

MULTIPLE ENDOCRINE NEOPLASIA: CASE REPORT

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SUMMARY – Hypoglycemia may occur as a component of type 1 multiple endocrine neoplasia syndrome. Insulinomas are rare tumors that often present a diagnostic dilemma for the clinician. The presence of inappropriately high plasma insulin and C-peptide concentrations at the time of symptomatic fasting hypoglycemia confirms the diagnosis of insulinoma. A. B., a 21-year-old girl, presented for evaluation of recurrent episodes of hyperhidrosis, confusion, and weakness with tremor, which was suggestive of hypoglycemia. Her body mass increased by 90 kg, with persistent symptoms of hypoglycemia. Because of her extremely excessive body weight of 158 kg, the only diagnostic method available was upper abdomen ultrasonography, which revealed a tumor mass of 26 mm in size, located at the tail of the pancreas. Hemipancreatectomy and splenectomy were performed in one act. After the surgery, clinical symptoms disappeared but the patient developed diabetes, postoperatively, which required introduction of insulin therapy. Her body weight gradually normalized, she lost 54 kg, and postoperative magnetic resonance and computed tomography controls produced normal findings.

Key words: *Multiple endocrine neoplasia type 1, diagnosis; Multiple endocrine neoplasia type 1, complications; Hypoglycemia, etiology; Case report*

Introduction

Multiple endocrine neoplasia (MEN) syndrome denotes a rare, heritable disorder with predisposition to tumors of the parathyroid glands, anterior pituitary, and pancreatic islet cells ('3 Ps')¹. Adenomas of the adrenal and thyroid gland can also occur. The prevalence of multiple endocrine neoplasia type 1 (MEN 1) is around 2 per 100,000^{2,3}. A genetic linkage analysis has implicated a region on the long arm of chromosome 11 (11q13) as the site of the 'MEN 1 gene', but the mechanism by which the genetic defect in MEN 1 leads to tumor formation has not yet been clarified. The actual outgrowth of a tumor is thought to require subsequent somatic inactivation, often by gross deletion, of the normal copy of the gene in

one cell, and such cell would then be devoid of the MEN 1 gene's normal tumor suppressor function and could gain a selective advantage over its neighbors, resulting in clonal proliferation⁴⁻⁹. Hyperparathyroidism is the most common manifestation of MEN 1, displaying almost 100% penetrance by age 40-50.

Anterior pituitary disease, i.e. clinically apparent pituitary tumors, develop in 15% – 20% of patients with MEN 1 when sought by computed tomography (CT) or magnetic resonance imaging (MRI), but the pathologic prevalence of pituitary tumors may be over 60%¹⁰. The most common type of pituitary tumor in MEN 1 is prolactinoma. The prevalence of prolactinoma is more than 50% in some branches of the kindred, and accounts for 50% of cases of hyperprolactinemia. The tumors are classified as microadenomas (<1 cm in diameter) and macroadenomas (less common in women; they may extend as suprasellar, parasellar, or anterior-inferiorly into the sphenoid sinus)¹¹.

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The symptoms may be related directly to the tumor, such as headache and diplopia, or to the specific hormone overproduction, e.g., oligo- or amenorrhea, galactorrhea, mild obesity, hirsutism, frictional dyspareunia, and loss of libido¹². Tumors may also produce growth hormone (30%) or ACTH (<10%), leading to acromegaly or Cushing's disease. MRI is slightly superior to CT in the detection of microadenomas.

Patients with serum prolactin level above 200 ng/ml usually have a MRI demonstrable tumor; serum prolactin level above 1000 ng/ml suggests cavernous sinus invasion. About 80% – 90% of microadenomas do not ??.

Insulinoma, i.e. insulin-producing pancreatic islet cell tumor of the pancreas, has been reported in about 80% of patients with MEN 1. Insulinomas are the most common islet cell tumors of the pancreas, with a reported incidence of 0.8 – 0.9 cases *per* 1 million population *per* year. These tumors occur slightly more often in women than in men, and the average age at presentation is between 40 and 50 years¹³. About 40% of these islet cell tumors originate from β cells, secrete insulin, and are associated with fasting hypoglycemia. In about 60% of cases, the islet cell tumors derive from non- β cell elements. Gastrin is the hormone most commonly secreted by the non- β cell tumors and is associated with intractable and complicated peptic ulceration (Zollinger-Ellison syndrome). Both β - and non- β cell tumors usually are multicentric and small in origin, and multiple adenomas or diffuse islet cell hyperplasia commonly occur. In about 30% of patients, the islet cell tumors are malignant, with local or distant metastases, but these tumors in MEN 1 syndrome often follow a more benign course than sporadic islet cell carcinomas. The incidence of malignancy appears to be higher in non- β cell tumors^{14,15}. The clinical symptoms of insulinomas are due to the hypoglycemia induced by excess insulin secretion.

The diagnosis of pancreatic endocrine tumors is usually made by the recognition of the clinical syndrome caused by excess hormone production. The most reliable method of diagnosing an insulinoma is the provocative test of fasting. Blood glucose and insulin levels are measured every 4–6 hours during fast. Eighty percent of patients with insulinoma become symptomatic within 24 hours of starting the fast, and almost all will be symptomatic if the fast is continued for 72 hours. The presence of an elevated insulin level higher than 6 μ U/ml along with concurrent hypoglycemia and an insulin – glucose ratio greater than 0.3 confirm the diagnosis. Measurement of the β cell products C-peptide and proinsulin is important

because they both are usually elevated in patients with insulinoma. Patients who surreptitiously administer insulin to themselves will usually have low levels of C-peptide and proinsulin. Once the diagnosis has been confirmed, localization studies are carried out. A majority of insulinomas are 10–15 mm in diameter and are evenly distributed throughout the pancreas^{16–18}. Dynamic CT scanning is usually the first localizing study done because it can detect about two thirds of primary tumors and a majority of metastatic lesions. When no tumor is seen on CT scan, visceral angiography with digital subtraction techniques is successful in visualizing lesions in some 60% – 90% of the time. Selective portal venous sampling is reserved mainly for patients whose tumors cannot be visualized with CT or angiography. Portal venous sampling can define the general area of the tumor in 90% of all patients and in about 75% of those in whom other localizing tests have been negative. Histologic diagnosis of these tumors can be made by CT-guided fine-needle aspiration.

Case Report

In 1996, at age 16, the patient experienced headache, galactorrhea, primary amenorrhea, and low height for her age. Laboratory tests showed an increased prolactin level exceeding 400 ng/ml. CT scan of the pituitary gland revealed a tumor mass, 1.5x0.9 cm in size (1.5 cm anteroposteriorly, 0.9 cm craniocaudally). Transnasal selective partial adenectomy was performed, and postoperative excisional biopsy showed a prolactinoma (chromophobic adenoma). Postoperatively, levothyroxine (100 mg) and hydrocortisone (30 mg) were prescribed as adjuvant therapy because of the postoperatively developed hypopituitarism. Laboratory tests showed decreased glucose levels, which have never been thoroughly explained because the patient left the hospital. Then, there had been no information on the patient's condition for four years, when she presented again with overt clinical symptoms of hypoglycemia, including weakness, tremor, and mental confusion. The patient's body weight was 158 kg (90 kg in excess from her previous presentation). Her high body mass was caused by persistent hypoglycemia, which forced her to take large amounts of carbohydrates. We knew that she had a tumor secreting insulin or insulin-like growth factor (IGF). Laboratory tests pointed to very low glucose levels. CT and MRI of the abdomen could not be performed because of the patient's high body weight (158 kg). An attempt was made to perform i.v. angiography, but the

hospitalization, glucose levels were within the normal range and therapy was discontinued. MRI and CT performed one year postoperatively, when the patient had lost 56 kg of her body weight, showed normal abdominal tissue.

The diagnosis of pancreatic insulinoma was verified by postoperative pathohistology (Fig. 5).



Fig. 5. Tumor tissue.

Methods

A plasma insulin concentration of 6 $\mu\text{U/ml}$ (36 pmol/l) or greater, when plasma glucose is below 45 mg/dl (2.5 mmol/l), indicates an excess of insulin and is consistent with insulinoma. Plasma glucose falls below 50 mg/dl (2.8 mmol/l) in some normal individuals and may occasionally remain above 50 mg/dl in a patient with insulinoma.

The measurement of C-peptide can be used to distinguish endogenous from exogenous hyperinsulinemia. All insulinoma patients had higher values, and normal individuals who were hypoglycemic had lower values. In case of proinsulin, the diagnostic criterion for insulinoma is 5 pmol/l or greater.

Transabdominal US shows pancreatic endocrine tumors as hypoechoic, well circumscribed masses within the pancreas, whereas liver metastases appear as hyperechoic lesions. The sensitivity of this technique for detection of primary tumors is between 19% and 32%, which is considerably below the sensitivity of other imaging techniques. It is therefore of limited value in the assessment of pancreatic endocrine tumors.

On non-enhanced CT scan, primary pancreatic endocrine tumors are poorly visualized. When i.v. contrast is administered, primary pancreatic endocrine tumors appear as rounded, enhancing lesions but may be extremely subtle. The likelihood of detection of pancreatic endocrine

tumors by CT depends on the tumor size and localization. Although localization of tumors as small as 0.7 cm in diameter has been reported, those of less than 2 cm cannot be found consistently. The sensitivity of CT for detecting primary insulinomas ranges between 31% and 59%.

On MRI, pancreatic endocrine tumors usually show low signal intensity on T1-weighted images and high intensity on T2-weighted images. The sensitivity of MRI is similar to that of CT.

Discussion

Insulinoma is an uncommon but important cause of hypoglycemia because it is usually curable. It may occur as an isolated abnormality or as a component of type MEN 1 syndrome. Diagnosis requires evidence that the symptoms occur in association with an abnormally low plasma glucose level, which is generally defined as <50 mg/dl in men, <45 mg/dl in women, and <40 mg/dl in children. Plasma insulin, proinsulin, C-peptide levels, and blood lactate with pH should be determined. Patients with insulin-secreting pancreatic tumor such as insulinoma usually have increased proinsulin and C-peptide levels that parallel the levels of insulin. An initial plasma insulin level of >6 $\mu\text{U/ml}$ and certainly that of >10 $\mu\text{U/ml}$ associated with hypoglycemia is inappropriately high and strongly suggest an insulin-secreting tumor.

Patients with insulinoma are frequently asymptomatic when they finally seek medical attention for isolated episodes of sudden confusion or unconsciousness that have occurred over a period of years and have become more frequent with time. The episodes characteristically occur in the postabsorptive period or after an overnight fast, and are sometimes precipitated by exercise.

Insulinomas are usually too small to be detected by standard x-ray or CT scan. Once the tumor has been localized, surgical exploration is performed. Insulinomas are more difficult to manage, since the lesions are often small and difficult to find, and multiple lesions commonly exist. If a single tumor cannot be found, total pancreatectomy may be required for appropriate control of hyperinsulinism. Distal pancreatectomy is recommended for small lesions near the pancreatic duct to minimize the risk of pancreatic fistula. Large lesions of the head of the pancreas may require pancreaticoduodenectomy, whereas those of the body and tail of the pancreas can be treated with distal pancreatectomy. Insulinomas are identified about 95% of the time at initial exploration. Blind resec-

tion is not recommended when no tumor is identified. A second exploration using intraoperative US has a greater than 90% chance of identifying and resecting the lesion^{18,19}. If no tumor is identified on second exploration, then pancreatic biopsy is recommended to rule out β cell hyperplasia, a condition that can be treated by subtotal pancreatectomy. Because pancreatic exploration involves significant risks of inducing pancreatitis and other complications, and because intraoperative identification of a small insulin secreting tumor requires experience in the area, patients with a presumptive diagnosis should be referred to a referral center for evaluation by experienced physicians prior to surgery. Forty percent of patients with MEN 1 develop adrenal tumors. Therefore, prior to surgical resection of endocrine tumors, all MEN 1 patients need to be screened by measuring urinary excretion of glucocorticoids, mineralocorticoids, catecholamines, vanillylmandelic acid, metanephrines, and sex hormones. Two drugs that inhibit insulin secretion are available, diazoxide and octreotide (a long-acting octapeptide analog of somatostatin); both drugs also have other effects and consultation with a physician experienced in their use is recommended. Resectability is defined by the absence of metastatic disease and of invasion of the superior mesenteric or hepatic arteries. In general, insulinomas carry quite a good prognosis.

Treatment of pituitary lesions is primarily surgical, although in some cases pituitary irradiation may suffice. Patients with prolactin levels of <100 ng/ml and normal CT or MRI scans, or those who only have microadenomas can be treated with bromocriptine or be kept under surveillance by an endocrinologist, neurosurgeon and radiotherapist²⁰. As hyperprolactinemic women are often hypoestrogenic and appear to be at an increased risk of developing osteoporosis, treatment with bromocriptine is preferred. Periodic monitoring of basal prolactin levels and radiographic evaluation of sella turcica are indicated in everyone with hyperprolactinemia. Patients should be evaluated at least quarterly and should undergo repeat CT or MRI annually for at least additional two years. The frequency of sellar x-rays can then be reduced if there is no increase in basal prolactin levels. Individuals with macroadenomas generally should be treated with bromocriptine or surgery only after thorough endocrine testing of pituitary function and consultation. Bromocriptine, a dopamine agonist, can be used to treat prolactinomas medically. Transsphenoidal hypophysectomy is reserved for patients who fail to respond to bromocriptine and who have non-prolactin secreting tumors. All patients with MEN 1 should be followed periodically by measuring serum prolactin and growth hormone levels.

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Sažetak

VIŠESTRUKA ENDOKRINA NEOPLAZIJA TIPA 1 (MEN 1): PRIKAZ SLUČAJA

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Hipoglikemija se može pojaviti u sklopu sindroma višestruke endokrine neoplazije tipa 1. Inzulinom je rijedak tumor koji često predstavlja dijagnostički problem za kliničara. Neuobičajeno visoke koncentracije inzulina i C-peptida iz plazme za vrijeme hipoglikemije potvrđuju dijagnozu inzulinoma. A. B., 21-godišnja bolesnica je primljena na kliniku zbog opetovanih epizoda slabosti, psihičke konfuznosti i umora s tremorom, što je ukazivalo na hipoglikemiju. Četiri godine ranije operirala je prolaktinom hipofize i otada nije imala kontrolnih pregleda. Iste godine javili su se simptomi hipoglikemije, uza značajan porast tjelesne težine od 90 kg zbog velikih količina ugljikohidrata koje joj je obitelj davala zbog čestih hipoglikemija. Jedina dostupna dijagnostička tehnika s obzirom na njezinu prekomjernu tjelesnu težinu od 158 kg, koja bi potvrdila dijagnozu inzulinoma, bio je ultrazvuk gornjeg abdomena. Ultrazvuk je pokazao tumorsku tvorbu veličine 26 mm u području repa gušterače. Izvedena je hemipankreatektomija uz splenektomiju. Klinički znaci hipoglikemije povukli su se nakon operacijskog zahvata, ali je tada u bolesnice nastupila šećerna bolest, pa je uvedeno u terapiju inzulin. Tijekom prve godine nakon operacije tjelesna se masa približno normalizirala, bolesnica je izgubila 54 kg. Na zadnjoj kontroli su magnetska rezonanca i kompjutorizirana tomografija pokazale uredan nalaz abdomena.

Ključne riječi: Višestruka endokrina neoplazija tipa 1, dijagnostika; Višestruka endokrina neoplazija tipa 1, komplikacije; Hipoglikemija, etiologija; Prikaz slučaja