Malignant insulinoma: The problems of tumour localization and management

A case report

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Summary

A case of malignant insulinoma in a Black patient is presented. An investigational protocol is suggested with a discussion of the newer techniques of pancreatic adenoma localization and the therapeutic measures available for the management of malignant islet cell tumours.

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Malignant insulinomas of the pancreas are rare tumours, accounting for 10% of cases of insulinoma in the Mayo Clinic series[1] and 16% of cases in the world literature,[2] with a likely bias towards malignant cases. At the time of diagnosis 69% have metastasized, usually to the liver. Ectopic pancreatic adenomas have a higher incidence of malignancy.[3]

New investigational techniques have evolved for the localization of pancreatic adenomas, but none is infallible. Some of the newer techniques and avenues of research which may yield fruitful diagnostic aid will be discussed.

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Case report

The patient, a 60-year-old Black man, presented at the Hillbrow Hospital with a history of having fainted with associated sweating, dizziness and palpitations. He had been admitted after two previous attacks, the only positive finding being hypertension, for which he was treated. On admission his blood sugar level was less than 1 mmol/l. He responded well to intravenous glucose administration. Apart from obesity and mild hypertension, examination proved negative.

An oral glucose tolerance test showed a characteristic flat curve. At the time of commencement of a 16-hour fast the insulin level was 182 μU/ml; the fast was stopped when the patient developed symptoms of hypoglycaemia at a blood glucose level of 1,7 mmol/l and an insulin level of 33 μU/ml (normal range 6 - 26 μU/ml).

Results of the following investigations were normal: serum gastrin and cortisol estimation, liver function tests including alkaline phosphatase measurement, barium meal, endoscopy, liver spleen isotope scan and grey-scale ultrasound examination of the liver. (The pancreas was not visualized.) Pro-insulin and C-peptide assays could not be obtained.

A transfemoral arteriogram was reported as showing a patent portal vein with an obstructed splenic vein with collateral drainage and associated multiple splenic varices. The pancreas was well visualized, except for the tail. The computed tomogram (CT) was also reported as being normal. Endoscopic retrograde cholangiopancreatography also failed to localize the tumour.

Percutaneous transhepatic portal vein insulin sampling at 2 cm intervals in the tributaries showed the insulin levels to be 167 μU/ml in the distal stump and 159 μU/ml in the proximal portion of the splenic vein, 61 μU/ml in the superior mesenteric vein, 48 μU/ml in the pancreaticoduodenal vein, 52 μU/ml in the right gastric vein and 33 μU/ml in the portal vein (Fig. 1).

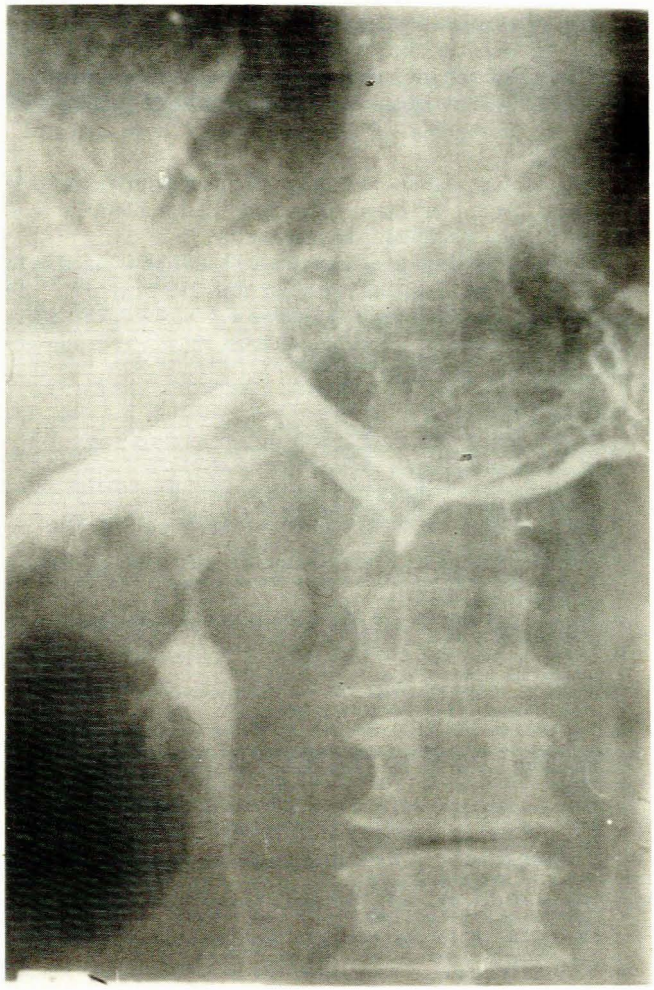

Fig. 1. Percutaneous transhepatic portogram demonstrating the splenic vein and proximal superior mesenteric vein.

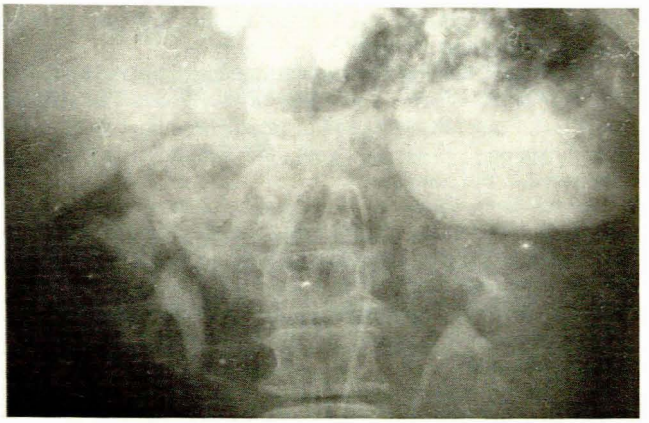

Fig. 2. Transfemoral arteriogram (venous phase) showing the tumour superomedial to the spleen.

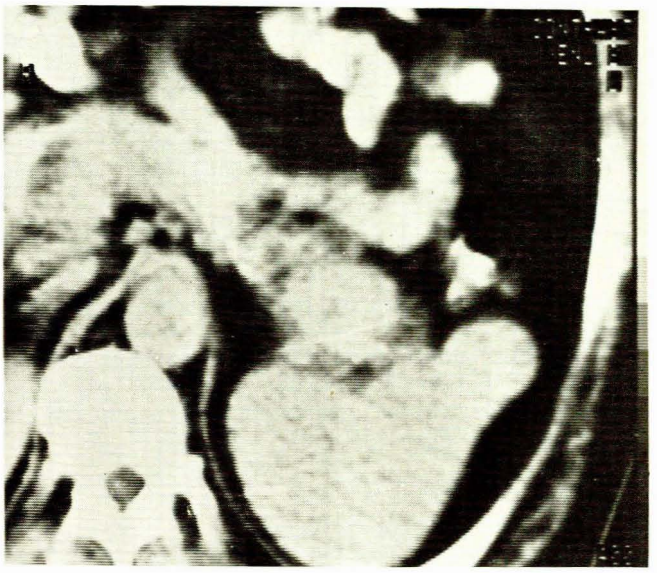

Fig. 3. CT scan with contrast. The insulinoma, anteromedial to the spleen, is in the tail of the pancreas.

Paradoxically, the portal vein insulin level was lower than that in the peripheral venous sample (149 μU/ml), since insulin is inactivated in the liver. Therefore, in conjunction with the finding of an obstructed splenic vein, it was surmised that the patient had a malignant insulinoma with a probable hepatic metastasis producing insulin.

At laparotomy a palpable lesion was found in the tail of the pancreas, measuring 3 x 3,5 cm with three hepatic metastases present in the apex of the right lobe. Frozen sections of peripancreatic lymph nodes were normal and a distal pancreatectomy with splenectomy was therefore carried out. Intra-operative glucose monitoring proved to be of no value and levels actually dropped after removal of the tumour. No splenic varices were demonstrated.

Histological examination showed a ß-cell malignant tumour of the pancreas with nuclear pleomorphism, numerous mitotic figures, perineural invasion and infiltration of the false capsule. Peripancreatic lymph nodes were normal. Biopsy of the liver metastasis revealed metastatic ß-cell tissue.

On retrospective review of the angiogram the tumour can be seen on the venous phase plates (Fig. 2) and also on the CT plates after contrast injections (Fig. 3).

During the postoperative period the patient was plagued by hypoglycaemia and diazoxide was therefore given to control the blood glucose level. He developed an inappropriate antidiuretic hormone-like syndrome, possibly because of the effect of diazoxide on glomerular filtration or because of bronchopneumonia. Diazoxide therapy was therefore terminated. Associated vasopressin production by the tumour cannot be excluded, as vasopressin levels were not assayed.

Three weeks postoperatively chemotherapy was commenced with fluoro-uracil, mithramycin and adriamycin, as streptozocin could not be obtained. Two weeks after the commencement of chemotherapy the blood glucose levels rose to 43 mmol/l and the patient required 12 IU insulin daily for control.

The hyperglycaemia could have been associated with glucagon production by the metastatic hepatic lesions, but this was never proved. The patient is now well, has a normal blood glucose level and does not require insulin administration.

Discussion

The technique of percutaneous transhepatic portal vein sampling was first described by Ingemansson *et al.*[4] with the locality of blood aspiration marked on the portogram. Turner *et al.*[5] used a similar technique of splenic vein cannulization intra-operatively and insulin was assayed within 50 minutes. At the adenoma site insulin levels should be greater than 200 μU/ml or three times the level of other sites, and portal vein levels should be greater than 500 μU/ml in order to be diagnostic. However, Dagett *et*

al.[6] used transhepatic portal vein sampling in 8 cases and only found localization accurate in 2 of these.

Isotopically labelled carriers with selective uptake by the adenoma remain a distinct possibility of the future. The scintigraphic technique has been used in phaeochromocytoma localization,[7] utilizing ^{131}I-labelled guanidine which is selectively concentrated in the tumour.

As has been shown by Tutt *et al.*[8] from the Mayo Clinic, intra-operative glucose monitoring and slope analysis of change are inaccurate. Intra-operative blood glucose levels are affected by pre-operative dextrose administration to control hypoglycaemia, general anaesthesia, administration of blood with citrate-phosphate-dextrose or, as in this case, by metastatic insulin secretion.

In a review by Broder and Carter[9] of 52 cases of pancreatic endocrine malignant tumours, which have similar behaviour patterns, the average age of the patients was 54 years, sex distribution was equal and 90% were Whites. As far as can be ascertained no other cases among South African Blacks have been reported. In contradistinction to benign adenomas, which are equally distributed along the pancreas, the study showed that 45% of malignant tumours occurred in the tail. At a 95% confidence level responders to streptozocin therapy survived 1 268 days versus 518 days for non-responders. Biochemical evidence of complete or partial remission was found in 64%, and 50% had a measurable response. However, 98% of the patients developed side-effects, the most serious being renal toxicity (65%) and hepatotoxicity (67%).

More recently streptozocin has been used in combination with fluoro-uracil in a randomized trial, with increased survival rates when compared with streptozocin alone.[10] A new drug, chlorozotocin, is being investigated, this having greatly reduced side-effects.[10]

Therapeutic embolization has been disappointing because of the lack of end-arteries in the pancreas. A possible future therapeutic measure is isotopic irradiation with isotope carriers with an affinity for islet cells.[3]

The most advisable approach to islet cell tumours should be to assay the suspected hormones, to attempt to localize the adenoma with subtraction view venous phase arteriograms and CT scans, followed by laparotomy. In a recent series of 60 patients with an insulinoma 58 of the tumours were palpated at operation.[11]

If no tumour is found, a biopsy specimen from the tail of the pancreas should be taken to exclude nesidioblastosis which would require a subtotal pancreatectomy.[12]

A blind 70% distal pancreatectomy should be avoided as this only has a reported success rate of between 23% and 35%.[13,14] The patient should preferably undergo more extensive investigations during or after the operation, such as splenic vein hormone assays, followed by re-operation.

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