PANCREATIC ISLET-CELL TUMOUR ASSOCIATED WITH CUSHING’S SYNDROME

Report of a case with Estimation of Tumour ACTH Content

by

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INTRODUCTION

CUSHING’S SYNDROME as a result of ectopic ACTH production has been recognised for several years. Many tumours arising in tissue thought to be derived from the primitive foregut appear to be capable of elaborating a variety of hormones, of which ACTH is the most completely documented. These include tumours of the lung, pancreas, bile ducts, thyroid, thymus and also from other sites such as colon (Crooke, 1946; Hallwright, North and Reid, 1964; Sasano, Fukuda, Saton and Tohoku, 1969; Bartholomew and Schutt, 1971; Anderson and McHugh, 1971; Rosai and Higa, 1972; Schteingart, Conn, Orth, Harrison, Fox and Bookstein, 1972). However, it is only recently as a result of improvements in radioimmunoassay techniques, that comparison of measurements of ACTH content of these tumours has become practicable. Pancreatic tumours, after bronchogenic tumours, are the entodermal derived tumours most frequently associated with ectopic ACTH production. Very few reports exist in the literature of cases where ACTH content of the pancreatic tumour has been determined using radioimmunoassay techniques (Sasano, Fukuda, Saton and Tohoku, 1969). It therefore seemed appropriate to record the following case report:

HISTORY

A 59-year-old male was admitted to the Lagan Valley Hospital in 1972 (Dr. Jean Langlands) with a 4-week history of polydipsia, and recent excess alcohol intake. Apart from mild chronic bronchitis he had been in good health prior to this illness. A tentative diagnosis of diabetes mellitus was made which did not respond to treatment. His muscular weakness increased and he developed severe hypokalaemia (2.1 mmol. per l). Adrenal overactivity was suspected and urinary steroid excretion was found to be raised. He was transferred to the Metabolic Unit, Royal Victoria Hospital (R.V.H. U.N.932311). His appearance was now more suggestive of Cushing’s syndrome, with considerable proximal muscle wasting and weakness but no obesity, hypertension or skin striae. His face was not unduly florid. He complained of pain over the left lower rib margin consistent with a collapsed 6th dorsal vertebra. Straight x-ray of abdomen suggested a pancreatic tumour or cyst but on examination no abdominal mass could be palpated.

Investigations were curtailed due to his poor general condition. Cortisol secretion rate was 122 mg per 24-hours. Plasma cortisol at 11 p.m. was 44 µg per 100 ml. 2 mg dexamethasone was then given by mouth: the plasma cortisol at
7 a.m. next morning was 49 μg per 100 ml, confirming the absence of a circadian rhythm and showing non-suppressibility of adrenal cortical function. Urinary 17-oxosteroid excretion was 21.5 mg in 24-hours and 17-oxogenic steroid excretion was 42.8 mg in 24-hours. An oral glucose tolerance test had been mildly abnormal. The highest blood sodium was 141 m mol/l, the lowest potassium 2.1 m mol/l, and the CO₂CP was increased to 39 m mol/l. Haemoglobin was 14.0g percent. Radiological examination showed extensive osteoporosis with collapse of the sixth dorsal and second lumbar vertebrae. Barium meal showed a large space-occupying mass displacing the stomach downwards and forwards.

At operation on 4th October, 1972 (Mr. T. L. Kennedy) a large malignant tumour was found involving the tail of the pancreas. It was possible to remove most of this tumour. There was also bilateral adrenal hyperplasia and a total adrenalectomy was performed. The blood pressure was low during the operative procedure. He did not recover consciousness presumably due to this hypotensive episode and he eventually died on the fifth post-operative day.

**Biopsy Specimens:** Both glands were enlarged. The left gland was received intact and weighed 17g., the right was in several pieces and weighed 12g. Histologically there was bilateral cortical hyperplasia involving primarily the zona fasciculata. Zones of lipid depletion alternated with zones of high lipid content.

The specimen of pancreas and tumour was received in two pieces. The tumour which arose in the tail of the pancreas consisted of an infiltrating carcinoma, the cells of which were arranged in sheets and cords and in areas resembling islet cells, being oval to spindle in shape with small round hyperchromatic nuclei and lightly staining cytoplasm. Mitotic figures were rare. In some sections the tumour was divided into imperfectly formed lobules by bands of hyaline stroma. No capsule was observed and invasion of the peri-pancreatic fat was seen in most sections taken. Granules could not be demonstrated in any of the sections examined, using Gomori's chrome alum haemotoxylin and Gomori's aldehyde fuschin.

ACTH estimation was by radio-immunoassay using the Amersham Radio-chemical Centre kit. ACTH level was 0.772 ug/g wet weight. No ACTH was found in normal pancreatic control material.

**At autopsy** the tumour was found to have been completely excised. The head and part of the body of the pancreas were intact but at the site of the operation an acute inflammatory process was seen. A few fragments of the right adrenal gland remained and showed a similar appearance to the biopsy specimens.

The pituitary was not enlarged but Crooke's hyaline change was found. Proximal limb muscles showed diffuse fibre involvement with no evidence of group atrophy. Sarcolemmal proliferation with marked fibre degeneration and occasional fibres showing abortive regenerative changes were observed. Peripheral nerves however showed no abnormality. The spinal cord was not available for examination.

**Discussion**

The rapid onset of Cushing's syndrome with severe hypokalaemia in an otherwise healthy adult is highly suggestive of inappropriate ACTH secretion by a tumour. Histologically the tumour in this case showed the generally accepted appearances of an islet cell-derived carcinoma of the pancreas, the inability to demonstrate granules histologically being well-recognised. The findings in the adrenal and
pituitary were typical of Cushing's syndrome secondary to excess ACTH production. The proximal muscle wasting was most probably a direct cortisone effect; as it was not possible to examine the spinal cord, CNS involvement could not be definitely excluded although the muscles did not show fibre group atrophy.

The association of adrenocortical overactivity and "non-endocrine" tumours was actually suspected before Cushing's original monograph was published (Brown 1928). The ectopic ACTH syndrome was first defined by Meador et al (1962) who showed elevated ACTH (bioassay) in the tumour and plasma, and decreased pituitary ACTH content. This syndrome is the best documented model of ectopic hormone production and at least 94 cases with positive tumour levels by bioassay or radioimmunoassay have been published (Rees and Ratcliffe, 1974). Tumours associated with ectopic ACTH production can be divided into four main groups—(i) oat cell carcinomas of bronchus; (ii) tumours of foregut origin (islet cell pancreatic tumours, carcinoids, thymoma and medullary carcinoma of thyroid); (iii) phaeochromocytomas and related tumours; and (iv) certain ovarian tumours. Many of these tumours are rather pleomorphic.

The amount of ACTH determined by radioimmunoassay in this pancreatic tumour was in the mid-range of ACTH content in reported cases of ectopic ACTH production by all types of tumour tissues (.001 to 1000 μg/g wet weight). This very wide range is confirmed for both bioassay and radioimmunoassay techniques, and presumably represents wide variation in the peptide structure of these ACTH-like compounds.

**Summary**

A case of ectopic ACTH production in an islet cell tumour of the pancreas associated with Cushing's syndrome of rapid onset is reported. The ACTH content of the tumour was determined by radioimmunoassay.

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**References**

Anderson, A. E. and McHugh, P. R. (1971). *Journal of Nervous and Mental Diseases*, 152, 427.

Bartholomew, L. G. and Schutt, A. J. (1971). *Cancer*, 28, 170.

Brown, W. H. (1928). *Lancet*, 2, 1022.

Crooke, A. C. (1946). *Journal of Pathology and Bacteriology*, 58, 667.

Hallwright, G. P., North, K. A. K. and Reid, J. D. (1964). *Journal of Clinical Endocrinology*, 24, 496.

Meador, C. K., Liddle, G. W., Island, D. P., Nicholson, W. E., Lucas, C. P., Nuckton, J. G. and Leutscher, J. A. (1962). *Journal of Clinical Endocrinology*, 22, 693.

Rees, L. H. and Ratcliffe, J. G. (1974). *Clinical Endocrinology*, 3, 263.

Rosai, J. and Higa, E. (1972). *Cancer*, 29, 1061.

Sasano, N., Fukuda, T., Saton, E. and Tohoku, J. (1969). *Journal of Experimental Medicine*, 99, 361.

Scheinberg, D. E., Conn, J. W., Orth, D. N., Harrison, T. S., Fox, J. E. and Bookstein, J. J. (1972). *Journal of Clinical Endocrinology*, 34, 676.