Acute pancreatitis and Cushing's syndrome

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Summary

A case of acute necrotizing pancreatitis in a 53-year-old man with an ectopic adrenocorticotrophin (ACTH) producing bronchial carcinoma is described. The aetiology of acute pancreatitis in relation to steroid therapy and malignancy is discussed and it is suggested that excess endogenous steroid production may also cause acute pancreatitis.

KEY WORDS: bronchial carcinoma, pancreatitis, Cushing's syndrome.

Introduction

Acute pancreatitis has been associated with a wide variety of clinical disorders, but the causal mechanisms that precipitate pancreatic autodigestion and necrosis remain unknown. Acute pancreatitis following drug ingestion is an uncommon but well recorded association that has assumed special importance because of its frequently reported fatal outcome (Schmidt and Creutzfeldt, 1976). Although not conclusive, the evidence for a causal association between acute pancreatitis and steroid therapy is strong (Reimenschneider, Wilson and Vernier, 1968).

The purpose of this report is to describe a previously unrecorded association between acute necrotizing pancreatitis and endogenous steroid excess in a man with Cushing's syndrome due to ectopic ACTH production.

Case report

A 53-year-old male presented with a 3-day history of increasing ankle oedema. He gave a 20-year history of chronic bronchitis. His cigarette consumption amounted to 40 pack years and he denied excessive alcohol consumption. Physical examination revealed central cyanosis and evidence of airflow obstruction, and the blood pressure was normal.

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Serum albumin, glucose, urea and electrolytes were initially all normal.

He was started on frusemide 60 mg daily with potassium supplements, but after 4 days there was no improvement. A more penetrated chest radiograph than that on admission suggested a right hilar mass compressing the bronchus intermedius and this was confirmed tomographically. Laboratory investigations now showed hyperglycaemia (glucose 15.3 mmol/litre) and hypokalaemic alkalosis: sodium 142 mmol/litre, potassium 2.6 mmol/litre, and standard bicarbonate 33.9 mmol/litre.

At fiberoptic bronchoscopy no tumour was visible and all specimens taken, including bronchial biopsies, were negative. Nevertheless, a clinical diagnosis of bronchial carcinoma with ectopic ACTH production was made and endocrine investigations were undertaken which were confirmatory (Table 1). On metyrapone (0.5 g 4 hourly) plus dexamethasone (0.5 mg twice daily), body weight and serum electrolytes returned to normal. Subsequent plasma cortisol levels were recorded at between 1,295 and 1,952 nmol/litre. He then began to complain of a nagging upper abdominal pain, relieved by antacids, but he refused to remain in hospital for further investigation or cytotoxic therapy. Additional drugs on discharge were glibenclamide, cyclophosphamide, amphotericin suspension and potassium supplements.

A week later he was re-admitted with severe abdominal pain, epigastric tenderness, absent bowel sounds and radiological signs of ileus. The serum amylase was measured at 5679 iu. Despite supportive measures he rapidly deteriorated, became shocked and died within a few hours.

A post-mortem examination confirmed the presence of a small cell (spheroidal type) bronchial carcinoma with metastases to the liver and left adrenal. Abdominally there was a florid purulent peritonitis with widespread fat necrosis. The pancreas was necrotic and friable, but 1 cm slices showed

TABLE 1. Measurements of plasma cortisol and ACTH show lack of diurnal rhythm and a failure of cortisol production to suppress following dexamethasone

	0900 hr	2400 hr
Plasma cortisol (nmol/litre)	1,714	1,683 (normal range 130–190)
Plasma ACTH (ng/litre)	1,000	1,370 (normal range 10–80)
	Response to 48 hr (8 mg/day) dexamethasone	
	0 hr	48 hr
Plasma cortisol (nmol/litre)	2,585	2,619

no macroscopic evidence of metastatic tumour and random histological samples were similarly negative. The adrenal glands were markedly hyperplastic, but the brain and pituitary gland were normal. Gall bladder and bile ducts were also normal.

Discussion

The link between ectopic ACTH production and small cell tumour of the bronchus is well described and is known to carry a poor prognosis (Crofton and Douglas, 1981). Abnormal glucose tolerance and a hypokalaemic alkalosis are recognized presenting features and are due to grossly elevated plasma cortisol and ACTH levels. These latter features serve to differentiate the condition from Cushing's disease when plasma ACTH levels >200 ng/litre or plasma cortisol >1,000 nmol/litre are most unusual (Hall *et al.*, 1980). Failure of ACTH production to suppress with dexamethasone and the reduced response to metyrapone are also typical of ectopic ACTH production.

Over 40 patients have been described with clinical evidence of pancreatitis related to cortisol excess from steroid therapy (Mallory and Kern, 1980). The evidence against excess steroids is not conclusive and uncritical acceptance would ignore the possibility that underlying disease or simultaneously prescribed drugs were responsible. Nevertheless, the case for a causal association is strong and based on the results of animal experiments, post-mortem studies of patients treated with steroids and a series of clinical case reports (Schmidt and Creutzfeldt, 1976). Post-mortem evidence of peri-pancreatic fat necrosis and lesions of the pancreatic acini have been observed in a high proportion of experiment animals treated with cortisol. In patients treated with adrenal steroids or ACTH prior to death, focal pancreatic lesions and peri-pancreatic fat necrosis were seen in 16 of 54 patients, compared with 2 of 54 patients in a control group (Carone and Liebow, 1957). Mechanisms implicated in the development of acute pancreatitis resulting from corticosteroids have been an alteration in pancreatic secretions leading to increased viscosity

and ductal ectasia, hyperlipaemia, fluid and electrolyte imbalance and intravascular coagulation (Schmidt and Creutzfeldt, 1976). Considering the frequency of steroid therapy, acute pancreatitis is surprisingly uncommon and apparently undescribed in association with Cushing's disease. Perhaps this is because plasma cortisols are not grossly evaluated in Cushing's disease, although they may be in Cushing's syndrome due to ectopic ACTH production. In the present case, as in other reported cases, it is difficult to separate the effects of steroid excess from concurrent drug therapy. Cytotoxic drugs, and in particular azathioprine, have themselves been incriminated as a cause of acute pancreatitis (Mallory and Kern, 1980). However, the authors are unaware of previous reports specifically implicating cyclophosphamide in low dosage, glibenclamide or metyrapone. There are several case reports incriminating frusemide (Mallory and Kern, 1980) and incontrovertible evidence of a relapse following re-challenge (Jones and Oelbaum, 1975). Frusemide seems an unlikely cause in our patient as he had stopped taking the drug at least a week before the onset of abdominal pain.

With regard to the underlying disease, primary malignant pancreatic tumours are said to predispose to acute pancreatitis in 3% of cases (Gambill, 1971). An association between acute pancreatitis and secondary malignancy is more tenuous and relates to large tumours which obstruct the common duct or disrupt the integrity of the collecting system. Interestingly, of the six case reports purporting to show an association between metastatic carcinoma and acute pancreatitis, all 6 arose from primary lung tumours. Metastatic carcinoma must be an uncommon precipitant of acute pancreatitis, taking into account that approximately 11% of oat-cell carcinomas will metastasize to the pancreas (Line and Deeley, 1971). The pancreas was so autolyzed in the case presented here that micro-metastases cannot be ruled out. However, the previously reported association between acute pancreatitis and metastatic carcinoma has laid emphasis on visible tumour or pancreatic enlargement and neither were true in the present case.

This report does not give sufficient evidence for a causal association between acute pancreatitis and Cushing's syndrome, but the authors feel that endogenous steroid excess should be added to the list of possible aetiological agents in the production of acute pancreatitis. The serious mortality of acute necrotizing pancreatitis strengthens the argument for aggressive correction of the underlying endocrine abnormality in patients with ectopic ACTH secretion.

Acknowledgments

We wish to thank Mrs J. Williams, Drug Information Pharmacist, Fazakerley Hospital, for her assistance and also Mrs Marion Jones for typing the manuscript.

References

CARONE, F.A. & LIEBOW, A.A. (1957) Acute pancreatic lesions in patients treated with ACTH and adrenal corticoids. *New England Journal of Medicine*, **257**, 690.

- CROFTON, S. & DOUGLAS, A. (1981) *Respiratory Diseases*, 3rd edn, p. 645. Blackwell Scientific Publications, Oxford.
- GAMBILL, E. (1971) Pancreatitis associated with pancreatic carcinoma. *Mayo Clinic Proceedings*, **46**, 174.
- HALL, R., ANDERSON, J., SMART, G.A. & BESSER, M. (1980) *Fundamentals of Clinical Endocrinology*, 3rd edn, p. 699. Pitman Medical Books, London.
- JONES, P.E. & OELBAUM, M.H. (1975) Frusemide-induced pancreatitis. *British Medical Journal*, **1**, 133.
- LINE, D.H. & DEELEY, T.J. (1971) The necropsy findings in carcinoma of the bronchus. *British Journal of Diseases of the Chest*, **65**, 238.
- MALLORY, A. & KERN, F. (1980) Drug induced pancreatitis: a critical review. *Gastroenterology*, **78**, 813.
- REIMENSCHNEIDER, T.A., WILSON, J.F., & VERNIER, R.L. (1968) Glucocorticoid-induced pancreatitis in children. *Pediatrics*, **41**, 428.
- SCHMIDT, H. & CREUTZFELDT, W. (1976) Etiology and pathogenesis of pancreatitis. In: *Gastroenterology* (Ed. H. L. Bockus), Vol. 3, 3rd edn, p. 1005. W. B. Saunders, Baltimore.

(Accepted 3 August 1983)