Acute Pancreatitis and Cushing's Disease

Kazuko HIRAMATSU, Junko MORIUCHI, Shigeru ARIMORI, Atsushi IDE, Toshiaki USUI, Kouhei TANAKA, Teiko SATO* and Yoshiyuki OSAMURA

Department of Internal Medicine, *Department of Pathology, Tokai University School of Medicine
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A 64-year-old woman with Cushing's disease died of acute necrotizing pancreatitis. This is the second case of this rare condition, in which acute necrotizing pancreatitis followed an ACTH-dependent hypercortisolism. The possibility that the tricyclic antidepressant drug, amitriptyline hydrochloride, induced the acute pancreatitis could not be ruled out; nevertheless, the present case may serve to add ACTH-dependent hypercortisolism to the possible causes of acute necrotizing pancreatitis.

(Key words: Acute pancreatitis, Cushing's disease, ACTH-dependent hypercortisolism)

INTRODUCTION

Corticosteroids can induce pancreatitis especially when administered to children (5). However, it still is unknown whether endogenous corticosteroids can cause acute pancreatitis in adults. In 1984, Clague et al. (2) reported a lethal case of acute pancreatitis which may have been caused by endogenous hypercortisolism. The present report represents the second case of acute necrotizing pancreatitis complicating Cushing's disease. Reviewing these two cases, the possibility of exogenous hypercortisolism causing acute pancreatitis is discussed.

CASE REPORT

A 64-year-old female was admitted to the endocrine ward of Tokai University Hospital because of hypertension, moon face and gait disturbance. She told of suffering from congenital hip joint dislocation and hypertension for the past 10 years. For last 3 years, she had been depressed and was admitted twice to the psychiatric ward because of a desire to commit suicide. Thyroid hormone (T4) measured during the period of her second admission revealed a free T4 of 0.52 ng/dl (normal range 0.7–2.2) and thyrotrophin (TSH) of 0.28 μIU/ml (normal range <4), reading which were compatible with hypothyroidism due to hypofunction of the pituitary. For further examination, she was transferred to the endocrine ward. Physical examination revealed a depressed countenance, moon face, hirsutism, petechiae, bruises and muscle weakness in the lower extremities, bed sores on the back, and reduced bilateral tendon reflexes. Blood pressure was high 178/82. Blood chemistry, blood picture, coagulation test and urinalysis were all normal initially. The pituitary reserve test was performed employing thyrotrophin releasing hormone (TRH), luteinizing hormone releasing hormone (LHRH) and insulin. The plasma glucose, cortisol, corticotrophin (ACTH), growth hormone (GH), TSH, prolactin (PRL), luteinizing hormone (LH) and follicle stimulating hormone (FSH) were measured before and after 15, 30, 60, and 120 mins. The basal level of ACTH was 109 pg/ml (normal range <50), maximum was 208 pg/ml with no response in TSH, PRL, GH, LH or FSH. The 17-hydroxy cortisol (17OHS) and free cortisol in 24h-urine, and the plasma cortisol levels, were not suppressed following the administration of 2 mg of dexamethasone. However, all values of the 3 parameters were suppressed following 8 mg of dexamethasone. The diurnal rhythm of both ACTH and cortisol also disappeared. Abdomi-
nal computed tomography scanning revealed bilateral enlargement of the adrenal glands. Thus, the patient was diagnosed as suffering from Cushing disease and partial pituitary hypofunction. A pituitary adenoma was suspected but could not be detected by imaging techniques such as computed tomography scanning and magnetic resonance imaging. Bromocriptine, 5.0 mg per day, was administered for controlling the hypercortisolism. The level of 24h-urinary free cortisol returned to within the normal range. Medications were still continuously required, like 37.5 mg of captopril and 1 mg of prazosin hydrochloride for hypertension; 200 mg of allopurinol for hyperuricemia; and 200 mg of amitriptyline hydrochloride for depression. One month later, the patient suddenly went into hypovolemic shock (Fig. 1). Physically, abdominal tenderness was not observed although the high level of plasma amylase; 2059 U/l (normal range >140 U/l), hyperglycemia 552 mg/dl (normal <118 mg/dl) and hypocalcemia 3.8 mEq/l (normal range 4.5–5.3 mEq/l) strongly suggested acute pancreatitis. The patient's condition was further complicated by acute renal failure and disseminated intravascular coagulopathy. Other abnormal data which supported the diagnosis; creatinine 2.9 mg/dl (normal range 0.5–0.8 mg/dl), FDP 1106 ng/ml (<100 ng/ml), platelet count 4.5 × 10⁴/µl (normal range 14–40 × 10⁴, and AT-III 12.0 mg/dl (normal range >22.5 mg/dl). The administration of heparin, gabexate mesilate, insulin and cortisol sodium succinate worked to relieve the symptoms and improved the abnormal laboratory parameters. However, the patient died 20 days later because of sudden cardiac arrest.

The autopsy confirmed the diagnosis of Cushing's disease because a basophilic adenoma 6 mm in diameter was found in the pituitary (Fig. 2) and the adrenal glands were enlarged bilaterally. The left adrenal weighed 7.5g and the right one 7.0g. The adenoma cells were immunohistochemically positive for ACTH. Thus the adenoma was diagnosed histologically as an ACTH-producing tumor. A severe necrotizing pancreatitis was the direct cause of death. Macroscopically, severe fat necrosis was observed in situ and around the pancreas, and also involved the duodenum, transverse colon and omentum. Abscess formation was found in the tail of the pancreas and subphrenicus. Microscopically, large parts of the pancreatic tail revealed parenchymal necrosis and an inflammatory reaction surrounding fat necrosis (Fig. 3). Hemorrhagic changes were minimal. Neither fibrosis, calcification, nor dilatation or plugging of the ducts was observed, and these results denied the pre-existence of chronic pancreatitis. Similarly, a pre-existing biliary tract disease such as biliary stones was also ruled out.

**CLINICAL COURSE**

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Fig. 1 Clinical course of acute pancreatitis in a patient with Cush- ing's disease.
Fig. 2 Adenoma of pituitary (HE, ×20). In the middle of the pituitary, a well-demarcated nodular lesion, 6 mm × 6 mm, is seen. The lesion was composed of monotonous basophilic cells.

Fig. 3 Acute necrotizing pancreatitis. (HE, ×48) Fat necrosis on the left, necrotic changes in the parenchyma (acinus) with accompanying inflammation consisting mainly of polymorphonuclear leucocytes.
DISCUSSION

In Japan, during period 1981 to 1988, a total of 373 cases of Cushing's disease was report-
ed (6). In that study, the total number of deaths was 38 and the leading causes of death were in-
fec tion (10 cases), followed by cerebrovascular disease (5 cases) and heart disease. The present
case was involved in that study, and was found to be the rare example in which acute necrotiz-
ing pancreatitis was the direct cause of death.

It has been reported that administration of corticosteroids probably is causally associated
with pancreatitis (4). The evidence is based on the high incidence of pancreatitis in children
who are treated with corticosteroids (5) and the pancreatitis which develops in experimental
animals receiving corticosteroids (1).

With regard to the question whether an endo-
dogenous excess of corticosteroids i.e., hyper-
cortisolism, is the possible cause of pancreatitis in adults, the present case appears to provide
positive evidence comparable to the case of Clague et al. (2). Further proof that Cushing's
disease was the direct cause of acute necrotiz-
ing pancreatitis in the present case required a
careful study to eliminate other causes of acute
pancreatitis, and indeed, a pre-existing chronic
pancreatitis, biliary tract disease, and a histo-
dy of drinking alcohol were safely ruled out. It
was more difficult disproving a possible connec-
tion between medication and the develop-
ment of acute pancreatitis. The medication ad-
ministered to our patient did not include any
drugs knwon to cause acute pancreatitis such
as azathioprine, sulphonamides, thiazide diuret-
ics, furosemide, estrogens, tetracycline, valproic
acid and pentamidine (4). The amitriptyline-
hydrochloride that was prescribed for the pa-
tient's depression did cause concern however.
Generally, the tricyclic antidepressants do not
cause acute pancreatitis, however, Jeffries and
Masson have reported a case of acute pancrea-
titis following overdose with amoxapine, and
concluded that amoxapine was probably, but
not certainly, the cause of the pancreatitis (3).
Although the total dose of amitriptyline hydrochloride was less than that of amoxapine,
the possibility of drug-induced acute pancreatitis remains.

If Cushing's disease caused the acute pan-
creatitus, we can speculate on an interesting
point. Endogenous hypercortisolism is classified
as either ACTH-dependent or ACTH-
independent. According to this classification,
both clague's case and our belong to the former group. In contrast, the condition in which
excess corticosteroid is administered is ACTH-
independent. Therefore, the combination of
hormones responsible for acute pancreatitis
seems to differ between children and adults. As
yet, however, the mechanism of corticosteroid
induced pancreatitis is unclear.

It is hard to speculate as to whether ACTH
has any unique effect on the development of
acute pancreatitis, besides inducing an excess
of corticosteroids, because the major function
of ACTH is to stimulate corticosteroid produc-
tion by the adrenal gland in vivo. Nevertheless,
physicians should remember that ACTH-
dependent hypercortisolism may lead to acute
pancreatitis.

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