Cryotherapy of hepatic metastases and regional perfusion with low-dose streptozotocin in the management of metastatic malignant insulinoma

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Abstract

A 67-year-old man with intractable hypoglycaemia due to a malignant pancreatic insulinoma with multiple hepatic metastases is reported. Continuous intravenous infusion of dextrose was necessary to prevent life-threatening hypoglycaemia; high-dose parenteral octreotide was ineffective and oral diazoxide was associated with intolerable gastrointestinal side-effects. Preoperative imaging failed to identify the primary tumour with certainty. At laparotomy, the tumour was located in the pancreas and excised. Intraoperative cryotherapy was administered to hepatic metastases inducing localised ice-ball formation and subsequent necrosis of the lesions. These interventions led to prompt resolution of the hypoglycaemia with normalisation of plasma concentrations of islet B-cell products. In an effort to consolidate the beneficial effects of surgery, chemotherapy was instituted post-operatively using the islet B-cell toxin streptozotocin. In an innovative therapeutic approach, the drug was infused via the hepatic artery for 5 consecutive days at a reduced dose calculated to induce an insulitis in the residual hepatic metastases analogous to that described in murine models of diabetes. The chemotherapy was well tolerated although the course of treatment was curtailed by problems with catheter placement. Nonetheless, the patient has, to date, remained well and free from hypoglycaemia during more than 3 years of follow-up. These therapeutic strategies appear to merit further evaluation.

Introduction

Metastatic malignant insulinoma is an uncommon tumour accounting for approximately 10% of all cases of insulinomas. The prognosis for patients with advanced disease is generally poor with a reported median survival rate of only 26 months following chemotherapy (Moertel et al. 1980). Nonetheless, individual patients have been reported with untreated metastatic disease who have survived for years or even decades.

Surgical ablation is regarded as the treatment of choice for malignant B-cell tumours. Removal of the
primary lesion and resection of as many secondary deposits as possible may add years of useful life. Hepatic arterial embolisation has also been used with therapeutic success. As an adjunct to surgery, or in patients in whom surgery is considered contra-indicated or inappropriate, medical therapy with diazoxide and chlorothiazide can be effective for prolonged periods (Marks & Rose 1981). More recently, the long-acting somatostatin analogue octreotide has been used, either alone or in combination with other agents (Stehouwer et al. 1989), although not all insulinomas have proved responsive. When intractable hypoglycaemia supervenes, chemotherapy may induce further remissions. The B-cell toxin streptozotocin has been the mainstay of chemotherapy and modest improvements in survival have been accomplished by combining the drug with 5-fluorouracil (Moertel et al. 1980). However, streptozotocin is associated with significant adverse dose-related effects, principally on renal function and haemopoiesis. In addition, gastrointestinal side-effects may prove dose-limiting at standard doses. We report a novel, and to date successful, therapeutic approach combining resection of the primary tumour and cryotherapy to hepatic metastases at laparotomy, with post-operative low-dose streptozotocin via the hepatic artery which induced complete remission from life-threatening hypoglycaemia in a patient with a metastatic malignant insulinoma.

**Patient and Methods**

A 67-year-old man was admitted to hospital as an emergency following a nocturnal tonic-clonic convulsion. During the preceding 10 months he had complained of transient visual disturbances accompanied by a vague sensation of pressure within his head. The symptoms were relieved by meals and he had gained approximately 15 kg in weight. He was on no relevant medication at the time of admission. On arrival the patient was conscious but drowsy. On physical examination, he was overweight but no other abnormalities were detected. Initial investigations revealed a capillary blood glucose (determined using a glucose-oxidase strip and reflectance meter) of 2.0 mmol/l. The venous plasma glucose concentration (analysed in the laboratory using a hexokinase method) was 2.3 mmol/l. A presumptive diagnosis of a hypoglycaemia-induced convulsion was made. After an overnight fast, the patient’s venous plasma glucose concentration was 2.5 mmol/l. This was accompanied by markedly elevated concentrations of immunoreactive insulin (1374 pmol/l) and C-peptide (2110 pmol/l), confirming a diagnosis of hypoglycaemia secondary to an insulinoma. During

![Figure 1](image-url) **Figure 1** Preoperative T1 weighted magnetic resonance scan with gadolinium enhancement demonstrating multiple hepatic metastases.
hypoglycaemia, the plasma proinsulin concentration was also elevated at 347 pmol/l, a recognised feature of insulinomas. An abdominal ultrasound scan demonstrated multiple ‘target lesions’ in the liver which were considered to have appearances typical of metastatic deposits. Subsequently, CT scanning confirmed the presence of hepatic metastases together with a small hypodense area in the pancreas. A magnetic resonance scan with gadolinium enhancement, whilst demonstrating the previously noted hepatic deposits, did not, however, identify a definite primary tumour in the pancreas (Fig. 1).

Despite frequent carbohydrate-containing meals the patient became biochemically hypoglycaemic on several occasions, episodes which were not always symptomatic.

A continuous infusion of 1 litre 12 hourly of 5% dextrose was necessary to maintain blood glucose concentrations above 3 mmol/l. At this stage the patient was transferred to the General Hospital, Birmingham for further evaluation and treatment. Infusions of 10% dextrose soon became necessary to avert hypoglycaemia although this therapy was not completely successful. In an attempt to alleviate the hypoglycaemia and sustain life in preparation for more definitive treatment, subcutaneous octreotide was administered as an adjunct to the intravenous dextrose commencing with a dose of 50 μg daily. This was rapidly escalated in increments to a maximum dose of 4.5 mg/24 h, delivered by continuous subcutaneous infusion. Disappointingly, the benefits of this higher dose were minimal. The ineffectiveness of high-dose octreotide may have been attributable to the expression of low-affinity somatostatin receptors by our patient’s tumour (Kubota et al. 1994). Octreotide was therefore replaced with diazoxide (100 mg t.d.s.) together with hydrochlorothiazide (Marks & Rose 1981). However, this therapy was also rapidly abandoned because of intolerable drug-induced nausea.

After several weeks of medical therapy an exploratory laparotomy was performed. At operation, a 2 cm diameter primary tumour was located in the tail of the pancreas which was excised. The histology of the tumour was that of an insulinoma and immunocytochemical studies confirmed positive staining for insulin and carcinoembryonic antigen. A prophylactic cholecystectomy was performed in anticipation of post-operative regional chemotherapy. At operation, multiple hepatic metastases were visible on the surface of the liver. These were treated with cryotherapy using a surgical cryoprobe (Spembly Medical 130 Cryo Unit, Surgical Technology Group, Andover, Hants, UK). Cryotherapy was administered by inserting the probe into the metastases under direct vision. The metastases were
frozen to induce a localised ice-ball, thawed and refrozen to produce subsequent necrosis of the lesions (Morris et al. 1993). Post-operatively, a prompt and dramatic improvement in blood glucose levels was observed and the intravenous dextrose infusion was successfully withdrawn following resolution of intestinal ileus. Thereafter, blood glucose concentrations remained normal without the need for frequent carbohydrate meals or specific anti-hypoglycaemic therapy. The patient was allowed home temporarily after being instructed in self-monitoring of capillary blood glucose. A post-operative CT scan (Fig. 2) demonstrated several residual metastases that had not been accessible with the cryoprobe.

In an attempt to consolidate the beneficial effects of surgery, the first of a series of 5-day courses of chemotherapy with the islet B-cell toxin streptozotocin was administered. We employed an innovative therapeutic approach with the aim of testing the hypothesis that multiple low-dose doses of streptozotocin, delivered via the hepatic artery, would induce an insulinitis in the remaining metastases analogous to that observed in a murine model of diabetes mellitus (Like & Rossini 1976). By extrapolation from the murine model, we calculated a reduced dose of streptozotocin (250 mg) which was administered daily for 5 days via a temporary catheter placed in the hepatic artery. Under prophylactic anti-emetic treatment with dexamethasone and ondansetron the first course of chemotherapy proved to be very well tolerated. The end-points for chemotherapy had been set in advance as either (a) the development of fasting hyperglycaemia or (b) unacceptable side-effects or complications of the treatment. Six weeks later, the patient was readmitted for the second course of chemotherapy. The hepatic artery catheter was again inserted via the right femoral artery and removed after 5 days. Unfortunately, mechanical difficulties in maintaining patency of the hepatic artery catheter on this second occasion resulted in the premature curtailment of the chemotherapy. Since the patient's clinical and biochemical status at this time was satisfactory no further attempts were made to administer streptozotocin since the probability of eradicating the metastases completely was judged to be relatively small. At review 12 months post-operatively, the patient was clinically well and had not experienced any symptomatic or biochemical episodes of hypoglycaemia. The only regular medication he was receiving was a beta-adrenergic blocker (sotalol) which had been prescribed for a recurrent atrial tachyarrhythmia. A follow-up CT scan showed a considerable improvement in the appearances of the liver metastases (Fig. 3). Fasting venous plasma glucose concentration at this review was 6.6 mmol/l with a normal plasma immunoreactive insulin concentration of 36 pmol/l and an appropriate

Figure 3 Abdominal CT scan appearance 14 months post-operatively.
C-peptide of 603 pmol/l. Oral glucose tolerance was normal with a 2-h plasma glucose concentration of 6.9 mmol/l following a 75 g glucose challenge. The period of follow-up is now in excess of 3 years and the patient remains in good health.

Discussion

Patients with malignant insulinomas may occasionally respond well to combinations of surgery, chemotherapy and/or hepatic embolisation. Removal of the primary pancreatic tumour and application of cryotherapy to hepatic metastases visualised at laparotomy produced an immediate, complete and sustained resolution of our patient's hypoglycaemia. Intra-operative cryotherapy has been hailed as a significant advance in the management of metastatic liver tumours (Morris et al. 1993). The technique has been used in patients with a variety of hepatic tumours and the accuracy and safety of the procedure are reported to be favourable (Morris et al. 1993). Experience in malignant insulinomas is, however, limited and no controlled trials comparing cryotherapy with conventional surgery for insulinomas have been performed. Whether the surgical manoeuvres alone would have resulted in freedom from hypoglycaemia for over 3 years in our patient is unknown. In order to consolidate the success of surgery we administered streptozotocin in a reduced dose by regional perfusion. When given in a sufficient quantity (200 mg/kg) as a single dose, streptozotocin will cause complete destruction of islet B cells in mice within 24 h through toxic effects which include alkylation of DNA. In the 1970s it was reported that sub-diabetogenic doses of the drug (40 mg/kg), administered daily for 5 days, produced diabetes mellitus of more gradual onset with hyperglycaemia occurring 5-6 days following the final injection (Like & Rossini 1976). This slower-onset diabetes is associated with a marked lymphocytic insulitis suggesting a cell-mediated immune response. We hypothesised that a reduced dose of streptozotocin, administered by regional perfusion, might destroy the residual functioning hepatic metastases in our patient. Recognising the pitfalls of extrapolating between species we cannot be certain whether we succeeded in inducing an insulitis within the metastases; biopsy of the lesions was considered to be unjustified. However, in view of the generally poor prognosis of patients with malignant insulinomas, further evaluation of these therapeutic strategies appears to be warranted.

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