Medical Memoranda

Hyperinsulinism and Cushing's Syndrome

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Many reports of the association of malignant neoplasms and Cushing's syndrome have appeared in the past few years, and a syndrome of ectopic adrenocorticotrophin production has been clearly defined (Bagshawe, 1960; Liddle *et al.*, 1963). The purpose of this paper is to describe its occurrence with malignant insulinoma and to draw attention to certain similarities between ectopic adrenocorticotrophin production and paraglandular syndrome.

CASE REPORT

A 43-year-old postman was first seen in hospital on 2 September 1962. He had been unwell for five weeks. He complained of being rather "hazy in the head" and of having "slowed-up" mentally. He felt agitated, had constant headaches, and a feeling of constriction in his chest. His speech had been slower and occasionally slurred. Owing to weariness, walking had become difficult, although he had no definite weakness or pain in his limbs. He complained of dryness of the mouth, with thirst, polyuria, and nocturia. His appetite remained good, and there was moderate constipation. Two to three weeks before consultation he gained weight rapidly, increasing from his usual weight of 11 st. 7 lb. (73 kg.) to 12 st. 7 lb. (79 kg.). He stated that his face appeared swollen and that sometimes his legs swelled. Acneiform spots had appeared on his trunk and face. Apart from malaria many years previously, he had always been in excellent health.

He gave the appearance of being well. His skin was heavily pigmented, especially in exposed areas and about the genitalia. His skin was thin and contained several small bruises. On the trunk many acne pustules were present. There was mild generalized stomatitis and his tongue was dry. The liver edge was just palpable. Moderate oedema of both legs was present, extending up to the knee. There were no other physical abnormalities. The blood-pressure was 140/70 mm. Hg. Urinalysis was normal. X-ray examination of the skull, chest, and pelvis, and an intravenous pyelogram revealed no abnormalities save generalized osteoporosis. A diagnosis was made of atypical Cushing's syndrome and investigations were undertaken to confirm and determine its aetiology.

INVESTIGATIONS

The results of relevant routine clinical laboratory investigations were as follows: haemoglobin 14.9 g./100 ml.; serum cholesterol 210 mg./100 ml.; protein-bound iodine 2.5 μ g./100 ml.; total protein 5.6 g.—normal electrophoresis; bilirubin 0.2 mg./100 ml.; alkaline phosphatase 10 K.A. units; S.G.O.T. 54 Sigma-Frankel units; S.G.P.T. 38 Sigma-Frankel units; bromsulphthalein 17% retention at 45 minutes. Sodium 140 mEq/l.; potassium 2.6 mEq/l.; chloride 92 mEq/l.; bicarbonate 42 mEq/l. Plasma cortisol 65 μ g./100 ml.; urinary 17-ketosteroids 27 mg./day, and 17-hydroxycorticosteroids 60 mg./day. Hypokalaemia and alkalosis persisted throughout the period of observation, being uninfluenced by large dietary potassium supplements, either alone or combined with aldactone. Apart from this, the main abnormalities in electrolyte distribution were a 15% reduction in total body potassium, and a 25% increase in intracellular (residual) sodium (Coppin and Shaw, 1963). Extracellular fluid volume was normal. The mean daily urinary excretion of calcium was 568 mg. (range 196-898 mg.), serum calcium averaged 9.5 mg. (range 8.8-12 mg.)/100 ml., and plasma inorganic phosphate 2.3 mg. (range 1.5-3 mg.)/100 ml.

There was constant glycosuria—mean excretion 10 g. (range 0.1-60 g.)/24 hours—but neither oral nor intravenous glucose tolerance

tests were grossly abnormal, and the glucose content of fasting specimens on each occasion was below average. The blood glucose, after 50 g. of glucose by mouth, rose from the fasting level of 54 mg./100 ml. to 130 mg. at 30 minutes, and was 157 mg. at 60 minutes, 166 mg. at 90 minutes, 150 mg. at 120 minutes, 116 mg. at 150 minutes, and 85 mg. at 180 minutes. The corresponding values for plasma insulin (Samols and Marks, 1963) were 65, 96, 100, 137, 100, 138, 78 μ U./ml. The glucose assimilation coefficient during the intravenous glucose tolerance test was 1.54; the fasting blood glucose concentration was 58 mg./100 ml.

Plasma cortisol and urinary steroid excretions were high. A.C.T.H. produced a moderate (30 μ g./100 ml.) rise of plasma cortisol and urinary 17-hydroxycorticosteroid (65 mg./24 hours) excretion, but dexamethasone—8 mg./day for four days—had no effect. Metopirone (metyrapone) produced a fall in plasma cortisol to 16 μ g./100 ml., and a moderate (30 mg./day) increase in urinary 17-hydroxycorticosteroid excretion, but severe malaise occurring after 24 hours prevented further Metopirone administration.

TREATMENT AND SUBSEQUENT COURSE

A diagnosis of Cushing's syndrome due to ectopic A.C.T.H. production of undetermined origin was made, and two-stage bilateral adrenalectomy was carried out in November 1962. Both adrenals were enlarged and hyperplastic (Dr. M. Beattie), the left weighing 11.5 g., the right 12 g. An opportunity was taken during the second operation to biopsy a hepatic metastasis. This showed secondary carcinoma, but further identification was not possible.

Recovery was uneventful, and the patient was discharged from hospital three weeks later on maintenance (50-mg.) doses of cortisone. He was readmitted less than 24 hours later in hypoglycaemic coma, and with a blood glucose concentration of 13 mg./100 ml. He was subsequently found to be unable to withstand fasting overnight without developing severe hypoglycaemia. The fasting plasma insulin concentration on two occasions was 350 μ U/100 ml.—that is, more than five times the upper limit of normal.

An attempt to make an intravenous tolbutamide tolerance test was unsuccessful, as consciousness was lost during the injection. The fasting blood glucose concentration was 20 mg./100 ml. and plasma insulin 420 μ U/ml. Seven minutes after tolbutamide and glucose—given to restore consciousness—the plasma insulin was 580 μ U/ml. and blood glucose 272 mg./100 ml. Sixty minutes later the blood glucose was 37 mg./100 ml., and plasma insulin 570 μ U/ml. The glucose assimilation coefficient *k* value was 3.15. A further 25 g. of glucose, given by mouth at 60 minutes, was associated with a rise in blood glucose to 44 mg./100 ml., but failed to elicit an insulinaemic response, while a second injection of tolbutamide 20 minutes later evoked an immediate (200 μ U/ml.) rise in plasma insulin to 675 μ U/ml.

On a three-hourly feeding regime, the patient was able to lead a more or less "normal" life at home for two months, though minor episodes of neuroglycopenia were not uncommon. Coma developed only twice, and on the second occasion (12 February 1963) he died—six and a half months after the onset of his illness, and three months after adrenalectomy.

Necropsy was carried out 36 hours after death (Dr. A. Tay). The body was that of a moderately obese man with marked cutaneous pigmentation. Pathological abnormalities were confined to the presence of a firm indurated mass, 18 mm. in diameter, in the tail of the pancreas, and multiple yellowish-white metastases in the liver. In particular, the thyroid, parathyroid, and pituitary glands were normal, as was the brain, which showed no evidence of an anoxic condition (Dr. J. B. Brierley), as is usual with death from hypoglycaemia.

Histological examination of a metastasis, using special staining techniques, was thought to be typical of malignant insulinoma, a moderate number of cells containing characteristic β granules (Dr. D. Dexter).

DISCUSSION

The principal feature of interest in the present case lies in the fact that it is the first in which the source of ectopic A.C.T.H. production has been shown conclusively also to secrete insulin. The results of insulin assay obtained conform to the pattern we have come to associate with that seen in cases of malignant insulinoma (unpublished observations).

A similar case to that described here has been reported (Balls *et al.*, 1959), in which Cushing's syndrome was associated with a large abdominal mass and hypoglycaemia. Biopsy revealed poorly differentiated carcinoma not diagnostic of the primary site of origin, but consistent with islet-cell carcinoma. Though assumed to be an insulinoma, special stains for α and β cells brought no success, and insulin could not be demonstrated either in primary or in metastatic tumours.

Hypoglycaemia is well recognized as a complication of non-islet-cell tumours, including gastro-intestinal, bronchial, and pancreatic carcinomas (Marks *et al.*, 1964), and functional adrenocortical tumours (Williams *et al.*, 1961). The mechanism of production of hypoglycaemia is unknown, and although plasma insulin-like activity is sometimes increased (Whitney and Heller, 1961), as in the case reported by Balls *et al.* (1959), this is neither invariable nor established as being due to insulin. In the present case hyperinsulinism due to insulinoma was established conclusively both biochemically and histologically.

The present case suggests that the syndrome of ectopic A.C.T.H. production may be linked to that of multiple endocrine adenomatosis (preferably termed pluriglandular syndrome) in which two or more endocrine glands are affected in the same individual, and which is often, but not invariably, familial.

In addition to the two cases of Cushing's syndrome due to islet-cell carcinoma already cited (Balls *et al.*, 1959), we have found accounts in the literature of 10 further cases (McLetchie and Scott, 1942-4; Castillo *et al.*, 1950; Rosenberg, 1956; Armando, 1957; Bourgeois *et al.*, 1959; Farrant and Insley, 1960; Meador *et al.*, 1962; Hallwright *et al.*, 1964; Jarrett *et al.*, 1964), and know of another; but in only four was hypoglycaemia a feature.

Though not as rare as formerly believed, Cushing's syndrome is nevertheless an unusual complication of neoplasia, only 72 cases having been reported up to 1963 (Engel and Kahana, 1963). Its association, therefore, on no fewer than 13 occasions with islet-cell carcinoma of the pancreas—an extremely rare neoplasm (Frantz, 1959)—suggests a more than casual relationship. In many of these patients, as in the present case, in which there was laboratory evidence (Raker *et al.*, 1962) of parathyroid overactivity, other endocrine glands were affected. Further pointers to a possible relation between pluriglandular syndrome and ectopic A.C.T.H. production is the comparative frequency with which the latter is the result of carcinoma developing in other "endocrine" glands—for example, ovary (Parsons and Rigby, 1958), testis (di Ferrante *et al.*, 1951), thyroid (Höckfelt *et al.*, 1959), thymus (Scholz and Bahn, 1959), argentaffin (Escovitz and Reingold, 1961), and chromaffin systems (Liddle *et al.*, 1963), especially when due account is taken of their rarity.

Recent descriptions of the association and probable production of carcinoid syndrome (Veer *et al.*, 1964) and thyrotoxicosis

(Zimmer, 1964) by malignant insulinoma serve still further to emphasize the relation between the syndrome of acquired ectopic hormone production and the pluriglandular syndrome, in which carcinomas of the insular organ are especially common (Berdjij, 1962; Miehler *et al.*, 1962).

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