症 例

CHDF saved a patient with acute pancreatitis and hyperlipidemia at the terminal stage of gestation

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Introduction

Acute pancreatitis is rare during pregnancy or puerperium with only about 100 cases reported so far in Japan. It often results in death of both mother and fetus, making the early diagnosis and treatment of acute abdominal disorders during pregnancy an urgent priority. In this report, we describe a case of acute pancreatitis complicated by hyperlipidemia that occurred during the terminal stage of pregnancy, and review the characteristics of 49 previously reported cases[1~3].

Key word : acute pancreatitis, hyperlipidemia, parturient Plasma exchange, contineous hemodiafiltratio

Case presentation

The patient was a 35-year-old woman who was pregnant twice previously with normal childbirth. She was 160cm tall and weighed 67kg. Nothing in the patient's history suggested alcohol addiction or cholelithiasis. Her mother had mild hyperlipidemia. The patient had a history of toxemia of pregnancy at the birth of her first child in 1996 and of hyperlipidemia at birth of her second child in 1999. Both children were delivered vaginally and were healthy. The third pregnancy proceeded normally, but the patient complained of nausea on the 5th day of the 38th week of gestation (January 9, 2001). Pain then developed in the epigastric region and the back. Laboratory examinations done at a nearby clinic showed very high levels of serum amylase (1129 IU), total cholesterol (1520 mg/dl), and triglycerides (13890 mg/dl). The diagnosis was acute pancreatitis complicated by hyperlipidemia. On day 1 of hospitalization, the fetus was considered in distress and an emergency cesarean section was performed. The fetus had already died. A large hematoma (chyle-like, odorless and highly viscous) was found in the mother's retroperitoneum, and drainage tubes were placed at 5 sites including the pancreatic bed. During the operation hemodynamics became unstable. The trachea was intubated, and the patient was transferred to the intensive care unit (ICU) of our hospital.

On admission, the blood pressure was 82/54 mmHg; the pulse was regular at 190 beats/min. The patient's consciousness was 2-2-1(5) on the Glasgow coma scale. The face was pallid with an agonized look. The extremities were cold and the abdomen was swollen. Copious bile continuously flowed out of the drainage tubes. Laboratory examinations showed a high concentration of chyle in the serum. The serum total cholesterol level was 1042mg/dl, the triglyceride level was 6200 mg/dl, and the blood and urine amylase levels were 815 IU/l and 4336 IU/l, respectively. Blood sugar was 197 mg/dl, but urine sugar was negative. The total serum protein level could not be determined. The total calcium level was only 5.7 mg/dl.

An abdominal radiogram showed distinct intestinal

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gas. Abdominal computed tomographic (CT) scanning (Fig) showed swelling of the pancreas. A pelvic CT scan revealed no anomaly in the uterus, and a CT scan of the brain showed no marked changes.

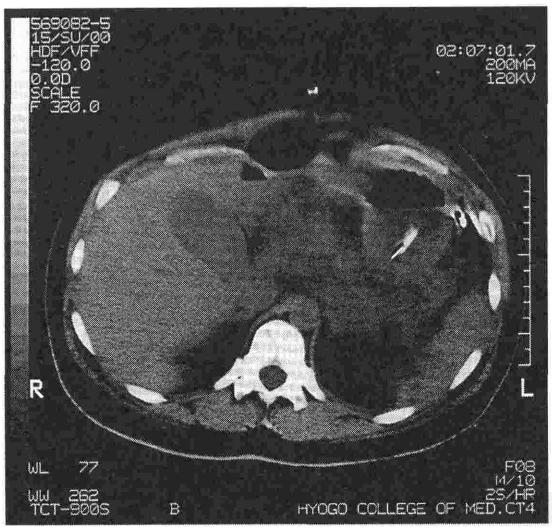

Fig. Abdominal computed tomographic (CT) scanning immediatery after surgery

The CT showed swelling of the pancreas with an irregular margin and a partially heterogeneous core. Inflammation of the adjacent fat extended from the peritoneum to the pronephric sub cavity.

To prevent acute pancreatitis and disseminated inravascular coagulation, a protease inhibitor (gabexate mesilate, 1500 mg/day) and a low molecular heparin preparation (Fragmin®, 5000 units/day) were administered. When the systolic blood pressure recovered to about 110 mmHg, plasma exchange was carried out for 3 hours with 3100 ml of fresh frozen plasma as replacement fluid, using a membrane filter (Plasma-flow OP-08W, Asahi Medical, Osaka, Japan). Plasma exchange was followed by continuous hemodia-filtration (CHDF) (blood flow 80 ml, dialysate 400 ml, replacement fluid 400 ml, filtrate 800 ml, for 18 hours in total, using Sublood B® for dialysate and replacement fluid). On day 3, plasma exchange was repeated (replacement volume 2980 ml, at the same conditions as before). Due to the improvement in hemodynamics and respiratory functions, the patient was extubated. The serum total cholesterol and triglyceride levels gradually decreased, and the patient was transferred to a general ward on day 6 (Table).

Discussion

Acute pancreatitis can be caused by various factors,

Table. Perioperative Laboratory Data

			2001.1.11	2001.1.12	2001.1.13	2001.1.14	2001.1.15	2001.1.16	2001.1.18	2001.1.23	2001.1.30
	normal range	unit	OD	1D	2D	3D	4D	5D	7D	11D	18D
TP	6.5-8.3	g/dl	3.9	nm	7.5	5.7	5	5.1	5	6.8	6.8
T-bil	0.2-1.2	mg/dl	3.1	1.5	1.8	0.9	0.7	1.6	2.9	3.7	1.6
AST	10-35	U/l	60	nm	76	65	36	39	20	30	24
ALT	5-35	U/l	792	nm	19	35	33	43	23	24	26
S-Amy	40-130	U/l	1297	815	772	296	166	115	87	116	154
U-Amy	50-500	U/l		4336	3856	1173	1707	1297	1949	560	2008
Crn	0.5-1.2	mg/dl	2.2	0.87	0.94	0.39	0.38	0.43	0.39	0.56	0.47
Ca	8.6-11.0	mg/dl	5.5	5.7	5.4	9.7	6.3	6.4	7	8	7.9
T-cho	130-220	mg/dl	1142	1042	608	424	249	294	175	143	139
TG	50-150	mg/dl	13010	6200	3291	2086	625	662	261	232	239
LDL-cho	85-140	mg/dl	-	55	78	75	110	137	-	-	-
HDL-cho	40-75	mg/dl	-	10	19	22	30	29	-	-	-
CRP	0.3以下	mg/dl	26	23	15.5	15.8	6.7	12.4	29.8	23.5	6.6

nm: not measured

TP: total protein, T-bil: total-bilirubin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, S-Amy: serum amylase, U-Amy: urine amylase, Crn: creatinine, Ca: calcium, T-cho: total cholesterol, TG: triglyceride, LDL-cho: low density lipoprotein-cholesterol, HDL-cho:high density lipoprotein-cholesterol, CRP: C-reactive protein

such as cholelithiasis, alcohol addiction, drugs, hyperparathyroidism, and hyperlipidemia. The onset of acute pancreatitis during pregnancy is rare, with an estimated incidence of 0.03%[4,5]. In Japan, less than 10% of all cases of acute pancreatitis occurring during pregnancy are associated with cholelithiasis[5], while in Europe and North America, cholelithiasis is found in about 50% of cases. Several theories have been proposed to explain the mechanism of acute pancreatitis during pregnancy. Increased abdominal pressure due to pregnancy may constrict the bile duct and impair pancreatic blood flow[5]. Alternatively, elevated progesterone levels may contract the duodenal mucosa, biliary tract, and the sphincter of Oddi muscle, resulting in bile retention[6]. On the other hand hyperlipidemia may be induced physiologically in pregnant women; plasma lipid levels begin to rise from the third month of pregnancy, reaching peak levels in the 33rd week[7]. Yoshioka and Eguchi.[8] have reported that hyperlipidemia occurs in 31.3% of pregnant women during the terminal stage of pregnancy, with serum cholesterol levels 0.5 to 1.5 times higher and serum triglyceride levels 1.5 to 2.5 times higher than the respective values in non-pregnant women. This marked hyperlipidemia during pregnancy may be attributed to increased triglyceride synthesis in the liver caused by increased release of fatty acids and decreased hydrolysis of very-low-density lipoprotein (VLDL) by lipoprotein lipase (LPL) in response to estrogen[9,10]. Other theories suggest that pancreatitis evolves from hyperlipidemia. Havel, et al.[11] has proposed that chylomicron and VLDL, accumulating in high levels in the blood during pregnancy, are hydrolyzed by lipases in the pancreatic capillaries, increasing the activities of platelets and coagulation factors. The consequent release of large quantities of free fatty acids induces micro thrombosis and lesions in the pancreatic capillaries, leading to pancreatitis.

We reviewed 49 reported cases of acute pancreatitis with hyperlipidemia that developed during pregnancy in Japan, including our patient. The ages of the patients, although some were unavailable, ranged from 22 to 35 years (mean 29.8 years). In 88% of the patients, acute pancreatitis with hyperlipidemia developed in the 28th week of gestation or later, as compared to the 38th week with our patient. Pancreatitis occurred during the first pregnancy in 10 patients and during subsequent pregnancies in 20. Most cases developed in multiparous women. In 88% of the patients, the associated hyperlipidemia was type V according to the World Heath Organization classification. The mean serum triglyceride level was extremely high (4842 mg/dl). The triglyceride level in our patient was 13010 mg/dl, the highest among the cases reported in Japan. This triglyceride level fell to 6200 mg/dl 4 hours after the cesarean section. This finding suggests that parturition has a profound effect on serum lipid levels.

Pancreatitis was treated by abdominal surgery in 44.7% of the patients and by drainage in 55.6%. Cesarean section was done in 88% of the women who underwent laparotomy. The maternal mortality rate was 5.4%; all fetuses or newborns of these women died. The fetal mortality rate was 18.9% overall and 29.4 % with women who underwent cesarean section. This slightly higher rate of fetal mortality may be attributed to the severe nature of pancreatitis among women who received cesarean section or to decreased production of pulmonary surfactants by newborns delivered before term.

The pathogenesis of severe acute pancreatitis remains controversial. Pancreatic enzymes may be activated by conditions, such as alcohol addiction, cholelithiasis and leak-out from the pancreas. These enzymes are then carried by the blood stream to a remote organ, resulting in disorder.

Recently, however, it has been proposed that intrapancreatic overproduction of cytokines or other humoral mediators induces cellular dysfunction directly or as a consequence of impaired tissue oxygen metabolism, leading to the functional failure of organs containing these cells[12,13]. In this respect, severe acute pancreatitis can be considered an aggravated form of systemic inflammatory response syndrome (SIRS). Acceptance of the concept of SIRS would justify treatment with humoral mediators.

Two major causes of death from severe acute

pancreatitis are multiple organ failure early after onset and sepsis due to infectious pancreatic necrosis or pancreatic abscess later in the disease. Intensive care for severe acute pancreatitis should include therapy for inflammation of the pancreatic parenchyma, SIRS, and organ failure, as well as the treatment and prophylaxis of infection. Treatment of either pancreatitis or SIRS should include blood purification. The objectives of blood purification are to eliminate various humoral mediators released by the pancreas or produced by inflammation or infection foci triggered by pancreatitis, to prevent or treat multiple organ failure, and to provide mechanical support and promote functional replacement against organ failure, particularly that involving the kidney and liver, thus preventing disease progression or hastening healing or remission.

Elimination of a substance by blood purification depends primarily on its molecular weight and secondarily on its protein-binding properties. It is therefore necessary to estimate the molecular weight of substance to be removed and to select the method of blood purification best suited for that substance. Usually, blood purification for pancreatitis is done by peritoneal perfusion and peritoneal dialysis because these techniques can directly remove pancreatic enzymes and humoral mediators such as cytokines from ascitic fluid, peritoneal macrophages primed by these factors, and necrotic debris present in the abdominal cavity. Peritoneal perfusion can effectively eliminate pancreatic enzymes of large molecular weight from the blood[14]. However, this treatment has several drawbacks, such as considerable protein and amino acid loss, difficulty in water and electrolyte management, and a high incidence of complications such as septicemia. In contrast, CHDF can efficiently remove from the blood most factors causing pancreatitis, such as enzymes released from the pancreas (e.g., phospholipase A2 and trypsin) cytokines, and humoral mediators. This technique has several advantages, such as minimal impact on hemodynamics, conservation of biologically useful proteins, and easy management of water, electrolyte and acid-base balance. One drawback of CHDF, however, is the risk of hemorrhagic complications due to continuous use of anticoagulants. These complications include gastrointestinal bleeding and recurrent hemorrhage. Another method used for blood purification in patients with severe acute pancreatitis is plasma exchange[15]. This method has several advantages, including the ability to remove macromolecular substances such as albumin and globulin, and concurrent supplementation of protease inhibitor from frozen fresh plasma and elimination of pathogenic substances. However, since large volumes of frozen fresh plasma are used, CHDF should be done cautiously, especially in view of the risk of transmitting infections such as hepatitis and the costs involved.

We used plasma exchange and CHDF to treat acute pancreatitis complicated by severe hyperlipidemia in our patient. CHDF was performed not only to effectively manage water and electrolytes, but also to prevent progression of SIRS to multiple organ failure. Most of humoral mediators have molecular weights as high as 20,000 to 40,000, as compared with 14,000 to 58,000 for pancreatic enzymes. In patients undergoing CHDF, which cannot remove macromolecules weighing 30,000 or greater, the use of plasma exchange should be considered when there is no improvement in response to CHDF alone or when serum levels of amylase or other pancreatic enzymes remain abnormally high. Plasma exchange can eliminate substances weighing up to 150,000 to 200,000 and concurrently supplement protease inhibitor. In our patient, acute pancreatitis was caused by hyperlipidemia. Plasma exchange is considered the most efficient means of eliminating both blood lipids and harmful factors associated with pancreatitis.

Conclusion

Two sessions of plasma exchange and CHDF for one day effectively lowered serum levels of lipids and other macromolecules thereby saving the life of a woman with acute pancreatitis complicated by severe hyperlipidemia in the terminal stage of the pregnancy.

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