MALIGNANT INSULINOMA

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SYNOPSIS

A 54-year-old woman presented with hypoglycaemia, particularly in the food deprived state. A large malignant insulinoma was subsequently surgically excised, following the usual diagnostic work-up. We believe it is the largest insulinoma reported so far in the local literature. It is also unusual to find a malignant insulinoma.

INTRODUCTION

Of the causes of fasting hypoglycaemia, organic hyperinsulinism is often actively looked for once the hypoglycaemic state is detected. The diagnosis thereafter is straight-forward following the demonstration of an inappropriate plasma insulin: glucose ratio. However, the problem lies in the early detection of the fasting hypoglycaemia. Instead of the usual sympathomimetic presentation of which most are aware, neuroglycopenic symptoms may predominate in such patients, adding to confusion and delay in diagnosis. The symptoms in the patient presented here were such that it was 1½ years before hypoglycaemia was detected.

CASE REPORT

A 54-year old Malaysian woman presented in mid-November 1980 for episodic abnormal mental behaviour, particularly on waking up in the morning, for the past 1½ years. She had consulted innumerable doctors in her country and was labelled variously as suffering from schizophrenia, temporal lobe epilepsy, transient cerebral ischaemia, narcolepsy and brain tumour. A typical episode, as recountered by her son, would consist of total disorientation, failure to recognise people or communicate rationally. There were also, on other occasions, inappropriate emotional responses, for example smiling for no reason and anger and violence unrelated to any provocation. Occasionally, she would lapse into an unconscious state. At no time was there associated pallor, sweatiness, tremors or a clammy feeling in the skin. These episodes would last between a few hours to as long as half a day, with recovery on most occasions towards the evening. Her appetite was good when she was normal and there was no loss of weight. There was no history of headache, head injury, drug or alcoholic ingestion and illness such as diabetes mellitus.

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Clinical examination revealed a healthy-looking woman, well orientated to time and space. No neurological deficit could be detected. Other systems were normal. No masses were felt per abdomen.

The next day following admission, she was discovered in a dazed but conscious state, unable to speak, recognise simple objects or obey commands. There were no signs to suggest associated sympathetic activity such as tachycardia, sweatiness or arterial hypertension. Plasma glucose was 33 mgm%. She responded promptly to intravenous glucose administration with full recovery of sensorium.

Subsequently, after an oversight fast, simultaneous plasma glucose and insulin samples were assayed. The results were as follows:

Time	Plasma Glucose (mg/100 ml)	Plasma Insulin (RIA)(uU/ml)	Insulin: Glucose Ratio
8.00 am	23	11	0.5
9.00 am	29	62	1.4
10.00 am	20	56	2.8

Her other investigations were normal.

In view of the demonstration of an abnormal insulin: glucose ratio, insulinoma was diagnosed. An abdominal CT scan demonstrated a large tumour in the region of the tail of the pancreas (Fig. one). Angiography confirmed the presence of a vascular growth in the same region (Fig. two).

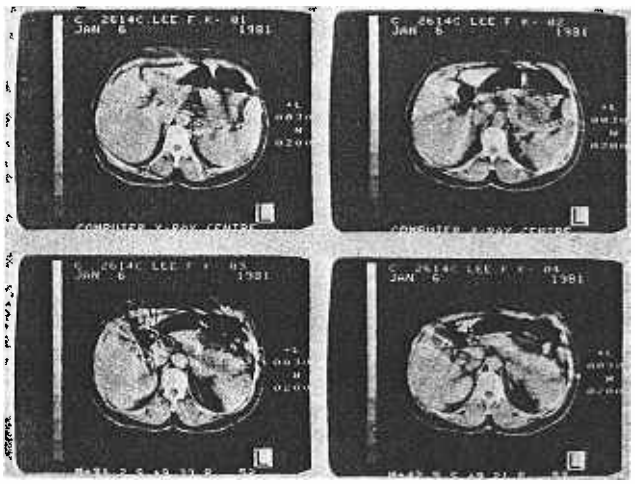

Fig. 1. C.T. Scan showing large pancreatic tumour

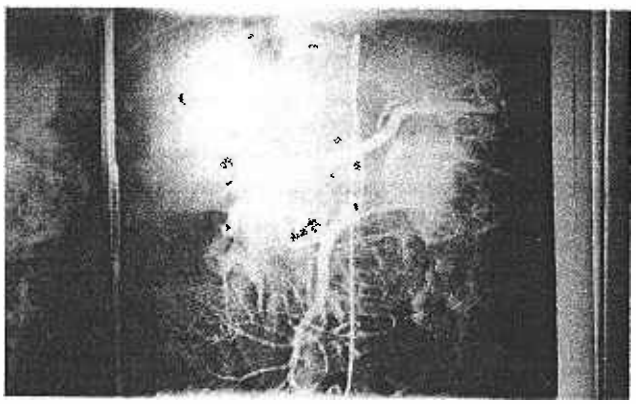

Fig. 2. Angiogram showing an extremely vascular pancreatic tumour.

At operation, a single well encapsulated tumour about 10 cm diameter was found in the tail of the pancreas (Fig. three). The rest of the pancreas and spleen were normal. The regional lymph nodes and liver were free of metastasis. Distal pancreatectomy with splenectomy was performed. Pre and post excisional blood sugar level monitoring was attempted but was not successful.

Histology of the tumour showed an islet cell carcinoma with intravascular tumour extensions and tumour infiltration into the pseudocapsule. The margin of pancreatic resection was free of tumour.

Post-operatively her recovery was uneventful apart from transient hyperglycaemia.

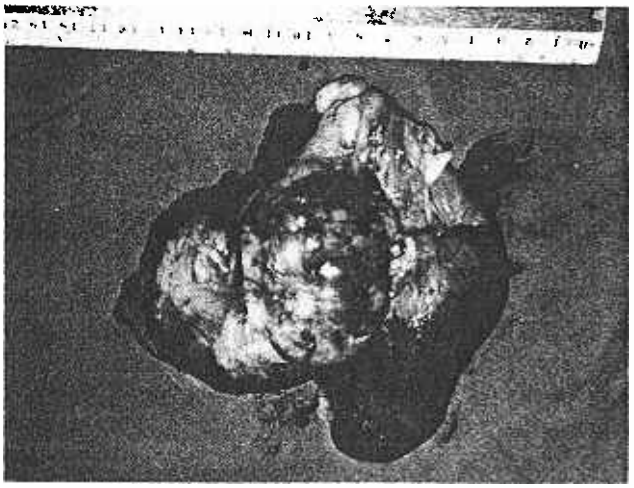

Fig. 3. Well encatsulated tumour (10 cm diameter letavotomany)

DISCUSSION

The diagnosis of organic hyperinsulinism rests on four conditions, (1) namely:

(1) the repeated occurrence of symptoms of food deprived hypoglycaemia which are chiefly those of neuroglycopenia.

(2) Confirmation that the symptoms are caused by hypoglycaemia (plasma glucose < 40 mgm%).

(3) Relief of these symptoms following the administration of glucose.

(4) Concomitant hyperinsulinaemia in the presence of hypoglycaemia and the absence of plasma insulin antibodies (to exclude factitious cases produced by self-administration of bovine or porcine insulin).

The first three conditions. constituting Whipples Triad, was clearly evident in our patient. Prolonged fasting, especially combined with physical activity. is probably the best provocative test in demonstrating Whipples Triad.

Simultaneous plasma insulin and glucose measurements in patients with insulinoma in most instances shows a plasma insulin (uU/ml): plasma glucose (mgm/100 ml) ratio of > 0.4 (2). In normal persons as the plasma glucose falls. plasma insulin simultaneously and concomitantly drops to produce a ratio of < 0.4. The use of this ratio in diagnosing cases of organic hyperinsulinism is highly specific but often

at the expense of sensitivity. Service et al (1) in a study of 60 patients at the Mayo Clinic reached the conclusion that any significant plasma insulin reading of 6 uU/ml should be considered suspicious of insulinoma, if the plasma glucose is below 50 mgm/100 ml in men or 40 mgm/100 ml in women, regardless of the insulin: glucose ratio. Extra-pancreatic tumour may produce substances with insulin-like properties and thus hypoglycaemia but these substances are non-immunoreactive and do not cross react with the radio-immunoassay methods for measuring insulin. Thus, the insulin: glucose ratio remains < 0.4 in such cases, though Whipples Triad may be satisfied.

Benign insulinomata are usually of small size and localisation can be a problem (3). In the series of patients studied by Service (1), 90% of the tumours were 2 cm diameter and 50% were ≤ 1.3 cm diameter in their longest dimension. The malignant tumours were usually larger in size compared to the benign ones, with a range of 2.5 cm to 12 cm diameter in their longest dimension. In view of their small size, ultrasound and CT scanning are of little value in preoperative localisation (4). Angiography and selective pancreatic vein catheterisation with blood insulin sampling appear to be more helpful, according to workers at the Mayo Clinic. But even then, with angiography, the accuracy of localisation is only at best 50 to 60% (5). In our patient's case, localisation posed no problem because of the size of the tumour.

The possibility of multiple tumours (10% in one series (6)) being present in the pancreas needs to be considered and during surgery the whole pancreas has to be exposed and explored systematically. Resection is relatively straight forward when the pathology has been localised. Problems arise when such tumours are not obvious. One stage total pancreatectomy with or without removal of the duodenum is probably not warranted. Intra-operative blood sugar level monitoring has been used to aid the extent and adequacy of pancreatic resection. (It is necessary to avoid glucose infusion in the pre-op and pre-excisional period, while monitoring the blood sugar level. This may not always be possible because of severe hypoglycaemia intra-operatively.)

In spite of the histological diagnosis of malignant insulinoma, our patient showed no evidence of hepatic or regional lymph node metastases at surgery. Liver scan performed pre-operatively was likewise normal. This is unusual as Broder (7) claims that in 90% of cases of malignant insulinoma, the liver is involved at the time of diagnosis. Our patient has remained asymptomatic without cytotoxic chemtherapy or diazoxide treatment following surgery in January 1981.

REFERENCES

1. Service FJ, Dale Allan JD, Elveback LR, JiangNS: Insulinoma: Clinical and diagnostic features of 60 consecutive cases. Mayo Clinic Pro 1976; 51: 417-428.
2. Foster DW, Ruberstein AH: Hypoglycaemia, insulinoma and other hormone secreting tumours of the pancreas. Harrisons Principles of Internal Medicine, 9th Edition p p 1758-1764, 1980.
3. Editorial: Diagnosis and treatment of insulin-secreting tumours. Lancet 1980; 1: 22-23.
4. Kaplan EL, Chen HL: Recent advances in the diagnosis and treatment of insulinomas. Surg Clinics N Amer 1979: 59: 119-130.
5. Fulton RE, Sheedy PF, McIlrath DC: Pre-operative localisation of insulin producing tumours of the pancreas. Amer J of Roentgenology 1975; 123: 367-377.
6. Stefanini P, Carbori M. Patrassi N. Basoli A: Beta islet cell tumour of the pancreas. Results of a study of 1067 cases. Surgery 1974; 75: 597-609.
7. Broder LE, Carter SK: Pancreatic islet cell carcinoma I. Clinical features of 52 patients. Ann Inter Med 1973: 79: 108-118.