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CASE REPORT

Acute Pancreatitis Complicated by Sheehan's Syndrome: A Case Report and Literature Review

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Key words: acute pancreatitis; Sheehan's syndrome; pituitary crisis; hypertriglyceridemia

Abstract A 44-year-old woman was transferred to the ICU of the First Affiliated Hospital of Jinan University for 2 days of persistent epigastric pain and 7 hours of unconsciousness. Her admission diagnosis was severe acute necrotizing pancreatitis (hypertriglyceridemia type) with multiple organ dysfunctions. The results of CT revealed a small area of necrotizing pancreatitis, which was not consistent with the severe clinical manifestations. Considering lack of hair and history of postpartum hemorrhage, hormone examination was carried out. According to the results of the examination, she was further diagnosed as Sheehan's syndrome and pituitary crisis. After hormone replacement therapy, her condition improved rapidly.

SEVERE acute pancreatitis (SAP) is a serious disease with many severe complications and has as high as 20%-25% of mortality rate. SAP is mainly caused by biliary stones, excessive alcohol consumption and hypertriglyceridemia. Sheehan's syndrome, also known as postpartum hypopituitarism, is caused by ischemic necrosis of the pituitary because of postpartum hemorrhage. Sheehan's syndromes associated SAP is a really rare condition. There are only five cases reported on this issue in published literatures.[1-5] Here, we present a case admitted to our hospital and compared her with the other five cases.

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CASE DESCRIPTION

A 44-year-old female farmer was transferred to the First Affiliated Hospital of Jinan University on account of two days of continuous upper abdominal pain and seven hours of confusion. She was diagnosed as acute pancreatitis in a local hospital. After treated

immediately, she did not improve. Even worse, she lapsed into conscious confusion and had lowered blood pressure, decreased oxygen saturation and less urine output, and finally was transferred to our hospital.

On admission, her temperature was 37°C, blood pressure 85/57 mm Hg, pulse rate 125 beats/min, and respiration 25 breaths/min. Physical examination showed abdominal distension, abdominal tension, upper abdominal tenderness and rebound tenderness, and decreased bowel sound. Laboratory test on admission revealed white blood cell 13.22×10^9/L, neutrophils 9.19×10^9/L, hemoglobin 101 g/L, red blood cell 3.71×10^{12}/L, platelet 194×10^9/L; amylase 71 U/L, calcium 1.66 mmol/L, potassium 3.5 mmol/L, sodium 131.0 mmol/L, chlorine 97.6 mmol/L, glucose 11.04 mmol/L, albumin 37.7 g/L, triglycerides (TG) 11.47 mmol/L, creatinine 323 μmol/L, urea nitrogen 9.81 mmol/L, lactic acid dehydrogenase 611 U/L, creatine kinase 1257 U/L, α-hydroxybutyrate dehydrogenase 323 U/L, high-sensitivity C-reactive protein 306.1 mg/L; pH 7.24, carbon dioxide partial pressure 6.00 kPa, oxygen partial pressure 9.4 kPa, HCO^-_3 3-19 mmol/L. Abdominal CT showed pancreas enlargement, pancreatic necrosis in the area of the head and neck, effusion surrounding the pancreas, omental bursa, spleen, kidney, right adrenal gland and bilateral colons (**Figure 1**). Ultrasonography revealed acute pancreatitis not accompanied with gallbladder stones and bile duct stones.

The diagnosis was severe acute necrotizing pancreatitis (hypertriglyceridemia type) complicated by multiple organ dysfunctions. She was immediately transferred to the ICU and received treatment. In addition to gastrointestinal decompression and supportive treatment, oxygen therapy, dopamine and continuous renal replacement therapy were administered.

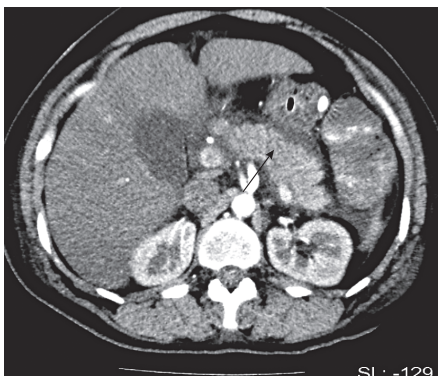

Figure 1. Abdomen CT scan on admission. The area indicated by the arrow is the swelling and exudation of the pancreas.

After giving birth to a child 22 years ago, she has been suffering postpartum menopause caused by postpartum hemorrhage. She received no hormone replacement therapy before. Given loss hair and a history of hypertriglyceridemia appeared after postpartum hemorrhage, hormone tests were performed. The results showed free triiodothyronine (FT3) 1.36 (3.5-6.5) pmol/L, free thyroid hormone (FT4) 2.75 (11.5-22.7) pmol/L, thyroid stimulating hormone (TSH) 0.328 (0.55-4.78) mIU/L, estradiol 65 (25-309) pg/ml, progesterone <0.1 ng/ml, follicle-stimulating hormone (FSH) 0.32 (5-40) IU/L, luteinizing hormone (LH) 0.13 (4.2-126) IU/L, prolactin <0.6 (5.0-40.0) ng/ml; normal levels of serum cortisol, urinary free cortisol 22.57 (32.4-278.6) nmol/24 h. After family hypertriglyceridemia was excluded, a diagnosis of Sheehan's syndrome and pituitary functional crisis was made. On the next day she regained consciousness after treated with 200 mg/d hydrocortisone. From the second day a small dose of levothyroxine (25 μg/d) was given, and increased gradually to 100 μg/d after 1 week. Her blood pressure was maintained approximately at the level of 92/67 mm Hg and her urine output increased to 260 ml/h after dopamine was stopped. Electrolyte disorders including hyponatremia and hypokalemia were corrected as well. Prior to discharge, swelling suddenly appeared in her right lower extremity with D-dimer value as high as 2715 ng/ml. Ultrasound showed decreased blood flow velocity in the right femoral vein, saphenous vein, popliteal vein, posterior tibial vein, which indicated mural thrombus in the right lower extremity. After low molecular weight heparin and magnesium sulfate wet packing were administrated for 2 weeks, she was improved and discharged.

DISCUSSION

Sheehan's syndrome, which was first reported by Sheehan in 1937, refers to serious complications arising from pituitary avascular necrosis led by postpartum hemorrhage,[6] and its incidence rate is as high as 10-20/100 000.[7] Its pathogenesis is not clear so far. It may attribute to hypopituitarism induced by excessive postpartum hemorrhage.[8] Patients with Sheehan's syndrome often present adrenal failure, hypogonadism and secondary hypothyroidism. The clinical manifestations are fatigue, anemia, amenorrhea, dry skin and

hair loss. Severe hypopituitarism can lead to coma or even death.[9, 10]

The manifestations of this patient indicated that she had Sheehan's syndrome associated SAP. The laboratory studies revealed she had a serious hypothyroidism and lower cortisol function. Thyroxine plays an important role in the biosynthesis and catabolism of cholesterol by participating in regulating metabolism of lipoprotein. A reduction in low-density lipoprotein receptor activity, as well as the activation of triiodothyronine controlled sterol regulatory element-binding protein 2, which was identified as a modulator of cholesterol biosynthesis through regulating rate-limit degrading enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase activity, might cause hypercholesterolemia in hypothyroidism.[11] In addition, a decrease in the stimulating actions of thyroid hormone on lipoprotein lipase, facilitates the catabolism of TG, thereby lowering TG level in blood.[12] The elevated low density lipoprotein and TG has been shown in hypothyroidism patients.[13, 14] TG level higher than 11.35 mmol/L is generally considered one of the important factors causing acute pancreatitis to happen.[15, 16] After excluding family hypertriglyceridemia, this case with TG level being as high as 11.47 mmol/L (1011 mg/dl) was diagnosed with hypertriglyceridemia pancreatitis.

The mechanism underlying hypertriglyceridemia induced acute pancreatitis was complicated. It has been proposed that the hydrolysates of TG catalyzed by pancreatic lipase extruding from the acinar cells of the pancreas can lead to the accumulation of free fatty acids, which can exert toxic effects on the acinar cells and capillaries in the pancreas.[17] In addition, the substantially formed chylomicrons in the pancreatic capillaries could congest the capillaries, thus leading to ischemia and acidosis. The enhanced free fatty acids can activate trypsinogen, which may finally induce acute pancreatitis.[18]

There are only five case reports on acute pancreatitis with Sheehan's syndrome in published literatures (**Table 1**).[1-5] Among these cases who aged from 32 to 52 years, this disorder occurred 7 years after menopause. Two of them had hypertriglyceridemia. In etiology, some scholars believed that estrogen replacement therapy is a direct cause of hypertriglyceridemia.[9] However, we thought this was not the case because our patient did not take any hormone-related drugs. For this cases, therefore, the occurrence of acute pancreatitis with Sheehan's syndrome might be the result of multiple factors such as hypopituitarism, thyroid hormone, and hypertriglyceridemia.

The patient suffered from respiratory failure, circulatory failure, and unconsciousness, which indicated that pancreatic encephalopathy occurred, but pituitary crisis cannot be excluded. Pancreatic encephalopathy and pituitary crisis may have mutually reinforcing effects and give rise to rapid deterioration of the patient's conditions. Among these cases, two of them had pancreatic necrosis, four had thyroid hormone deficiency, four had hypotention and even presented more severe after treatment. After acute pancreaitis treatment, the symptoms did not improve significantly, with an increased amylase level and persistent hypoglycemia and hypocalcemia, which suggested pancreatitis became worse.[2-4] Repeated CT scan showed no obvious lesions, which was inconsistent with the severe manifestations of pancreatitis.[5] After hormone replacement therapy, four of them improved well,[2-5] which proved that pituitary crisis occurred. Pituitary crisis and pancreatitis can promote each other. Hypothyroidism may cause bacterial translocation by reducing intestinal mucosal barrier function, thus aggravating infection.[5]

On the tenth day after admission, the patient experienced gradual onset of swelling and pain involving the right leg. Ultrasound on the lower limbs revealed a thrombosis in the right popliteal vein, right femoral vein, right saphenous vein, and right posterior tibial vein. After retrieving literatures, we found a few reports on Sheehan's syndrome complicated by deep vein thrombosis. Shahnaz *et al*.[19] reported a case whose thrombosis might be induced by disorder of autoimmunity in 2013. In addition, Tanriverdi *et al*.[20] regarded that hypopituitarism and growth hormone deficiency could increase the risk of cardiovascular thrombosis. For this case, the high blood viscosity brought about by tissue fluid exudation which was stimulated by a large number of inflammatory cytokines, as well as lying in bed for a long period, may increase the risk of deep venous thrombosis.

As far as treatment, the patient received plasma exchange for 3 times. As soon as hypopituitarism was confirmed, she received hormone replacement immediately as well. Antilipemic agents, such as fibrates, were used when plasma exchange therapy finished. It has been reported that plasma exchange is effective for hypertriglyceridemia-induced acute

Table 1. Clinical data of five acute pancreatitis cases with Sheehan's syndrome

Items	Zhang *et al*.[1]	He *et al*.[2]	Shen *et al*.[3]	Zhen *et al*.[4]	Chen *et al*.[5]
Year of publication	2006	2006	2011	2011	2017
Age (yrs)	32	50	52	48	40
Time of menopause (yrs)	7	25	24	25	9
Blood pressure (mm Hg)	78/50	60/20	80/60	80/55	135/82
Amylase (U/L)	301	284	361	630	87.9
Pancretic necrosis	-	+	+	-	-
Calcium (mmol/L)	1.79	1.34	unavailable	2.4	1.87
Sodium (mmol/L)	unavailable	129.4	unavailable	125	135.9
Potassium (mmol/L)	unavailable	unavailable	unavailable	3.4	3.90
Glucose (mmol/L)	unavailable	13.6	unavailable	11.6	10.0
FT3 (pmol/L)	unavailable	31.62	0.4	1.22	1.49
FT4 (pmol/L)	unavailable	2.69	0.75	8.0	2.53
TSH (μIU/ml)	unavailable	normal	0.972	normal	normal
Estrogen	unavailable	decrease	normal	decrease	decrease
Cortisol	unavailable	decrease	unavailable	normal	normal
Triglyceride (mmol/L)	29.06	12.77	unavailable	unavailable	unavailable
Hormone deficiency	estrogen	thyroid, progesterone, cortisol	thyroid hormone	thyroid, progesterone, estrogen	thyroid, estrogen
HRT	estrogen	stop HRT	stop HRT	no	no

FT3: free triiodothyronine; FT4: free thyroid hormone; TSH: thyroid stimulating hormone; HRT: hormone replacement therapy.

pancreatitis.[21-24] Plasmapheresis should be continued until TG level lower than 5.67 mmol/L.[24] Moreover, enhancing lipoprotein lipase activity with insulin and heparin has been proved to be an effectively alternative modality for patients with hypertriglyceridemia-induced acute pancreatitis.[25-27] In order to prevent the deterioration of pituitary crisis, glucocorticoids were adminstrated first and followed by thyroid hormones. Not giving thyroid hormone first can avoid the increase in whole body metabolism, which may be helpful in minimizing glucocorticoids dosage. Furthermore, thyroid hormone given first would block the hormonal feedback loop induced by hypopituitarism and secondary adrenal atrophy, subsequently inadequacy of body's glucocorticoid supply would be exacerbated, which may deteriorate adrenal crisis.[28] After hormone replacement, the patient's condition improved rapidly, which in other hand confirmed that her unconsciousness was the result of pituitary crisis not pancreatic encephalopathy.

In conclusion, although Sheehan's syndrome with SAP is relatively infrequent, we still need to pay more attention on it. Our case and the other five reported cases showed that patients with Sheehan's syndrome accompanied by acute pancreatitis always present more severe even when no pancreatic necrosis appeares or necrosis is slight. Therefore, making a diagnosis just based on the results of CT scan which may not reflect the emerging situations accurately when patients are complicated with Sheehan's syndrome, may delay the treatment, deteriorate the patent's conditions rapidly, and even cause pituitary crisis or myxedema coma. Therefore, for women with high TG type acute pancreatitis, we suggest primary hypothyroidism or secondary hypothyroidism induced by Sheehan's syndrome should be excluded first.

Conflict of Interests Statement

The authors declare no conflict of interests.

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