 12.8 seconds (control 11.8 seconds). Repeat CT scan of abdomen was done (day 22 of illness), which revealed same findings as above, no new collection. In view of rising creatinine and worsening of anemia and thrombocytopenia, diagnosis of severe acute pancreatitis with sepsis leading to multi-organ dysfunction was made; and referred to our intensive care unit (ICU).

At time of admission in ICU he was febrile (38.8 °C, 101.8°F), pale, drowsy, heart rate 110 min^{-1}, blood pressure 150/90 mmHg, respiratory rate 16-18 min^{-1}. On per abdominal examination there was no abdominal distention. His urine output was 75-100 mL/h. Laboratory investigations revealed hemoglobin 4.9 g/dL, total leukocyte count 12,000 mm^{-3}, platelets 22,000 mm^{-3}, reticulocyte count 4%, general blood picture showed schistocytes, blood urea nitrogen 158 mg/dL, creatinine 6.9 mg/dL, total bilirubin 10.2 mg/dL, direct bilirubin 6.99 mg/dL, SGOT 67 IU/L, SGPT 94 IU/L, prothrombin time 14 seconds (control 11.8 seconds), fibrinogen level 294 mg/dL, LDH 3,927 mg/dL. Due to significant drop in hemoglobin level, possibility of bleed (intra-luminal or retroperitoneal) was ruled out by ultrasonography, nasogastric lavage, stool for occult blood; and subsequently CT angiography of the abdomen was also turned out to be normal. Coombs test was negative. Possibility of infection was also ruled out by doing investigations for malaria, dengue, leptospirosis and routine blood culture. As per International Society of Thrombosis and Haemostasis disseminated intravascular coagulation scoring system, patient was not compatible with overt disseminated intravascular coagulation due to his normal fibrinogen level and also, he never had prolonged prothrombin time (all reports were less than 3 seconds prolonged). Patient was diagnosed to have thrombocytopenic purpura, as he was having classical pentad of thrombocytopenic purpura, i.e., thrombocytopenia, micro-angiopathic hemolytic anemia, renal failure, encephalopathy and fever; plasmapheresis at 40 mL/kg/cycle with total 7 cycles was initiated. After 3rd cycle of plasmapheresis, patient showed dramatic improvement in both clinically and laboratory parameters as shown in Table 1. Due to unavailability, we could not measured ADAMTS 13 level in our case. He was transferred out from our ICU to ward after 10 days of stay.

DISCUSSION

In a recent article, Chaudhry *et al*. reviewed all published cases (27 patients) of acute pancreatitis-induced thrombocytopenic purpura [5]. About two third of patients were male with median 2 days (1-15 days) of interval between diagnosis of thrombocytopenic purpura after the diagnosis of pancreatitis [5]. Three patients have relapse thrombocytopenic purpura after second episode of pancreatitis. In our case, thrombocytopenic purpura was diagnosed after 3 weeks of diagnosis of acute pancreatitis, during his second admission due to recurred abdominal pain and vomiting but with same findings of pancreatitis as previous one in repeat CT of the abdomen.

However, in acute pancreatitis-induced thrombocytopenic purpura, the ADAMTS 13 deficiency was

Table 1. Laboratory parameters of the patient during his illness.

Day of illness (day in ICU)	***Reference range***	**1 First admission**	**15 Discharge**	**21 Re-admission**	**22**	**23**	**24 (1) [a]**	**25 (2)**	**26 (3)**	**27 (4)**	**28 (5)**	**29 (6)**	**30 (7)**	**31 (8)**	**32 (9)**
Hemoglobin (g/dL)	*14-18*	12.8	13.3	10.5	8.5	5.9	4.9	6.9	6.7	6.0	6.4	7.4	8.0	8.3	8.5
Platelet (x1,000 mm^{-3})	*150-400*	230	264	63	58	23	22	45	78	82	161	234	277	309	312
LDH (mg/dL)	*85-450*	228	277	1,761	-	-	3,927	-	-	1,937	-	1,181	-	893	331
Total bilirubin (mg/dL)	*0.1-1.3*	0.46	0.26	1.93	-	5.91	10.22	8.17	-	5.20	-	-	-	1.20	0.90
Direct bilirubin (mg/dL)	*0-0.4*	-	0.08	0.61	-	3.22	6.99	5.75	-	3.10	-	-	-	0.80	0.45
SGOT (IU/L)	*5-40*	-	42	55	-	77	67	74	-	55	-	-	-	42	42
SGPT (IU/L)	*5-40*	-	52	29		15	94	59		18				32	16
BUN (mg/dL)	*8-25*	20	16	58	100	139	158	-	-	76	-	61	-	25	18
Creatinine (mg/dL)	*0.5-1.6*	0.80	0.65	3.19	4.75	5.83	6.90	-	-	5.83	-	5.57	-	1.90	2.00
Prothrombin time (s)	*Control±1.0*	-	14.2	12.8	-	-	14.0	-	-	-	-	-	-	-	-
Control			*12.8*	*11.8*			*11.8*								
Plasma exchange therapy		-	-	-	-	-	+	+	+	+	+	+	+	-	-

BUN: blood urea nitrogen

[a] General blood picture at day 24 (first ICU day): schistocytes

not found consistent and it was only moderate in most reported cases. Out of 12 cases, in which ADAMTS 13 was measured, three patients had normal values while only two patients had very severe deficiency of this enzyme [5]. This raises doubts about the sole responsibility for this enzyme in the pathogenesis of thrombocytopenic purpura, a concept which has been supported by experimental observations where the deficiency of the enzyme itself was not found to be causative for thrombocytopenic purpura [6].

As acute pancreatitis is an inflammatory state, there are increased levels of cytokines including interleukins (IL-8, IL-1, IL-6) and tumor necrosis factor-alpha (TNF-alpha), that may stimulate ultra-large, VWF multimer release from endothelial cells [7, 8]. This could be the reason for relative deficiency of ADAMTS-13 protease enzyme in acute pancreatitis, which gets consumed quickly [8]. Similar concept, i.e., opposite changes of ADAMTS 13 and VWF, has been found in patients after cardiac surgery [9].

Furthermore, the inflammatory state may augment the risk of thrombocytopenic purpura through the activation of complement system by pancreatic enzymes, leading to micro-vascular damage and ADAMTS 13 deficiency [10]. The role of nitric oxide (NO) may also be relevant to development of thrombocytopenic purpura following acute pancreatitis [8]. Endothelial NO has vasodilator properties and can behave as a strong platelet anti-aggregator agent, thus maintaining the patency of the vasculature. There is evidence that pancreatic endothelial NO synthase is decreased in acute pancreatitis and this may therefore predispose to the development of a thrombotic microangiopathy such as thrombocytopenic purpura [8, 11]. Moreover, after development of thrombocytopenic purpura, condition persist due to decrease in NO levels, as free hemoglobin scavenges NO directly, and arginase (released from the hemolyzed red cell) metabolizes arginine, an essential precursor for NO synthesis [12, 13].

Almost every reported case of acute pancreatitis-induced thrombocytopenic purpura was treated with plasma exchange therapy (2-19 cycles), as it helps in removing large von Willebrand factor molecules and providing fresh VWF molecule, leading to resolution of thrombocytopenic purpura in all but one case [8].

CONCLUSION

Thrombocytopenic purpura is a life threatening but treatable condition that may precipitate by acute pancreatitis due to multiple mechanisms, including excess release of VWF in response to endothelial damage, activation of complement system, deficiency of nitric oxide, in addition to deficiency of ADAMTS 13 enzyme. A high clinical suspicion is required to make an early diagnosis and allow early initiation of plasma exchange therapy, resulting in a good prognosis.

Conflict of interest The authors have no potential conflict of interest

References

1. George JN. Clinical practice. Thrombotic thrombocytopenic purpura. N Engl J Med 2006; 354:1927-35.

2. 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; 102: 60-8.

3. Sadler JE. Von Willebrand factor, ADAMTS13, and thrombotic thrombocytopenic purpura. Blood 2008; 112:11-8.

4. Ridolfi RL, Bell WR. Thrombotic thrombocytopenic purpura. Report of 25 cases and review of the literature. Medicine 1981; 60:413-28.

5. Chaudhry MS, Saweirs MWM. Thrombotic thrombocytopenic purpura precipitated by acute pancreatitis. Transf Apheres Sci 2011 .

6. 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.

7. Bernardo A, Ball C, Nolasco L, Moake JF, Dong J. 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.

8. Thachil J. Lessons from acute pancreatitis-induced thrombotic thrombocytopenic Purpura. Eur J Int Med 2009; 20: 739-43.

9. Mannucci PM, Parolari A, Canciani MT, Alemanni F, Camera M. Opposite changes of ADAMTS 13 and von Willebrand factor after cardiac surgery. J Thromb Haemost 2005;3:397-9.

10. Ruiz-Torres MP, Casiraghi F, Galbusera M, Macconi D, Gastoldi S, Todeschini M, et al. Complement activation: the missing link between ADAMTS-13 deficiency and microvascular thrombosis of thrombotic microangiopathies. Thromb Haemost 2005;93:443-52.

11. DiMagno MJ, Williams JA, Hao Y, Ernst SA, Owyang C. Endothelial nitric oxide synthase is protective in the initiation of caerulein induced acute pancreatitis in mice. Am J Physiol: Gastrointest Liver Physiol 2004; 287: 80-7.

12. Olson JS, Foley EW, Rogge C, Tsai AL, Doyle MP, Lemon DD. NO scavenging and the hypertensive effect of hemoglobin-based blood substitutes. Free Radic Biol Med 2004;36:685-97.

13. Schnog JJ, Jager EH, van der Dijs FP, Duits AJ, Moshage H, Muskiet FD, et al. Evidence for a metabolic shift of arginine metabolism in sickle cell disease. Ann Hematol 2004;83:371-5.