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Original Article

Management Challenges in a Child with Hyperinsulinemic Hypoglycemia

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Abstract. Malignant insulinoma is very rare in children. Herein, we present a case of a child with malignant insulinoma along with islet cell hyperplasia. She initially presented with features of hyperinsulinemic hypoglycemia at 18 mo of age. Magnetic resonance imaging (MRI) of the abdomen showed a mass at the junction of the head and body of the pancreas. The tumor was enucleated. Five months later symptoms of hypoglycemia recurred. A subtotal pancreatectomy was performed. She continued to have hypoglycemia, although less frequently. She was put on increasing doses of diazoxide. Seven months later, MRI of the abdomen and a PET scan revealed metastatic deposits in the liver, which were confirmed by histopathology and immunostaining. To the best of our knowledge, this is the youngest child with metastatic insulinoma reported so far.

Key words: malignant insulinoma, childhood, liver metastasis

Introduction

Persistent hyperinsulinemic hypoglycemia (HIH) in children is a big diagnostic and management challenge. Children usually have microadenoma, microadenomatosis or functional disorders. Insulinoma is rare and usually benign (1). Around 75 cases of childhood insulinoma have been reported in the last 45 years. Of these, only 3 were found to be malignant and only one was reported to be associated with active liver metastasis (2). Herein, we discuss a case of persistent HIH due to malignant insulinoma.

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Patient Report

Baby D K was the product of a normal vaginal delivery at full term to nonconsaguineous parents, was first in birth order and had an average birth weight. The perinatal period was uneventful. Early developmental milestones were normal. She presented with a history of recurrent episodes of transient loss of consciousness, falls, drowsiness and excessive sweating at the age of 18 mo. She was treated as a case of seizure disorder but there was no response to antiepileptics (phenytoin).

Thereafter, she was reevaluated and found to have low postabsorptive blood glucose (40 mg/dl) with a high serum insulin level (10.8 μIU/ml).

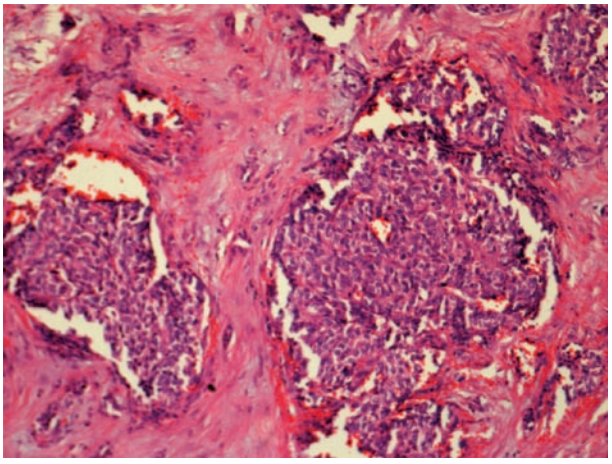

Fig. 1. Section from a pancreatic mass showing a neuroendocrine tumour arranged in a nest-like pattern surrounded by fibrocollagenous tissue (Hematoxylin & Eosin × 100).

Table 1 Laboratory data

Parameters (units)	Value	Normal range
Urea (mg/dl)	14	10–50
Creatinine (mg/dl)	0.4	0.5–1.8
S. Sodium (mEq/l)	141	130–149
S. Potassium (mEq/l)	4.8	3.5–5.0
S. calcium (mg/dl)	10.2	8.1–10.4
S. phosphorus (mg/dl)	4.6	2.5–4.5
S. bilirubin (mg/dl)	0.5	0.8–1.0
Serum total protein (gm/dl)	7.0	6.6–8.7
Serum albumin (gm/dl)	4.8	4–5.5
Serum globulin (gm/dl)	2.2	3.8–4.0
SGOT (U/L)	56	Up to 50
SGPT(U/L)	50	Up to 50
S alkaline phosphatase (IU/L)	369	240–840
T4 (nmol\L)	80	5.1–14.1
TSH (μIU/ml)	2.46	0.27–4.2
HbA_{1C} (%)	4.1	<5
Blood glucose (mg/dl)	50	60–110
S. insulin (μU/ml)	60.90	2.6–24.9

Her urine was negative for ketones, aminoacidogram was normal and ferric chloride test was negative. The results of a computed tomography (CT) scan of her head were normal. Magnetic resonance imaging (MRI) of the abdomen revealed a tumor (1.4 × 1.2 cm) at the junction of the head and body of the pancreas. The tumor was enucleated.

Histopathology showed that it was a neuroendocrine tumour, consistent with a clinical diagnosis of insulinoma (Fig. 1). The lymph nodes were free of tumors. The patient remained asymptomatic for the next 5 mo. After that, she began to experience episodes of hypoglycemia again. This time, the patient was referred to the Endocrinology Department (at the age of 24 mo). Anthropometry revealed a height of 94 cm (97^{th} centile, CDC growth charts, developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion; http://www.cdc.gov/growthcharts) and weight of 14 kg (90^{th} centile, CDC growth charts). The results of a physical examination were essentially normal. There was no midfacial hypoplasia, hemihypertrophy, midline facial defects, skin lesions or hypertelorism. There was no family history of diabetes, multiple endocrine neoplasia (MEN) syndromes or similar illness or gestational diabetes in the mother. Details of the laboratory tests are provided in Table 1.

The results of a chest X-ray and electrocardiogram were normal. MRI of the abdomen for the pancreas was normal. She continued to have hypoglycemia despite aggressive medical management with intravenous glucose, octreotide and diazoxide. Therefore, a subtotal distal pancreatectomy (90%) was performed. The frequency of hypoglycemic episodes decreased after the subtotal pancreatectomy. This child was continued on octreotide and diazoxide, and as her blood glucose stabilized, octreotide was tapered off. She remained asymptomatic for one month. As she started having recurrent episodes of hypoglycemia, the dose of diazoxide was increased to 15 mg/kg/day.

Approximately 8 mo later, she required

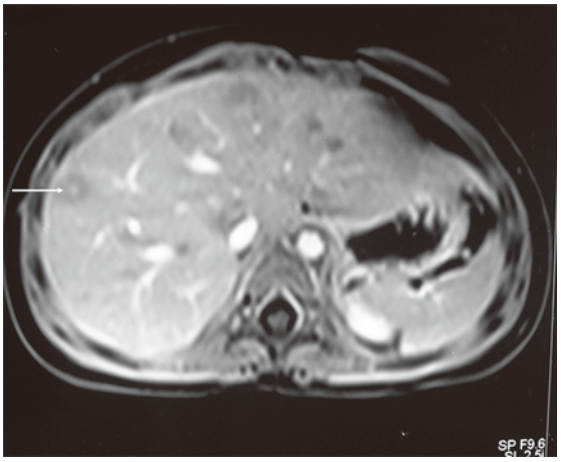

Fig. 2. MRI of the abdomen (post contrast) showing multiple nodules in both lobes of the liver with faint central enhancement (arrow).

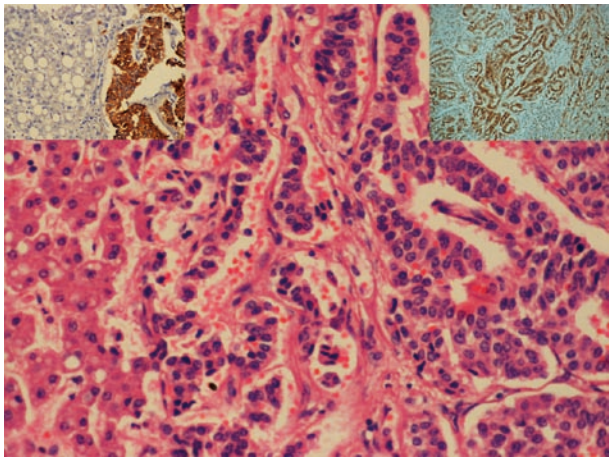

Fig. 3. Sections from a liver nodule showing a neuroendocrine tumour with a trabecular pattern and nuclei having stippled chromatin. Insets shows positive staining for synaptophysin (left) and insulin (right; Hematoxylin & Eosin × 200).

hospitalization. She was restarted on octreotide and needed to be on intravenous glucose continuously to maintain euglycemia. The child had developed hypertrichosis and pedal edema attributable to diazoxide. Ultrasonography and MRI of the abdomen revealed nodules in the liver (Fig. 2). Increased uptake in corresponding areas in the liver was observed in a positron emission tomography (FDG-PET) scan that was suggestive of a metastatic lesion. She was on continuous intravenous glucose, diazoxide and octreotide during this time. A few weeks later, she developed septicemia and died. Her blood cultures revealed growth of enterococcus. An autopsy showed malignant endocrine neoplasm in the residual pancreas along with diffuse islet cell hyperplasia. There were multiple metastases in both lobes of the liver. The tumour cells were immunocytochemically positive for synaptophysin and insulin, thereby confirming a diagnosis of malignant insulinoma (Fig. 3, insets). The lymph nodes were free of any malignant infiltration. The other endocrine glands were normal.

Discussion

Insulinomas are very rare tumors. The reported incidence is only 4 per million person-years (1, 2).

They are more common in adults. The median age at diagnosis is 50 yr for solitary tumors and 23 yr for MEN 1 (2). In the Mayo series, of 145 cases of benign insulinoma operated upon from 1982 to 1998, the youngest reported case was in a 15-yr-old patient (1). Out of 31 patients with benign insulinoma evaluated at our hospital from 1992 to 2005, the youngest reported case was again in a 15-yr-old patient (3). In another large series of malignant pancreatic tumors in children and adolescents from 1967 to 2002, none of the seventeen patients operated upon and treated had a malignant insulinoma (4). Insulinomas are mostly solitary, benign (90–95%), small tumors with an average size of 1 to 2 cm [up to 15 cm reported] (1, 2). It is very difficult to clinically or biochemically differentiate benign from malignant tumors. In one of the series, tumor risk factors such as a

size >20 mm, local invasion and angio-invasion, cell atypia, metastasis and nonfunctioning nature have been described to differentiate malignant tumors from benign tumors (5). Nuclear DNA ploidy, cytological changes, etc. have failed to distinguish benign from malignant tumors (6). Elevated levels of chorionic gonadotropin, its subunits and a high percentage of proinsulin has been linked with malignancy (7), which subsequent studies have not confirmed (8–10). Thus, metastasis to the peripancreatic lymph node and liver is the only definitive pointer to the malignant nature of the insulinoma. Recently, allelic loss of chromosome 3p25 has been used as a molecular marker for this distinction (11). The prognosis for long-term survival for malignant insulinoma is very bleak (29%) compared with benign insulinomas [91%] (1).

To date, 75 cases of childhood insulinoma have been published (2). Out of these, only three cases have been reported as malignant (12–14). Our patient had the tumor enucleated and underwent subtotal pancreatectomy five months later because of persistent hypoglycemia and inadequate response to octreotide and diazoxide. However, even this could not relieve her symptoms. She later showed evidence of metastatic deposits. The young age at diagnosis, rapidity of events and poor response to octreotide and diazoxide point to the aggressive nature of the insulinoma in this case.

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