MANAGEMENT OF ENDOCRINE DISEASE

A clinical update on tumor-induced hypoglycemia

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Abstract

Tumor-induced hypoglycemia (TIH) is a rare clinical entity that may occur in patients with diverse kinds of tumor lineages and that may be caused by different mechanisms. These pathogenic mechanisms include the eutopic insulin secretion by a pancreatic islet β-cell tumor, and also the ectopic tumor insulin secretion by non-islet-cell tumor, such as bronchial carcinoids and gastrointestinal stromal tumors. Insulinoma is, by far, the most common tumor associated with clinical and biochemical hypoglycemia. Insulinomas are usually single, small, sporadic, and intrapancreatic benign tumors. Only 5–10% of insulinomas are malignant. Insulinoma may be associated with the multiple endocrine neoplasia type 1 in 4–6% of patients. Medical therapy with diazoxide or somatostatin analogs has been used to control hypoglycemic symptoms in patients with insulinoma, but only surgical excision by enucleation or partial pancreatectomy is curative. Other mechanisms that may, more uncommonly, account for tumor-associated hypoglycemia without excess insulin secretion are the tumor secretion of peptides capable of causing glucose consumption by different mechanisms. These are the cases of tumors producing IGF2 precursors, IGF1, somatostatin, and glucagon-like peptide 1. Tumor autoimmune hypoglycemia occurs due to the production of insulin by tumor cells or insulin receptor autoantibodies. Lastly, massive tumor burden with glucose consumption, massive tumor liver infiltration, and pituitary or adrenal glands destruction by tumor are other mechanisms for TIH in cases of large and aggressive neoplasias.

Introduction

Hypoglycemia not associated with diabetes and/or its therapy is an uncommon clinical disorder. In people without diabetes, the diagnosis of hypoglycemia is usually established when venous plasma glucose is <55 mg/dl (3 mmol/l) and supported by the presence of Whipple's triad (symptoms, signs, or both consistent with hypoglycemia, a low plasma glucose concentration, and resolution of those symptoms or signs after raising plasma glucose concentration) (1).

In ill or medicated adults without diabetes, the most common causes of hypoglycemia are drugs other than insulin or insulin secretagogues. Other etiologies are critical illnesses and hormone deficiencies (cortisol and glucagon). In seemingly well non-diabetic individuals, hypoglycemia is usually associated with endogenous hyperinsulinism due to nesidioblastosis, tumor β-cell disorders, and insulin autoimmune hypoglycemia. On other occasions, the etiology of hypoglycemia in these patients can be accidental, surreptitious, or malicious (1). Lastly, tumor hypersecretion of several factors with hypoglycemic effects have also been documented.

Tumor-induced hypoglycemia (TIH) is a rare clinical type of hypoglycemia that usually appears as a result of insulin hypersecretion by a pancreatic islet β-cell tumor (insulinoma). However, TIH can also be developed by other non-pancreatic tumors (non-islet-cell tumor

hypoglycemia (NICTH)). This review focuses on the most updated and relevant clinical, diagnostic, and therapeutic aspects related to TIH, as well as different clinical situations related to insulinoma, the most common cause of TIH.

Pathophysiology of TIH

Several pathogenetic mechanisms may explain TIH (Table 1 and Fig. 1). The most common cause, although rare, is tumor hyperinsulinism induced by a pancreatic islet β-cell tumor (insulinoma). However, NICTH is nowadays a well-recognized etiology of TIH (2). In this case, the main etiology of hypoglycemia is the release by the tumor of insulin-like growth factor 2 (IGF2) or its high-molecular-weight precursor (big IGF2) (3, 4, 5, 6, 7, 8, 9, 10, 11). Other mechanisms for NICTH are IGF1 tumor

Table 1 Pathogenic mechanisms and types of tumors associated with tumor-induced hypoglycemia.

Insulin-secreting tumors
  Eutopic tumor insulin secretion: pancreatic islet β-cell tumor
    Insulinoma
  Ectopic tumor insulin secretion: non-islet-cell tumors
    Bronchial carcinoid
    Gastrointestinal stromal tumor
    Squamous cell carcinoma of the cervix
    Schwannoma
    Neurofibrosarcoma
    Paraganglioma
    Small-cell carcinoma of the cervix
Mechanisms other than excess tumor insulin secretion
  Tumor IGF2 precursors secretion (big IGF2) 'IGF2-oma'
    Leiomyosarcoma
    Fibrosarcoma
    Adrenal carcinoma
    Desmoplastic small round cell tumor
    Hemangiopericytoma
    Pheochromocytoma
    Renal sarcoma
    Uterine leiomyoma
    Hepatocellular carcinoma
    Gastric carcinoma
  Tumor somatostatin secretion 'Somatostatinoma'
    Pancreatic neuroendocrine tumor
    Ovarian neuroendocrine tumor
  Tumor IGF1 secretion 'IGF1-oma'
    Large-cell carcinoma of the lung
  Tumor glucagon-like peptide 1 (GLP1) secretion 'GLP1-oma'
    Ovarian neuroendocrine tumor
    Pancreatic neuroendocrine tumor
  Autoantibodies to insulin or its receptor 'Tumor autoimmune
    hypoglycemia'
  Other tumor-related factors
    Massive tumor burden
    Massive liver tumor infiltration
    Pituitary and/or adrenal glands tumor destruction

secretion (12), the production of autoantibodies to insulin (13) or its receptor (14), or more rarely, the secretion of glucagon-like peptide 1 (GLP1) (15, 16), and massive tumor burden (17). Lastly, ectopic insulin secretion by a non-islet-cell tumor has also been exceptionally reported (18, 19, 20, 21, 22, 23).

Insulin-secreting tumors

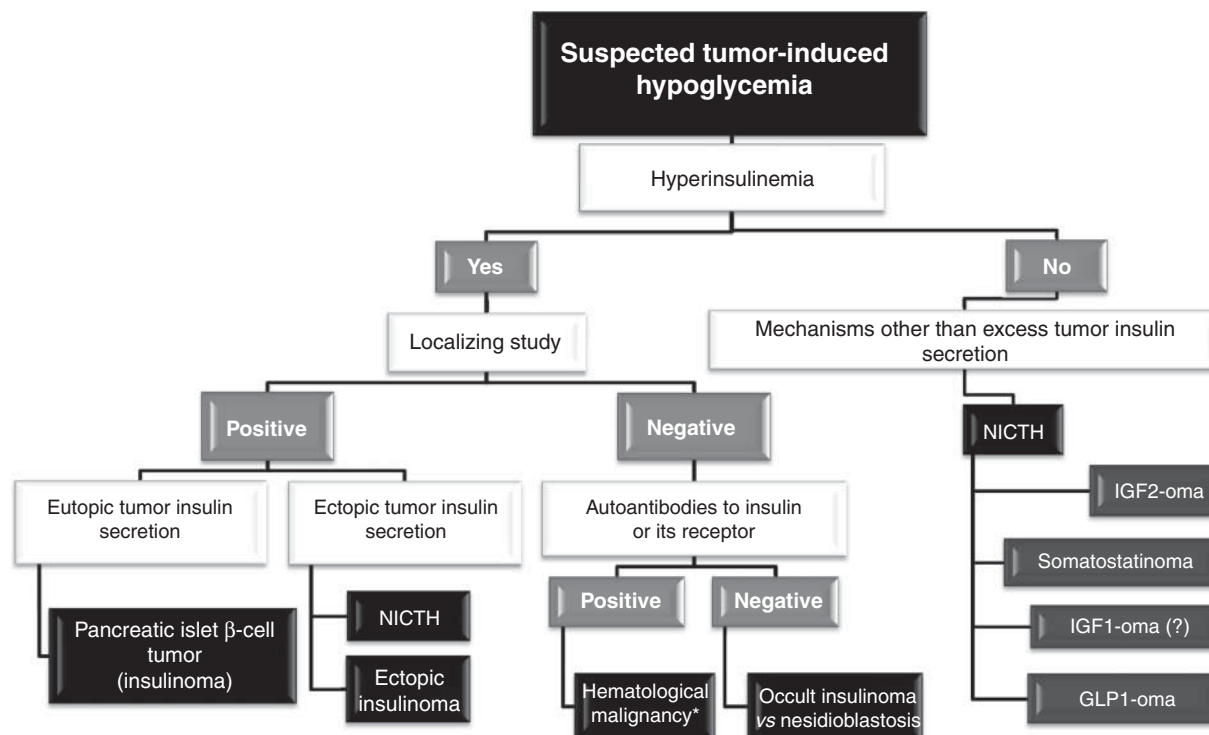### Eutopic tumor insulin secretion: pancreatic islet β-cell tumor (insulinoma)

Insulinoma is a rare tumor with an incidence of 0.4/100 000 person-years (four cases per million per year), more frequently observed in the fifth decade of life (median age 47 years, range 8–82 years) and with a slight predominance (∼60%) for the female sex (24). This tumor is the most common (∼25%) functioning pancreatic neuroendocrine tumor (pNET). Insulinomas are usually single, small (usually <2 cm diameter), well-circumscribed, benign, sporadic, intrapancreatic tumors, and evenly distributed throughout the pancreas (Fig. 2) (24, 25, 26, 27).

Hypoglycemic symptoms secondary to excessive and uncontrolled secretion of insulin by the tumor usually occur in the fasting state (73%); however, they can also be present only in the postprandial state (6%) and in both fasting and postprandial states (21%) (28). Correct diagnosis is often delayed until 2 years from the onset of symptoms due to the fact that, on many occasions, neuropsychiatric or neurologic symptoms are misunderstood (1, 24, 29). Hypoglycemic symptoms can be neurogenic (autonomic) (hunger, sweating, paresthesia, palpitations, diaphoresis, anxiety, and tremor) and neuroglycopenic (confusion, visual disturbances, behavioral changes, epileptic seizures, confusion, and coma) (30). Weight gain and obesity as a consequence of frequent small meals to avoid hypoglycemic symptoms is a well-known clinical sign of insulinoma (31, 32).

Biochemical diagnosis of insulinoma is established when hypoglycemia, supported by the presence of Whipple's triad, is associated with endogenous hyperinsulinism showing the following criteria: fasting plasma glucose concentrations are <55 mg/dl (3.0 mmol/l), plasma insulin concentrations ≥3 μU/ml (18 pmol/l), plasma C-peptide concentrations ≥0.6 ng/ml (0.2 nmol/l), plasma proinsulin concentrations ≥5 pmol/l, plasma β-hydroxybutyrate levels ≤2.7 mmol/l, change in blood glucose ≥25 mg/dl (1.4 mmol/l) at 30 min after 1 mg i.v. glucagon, a negative sulfonylurea screen in the plasma

Figure 1

Diagnostic algorithm for patients with suspected tumor hypoglycemia. *After excluding other non-tumor causes of autoimmune hypoglycemia. NICTH, non-islet-cell tumor hypoglycemia.

and/or urine and no circulating antibodies to insulin (1). When Whipple's triad has not been documented in a patient with suggestive clinical evidence of hypoglycemia or when biochemical study during the hypoglycemia could not be performed, the patient should undergo a supervised 72-h fast test with the aim to reproduce the hypoglycemic episode. Diagnosis of insulinoma must be confirmed by localizing the tumor by conventional imaging, such as computed tomography (CT), magnetic resonance imaging (MRI), and transabdominal ultrasonography. These localizing techniques detect most insulinomas (Fig. 2); however, due to the small size of some tumors, a negative study does not always exclude its presence (1, 33, 34).

Although medical therapy with frequent carbohydrate meals and diazoxide (∼200–600 m/day orally) or somatostatin analogs may control hypoglycemic symptoms in 50–60% of patients, only surgery is curative (26, 29). Therefore, once the tumor has been located, the treatment of choice is surgical excision. The surgical method usually employed (∼60%) is enucleation of the tumor, followed by partial pancreatectomy (24). Although the majority of the interventions have been made using open surgery,

laparoscopic surgery is a surgical option in some centers with a morbidity rate comparable with that for the open approach. When the tumor is not found during laparoscopy, laparoscopic ultrasonography seems to be the most efficient tool to localize it and probably to prevent conversion (35, 36). Those tumors located in the body or tail of the pancreas can better benefit from the laparoscopic approach (37). Alternative medical treatment may be necessary for symptomatic patients with unresectable tumors and for those who are not candidates for surgical treatment or refuse surgery (1, 33, 34). The alternative option of endoscopic ultrasonography (EUS) or intraoperative (IO) US-guided ethanol fine-needle injection has recently been reported for the treatment of symptomatic insulinomas requiring extensive resection and for poor surgical candidates (38). Highlights of different special clinical situations related with insulinoma are presented below.

Occult insulinoma ▸ A small number of insulinomas remain occult after conventional (ultrasonography, CT scan, or MRI) localizing preoperative study (26).
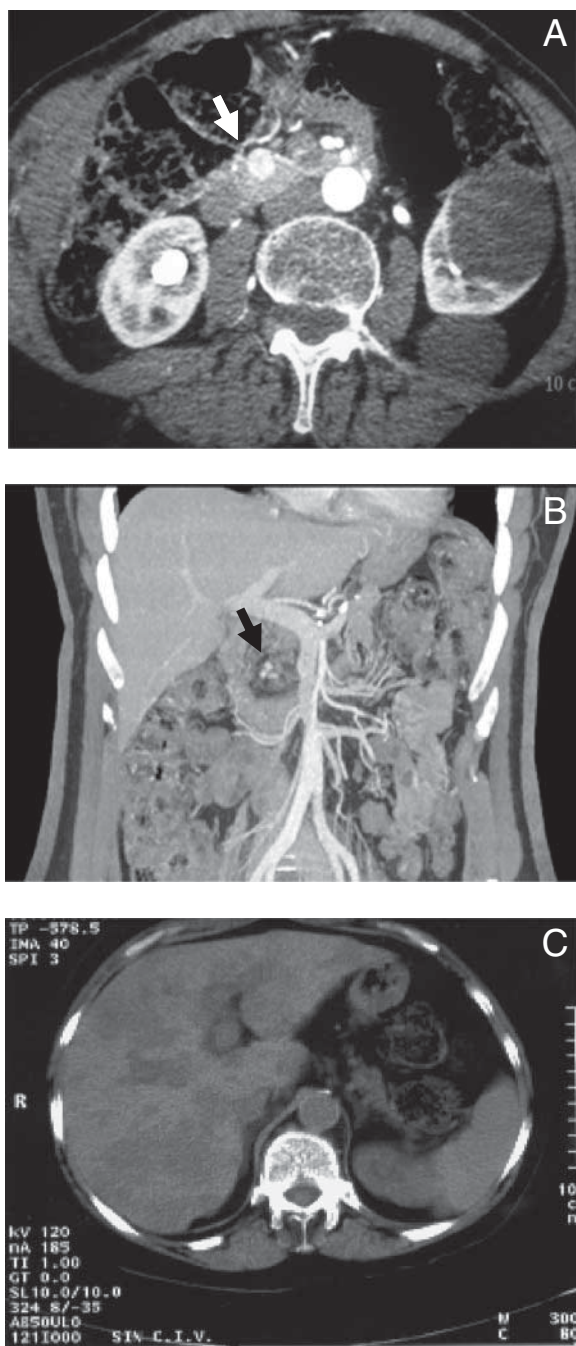
Figure 2

Abdomen CT scan image with i.v. contrast in a woman with a 1.5 cm benign insulinoma (white arrow) located in the head of the pancreas (A). Abdomen CT scan with contrast showing three small images (black arrow) compatible with multiple insulinomas in the head of the pancreas in a female patient (B). CT scan without contrast of the abdomen showing multiple liver metastases in a female patient with malignant insulinoma (C).

In some cases, pancreatic dynamic consecutive enhanced CT scanning may help to localize the tumor (39). Somatostatin receptor scintigraphy detects between 20 and 50% of affected patients with benign insulinomas (34, 40). The abundance of GLP1 receptors (GLP1R) in pancreatic β-cells in insulinomas has led to the development of GLP1R scanning by using GLP1-like radioligands with high binding affinity to GLP1Rs to localize occult insulinomas (41). GLP1R scan with ^{111}In-DOTA-exendin-4 successfully detected two occult insulinomas not identified by conventional localizing study (42).

Selective arterial calcium stimulation (SACS) with hepatic venous sampling for insulin quantification, with an endpoint of a greater than twofold increase in hepatic venous insulin levels over baseline, has shown a high sensitivity (93%) for localization of insulinoma (28). The combination of SACS with EUS achieved tumor localization in all patients diagnosed in the period 1998–2007 at the Mayo Clinic, avoiding blind pancreatic exploration (28). Occult insulinomas are usually located within the pancreatic head (43, 44). Given the associated morbidity and lack of surgical success, blind distal pancreatectomy and progressive pancreatectomy are not recommended in cases of occult insulinoma at the present time (26, 44). Palpation and intraoperative ultrasonography (IOUS) permit detection of virtually all insulinomas, including reoperated cases (26, 44, 45). Lastly, the use of gamma-probe intraoperatively after ^{111}In-DOTA-exendin-4 administration permitted the detection and successful surgical removal of all insulinomas in a series of six patients, one of them with ectopic insulinoma (42).

Extrapancreatic (ectopic) insulinoma ▶ Ectopic insulinoma is an extremely rare (∼2%) entity whose diagnosis should be suspected when a biochemically confirmed insulinoma is not localized (26). These tumors are usually located in the duodenal wall, although other locations such as duodenohepatic ligament and surrounding tissues of the pancreas have been reported (46, 47). Ectopic insulinomas usually develop on the ectopic (heterotopic, accessory, or aberrant) pancreas, an entity reported in 0.5–15% of autopsies and in 1 out of 500 abdominal surgeries, mainly found in the stomach, duodenum, and jejunum (46, 47, 48).

Insulinoma associated with multiple endocrine neoplasia type 1 ▶ Insulinoma is the second most common (10–30%) functioning pancreatic tumor associated with multiple endocrine neoplasia type 1 (MEN1), after

gastrinoma. On the contrary, only 4–6% of patients with insulinoma will develop *MEN1* (1, 28, 49). Unlike sporadic insulinomas that usually develop after the age of 40 years, MEN-associated insulinomas occur usually before 40 years of age and even before 20 years (24, 50). This explains why in 10% of *MEN1* patients insulinoma will be the first tumor to appear. On many occasions, tumors are multiple at the time of diagnosis and up to 10% can be associated with other pNETs (49). Metastases are present in up to 50% of patients with MEN1-associated insulinomas, compared with <10% of non-*MEN1* insulinomas (51). In the absence of distant metastases, surgery is advocated for *MEN1* insulinomas. Surgical therapy ranges from enucleation in isolated tumors to distal subtotal (80–85%) pancreatectomy combined with enucleation of tumors in the pancreatic head in those cases with multiple tumors (49, 51). Surgery is usually performed in MEN1-associated insulinoma even if the tumor cannot be identified by imaging due to the intense symptoms caused by hyperinsulinemia. Lastly, because insulinomas in these patients are usually multicentric, complete surgical resection is more difficult and local tumor resection often results in disease recurrence (52, 53).

Recurrent insulinoma ▸ Insulinoma-induced hypoglycemia can recur after successful surgical removal (54). It can develop from 4 to 20 years after initial surgery. Recurrence rate for insulinoma after initial pancreatic exploration was 5 and 7% at 10 and 20 years, respectively, in patients with sporadic insulinoma and 21% at 10–20 years in patients with MEN1, in a 60-year observation period study (from 1927 through 1986) performed in 224 Mayo Clinic patients (24). Recurrence of hyperinsulinemic hypoglycemia after a brief interval (<4 years) during which hypoglycemia (both symptomatic and biochemical) is absent suggests regrowth of remnant insulinoma (54).

Malignant insulinoma ▸ Approximately 5–10% of insulinomas are malignant with distant metastasis at diagnosis (Fig. 2), mainly to the liver and regional lymph nodes, with a reported 10-year survival rate of <20% (55). On many occasions, they are indolent tumors associated with prolonged survival. The patient can undergo pancreas and liver resection (if possible) during the same operation. Lymph node dissection should also be performed if there was evidence of nodal disease. Resection of liver metastases must be considered especially when metastatic disease is confined to the liver and surgery can remove >90% of tumor (27, 56). This surgery may provide

effective palliation and probably prolonged survival. Other approaches for the treatment of liver disease include hepatic artery embolization, radiofrequency ablation, and crioablation (27). As opposed to benign insulinomas, malignant insulinomas often express somatostatin receptor subtype 2, showing positive somatostatin receptor scintigraphy in 73% of cases (57), which can be targeted therapeutically with long-acting somatostatin analogs and peptide radionuclide receptor therapy (58, 59).

Malignant insulinomas generally respond poorly to traditional chemotherapeutic agent regimens (fluorouracil, doxorubicin, and streptozocin) (60). Rapamycin (sirolimus) and everolimus, a rapamycin analog, are mammalian targets of rapamycin receptor antagonists that may provide a useful tool for stabilization of tumor growth and controlling hypoglycemia in malignant insulinomas by reducing the malignant β-cell growth and proliferation as well as inhibiting insulin production (60, 61, 62). In fact, the addition of everolimus resulted in abolition of hypoglycemia and stabilization of disease on imaging over 45 months in a patient with untreatable metastatic insulinoma and intractable hypoglycemia (62). In selected patients with unresectable liver metastases of malignant insulinoma, liver transplantation (LT) is a therapeutic option (63). Although this technique has achieved prolonged survival, up to 5 years, in some reported patients (64), the limited clinical experience due to the small sample size (4% of all cases of LT for metastatic NETs) (63)) has led to this therapeutic procedure being currently considered as an investigational approach for patients with liver metastatic insulinoma.

Ectopic tumor insulin secretion: non-islet-cell tumors

A small number of non-islet-cell tumors have been associated with ectopic insulin secretion so far (Table 1) (18, 19, 20, 21, 22, 23). Among them are bronchial carcinoid tumor (18), squamous-cell carcinoma of the cervix (19), neurofibrosarcoma (65), schwannoma (20), paraganglioma (21, 23), small-cell carcinoma of the cervix (22), and gastrointestinal stromal tumor (66). Although in some of these cases there were alternative mechanisms for hypoglycemia and the possibility of pancreatic insulinoma was not definitely excluded, other more recent clinical reports (22, 23) have clearly shown that non-islet-cell tumors were the origin of the hyperinsulinemia on the basis of the detection of proinsulin mRNA and insulin protein within the tumor cells.

Mechanisms other than excess insulin

Tumor IGF2 precursors secretion (big IGF2) 'IGF2-oma'

NICTH due to IGF2 was initially reported by Daughaday *et al.* (1988) (67) in a 67-year-old woman who presented with recurrent severe hypoglycemia and a large thoracic leiomyosarcoma which resolved after tumor resection. The tumor showed high concentrations of *IGF2* mRNA and IGF2 immunoreactive in form of a large precursor molecule, and a similar fraction of high-molecular-weight IGF2 in the patient's serum. Since the first report there have been many clinical cases of NICTH secondary to IGF2 tumor hypersecretion by other types of tumors (3, 4, 5, 6, 7, 8, 9, 10, 11, 68) (Table 1). This pathogenic mechanism is the main cause of NICTH (2, 69) and the term 'IGF2-oma' has been proposed to describe these types of tumors (70).

The main mechanism in IGF2-induced NICTH is the overexpression of the *IGF2* gene (structurally homologous to the insulin gene) by the tumor which is associated by the tumor secretion of incompletely processed precursors of IGF2 (pro-IGF2 or big IGF2) with a persistent insulin-like activity (2, 69, 71, 72). Pro-IGF2 is expressed in a broad spectrum of malignant and benign tumors and binds poorly to its binding proteins, thus increasing the likelihood that the molecule freely penetrates tissue spaces. Big IGF2 suppresses both GH and insulin at pituitary and pancreas levels respectively. Owing to the suppression of GH secretion, synthesis and secretion of IGF1 and IGF-binding protein 3 (IGFBP3) are also decreased. Although the serum level of total IGF2 may be normal, both the ratios pro-IGF2:IGF2 and IGF2:IGF1 may be elevated (2, 69, 73). In one study, the IGF2:IGF1 ratio ranged from 16.4 to 64.2 with a mean of 35.0 ± 2.2 in a group of patients with NICTH with big IGF2 (69). Lastly, basal-immunoreactive insulin levels are low in these patients (69, 74) (Table 2). The elevated bioavailability of both big and free IGF2 increases peripheral glucose consumption and decreases glucose production in the liver giving rise to the development of hypoglycemia (1, 2, 69).

In a retrospective study performed in 78 patients (44 males, 56%; age at diagnosis 62 ± 1.8 years, range; 9–86 years) with NICTH and high serum levels of big IGF2, Fukuda *et al.* (2006) (69) found that hypoglycemic attack (confusion, incoordination, difficulty in waking in the morning, and sweating and coma) was the onset of disease in 48%, but the tumor was revealed before the occurrence of hypoglycemia in 52%. Hepatocellular carcinoma and gastric carcinoma were the most common causes of NICTH and the diameters of the tumors were more than 10 cm in 70% of the patients. All these data suggest that hypoinsulinemic hypoglycemia associated with the presence of a large tumor supports the diagnosis of IGF2 producing NICTH (69).

Treatment should be aimed at immediate correction of hypoglycemia, followed by treatment directed at the underlying tumor and, finally, prevention of recurrent hypoglycemia if the tumor cannot be cured. In these cases, long-term management with glucocorticoid therapy has been demonstrated to consistently reverse the biochemical abnormalities caused by tumor-derived big IGF2 and it has been suggested that this therapy alone or in combination with human growth hormone, with or without the addition of long-acting glucagon, is the most effective therapy in alleviating intractable hypoglycemia (75).

Table 2 Pathogenic mechanisms and types of tumors associated with tumor-induced hypoglycemia.

	Insulin	GH	IGF1	IGF2	Big IGF2	IGFBP3	Others	Associated clinical disorders
Insulinoma	↑	–	–	–	–	–	High levels of C-peptide and proinsulin Negative sulphonylurea and circulating insulin autoantibodies	MEN1 (∼10%)
IGF2-oma	↓	↓	↓	↔/↑	↑↑	↓	Increased ratios: pro-IGF2:IGF2 and IGF2:IGF1	
Somatostatinoma	↓	↓	↔↓	?	?	?	High somatostatin Low counter-regulatory hormones levels	Type 2 diabetes Cholelitiasis Diarrhea Acromegaly (?)
IGF1-oma	↓	↔	↑↑	↔	↔	↔		
GLP1-oma	–	–	–	–	–	–	High levels of glucagon, somatostatin and GLP1	Type 2 diabetes
Tumor autoimmune hypoglycemia	↑↑	–	–	–	–	–	Autoantibodies to insulin or insulin receptor	Hematological malignancies

Tumor somatostatin secretion 'Somatostatinoma'

Somatostatin-producing tumors or somatostatinomas are rare NETs (~1% of gastroenteropancreatic-NETs) derived from D cells with an annual incidence of 1 in 40 million (76). Since its first description by Larsson *et al.* (1977) (77), about 200 cases have been reported. Somatostatinomas usually arise in the pancreas and duodenum (~90%) with approximately equal frequency (78, 79). Extrapancreatic somatostatinomas (carcinoid somatostatinomas) can arise in other locations such as jejunum (80) and ovary (81). The most common symptoms are abdominal pain and weight loss and, in some instances (~10%) they produce somatostatinoma syndrome (diabetes mellitus, cholelithiasis, and diarrhea with steatorrhea) due to excessive secretion of somatostatin, a hormone that inhibits gastrointestinal motility and secretion as well as the release of many hormones including insulin and glucagon. Somatostatinoma-induced hypoglycemia is uncommon with isolated cases reported to date (81, 82, 83, 84). In three out of four reported cases, the tumor was located in the pancreas (82, 83, 84) and only one in the ovary (81). The mechanism of somatostatinoma-induced hypoglycemia is not clear. It seems to be related to the suppression of glucagon, GH, and other counter-regulatory hormones by somatostatin. As somatostatin-producing endocrine tumors are frequently malignant (~70), surgical resection is the first-line therapy for localized tumors (85). Hypoglycemia is rarely sensitive to the hyperglycemic effects of diazoxide (82). Blood glucose level is usually stabilized after surgery (81, 84) or chemotherapy (82).

Tumor IGF1 secretion 'IGF1-oma'

NICTH due to overproduction and secretion of IGF1 (IGF1-oma) is an exceptional event. In fact, to our knowledge, only one patient has been reported so far (12). She was a 64-year-old woman admitted due to severe recurrent non-hyperinsulinemic hypoglycemia. No signs of acromegaly were present. The patient was diagnosed with pulmonary large cell carcinoma with axillary metastasis. Serum total and free IGF1 concentrations were elevated, whereas GH, IGFBP3, acid-labile subunit, and big IGF2 were normal, and serum insulin and C-peptide were suppressed. Immunohistochemistry demonstrated IGF1 peptide in some tumor cells and *IGF1* mRNA was detected by *in situ* hybridization in virtually all tumor cells. Hypoglycemic episodes did not recur after chemotherapy. The mechanism of hypoglycemia proposed by the authors would be related with an increase in the amount of free IGF1 which would reach insulin target tissues exerting insulin-like effects. The absence of acromegalic features might be explained by the absence of a sustained combined elevation of GH and IGF1 and the relatively short duration of paraneoplastic hormonal changes (12).

Tumor GLP1 secretion 'GLP1-oma'

GLP1 is a gut peptide that stimulates both insulin release from pancreatic β-cells and β-cell hyperplasia. Paraneoplastic GLP1 hypersecretion causing reactive hypoglycemia was initially reported in 2003 in a patient with an ovarian NET (15). She was a 45-year-old woman with type 2 diabetes who developed episodes of symptomatic postprandial hypoglycemia which were cured with tumor surgery. Nine years later, in 2012, a second clinical case was reported (16). He was a 56-year-old male with a previous diagnosis of diabetes who presented with fasting hypoglycemia. Clinical study demonstrated a glucagon-secreting pNET, which was the likely cause of diabetes, whereas hypoglycemia was caused by insulin secretion from hyperplastic β-cells stimulated by metastases-derived GLP1. However, severe hypoglycemia is not always associated with GLP1 tumor secretion. In fact, two other patients with GLP1- and GLP2-producing NETs and with the absence of symptomatic hypoglycemia have been previously reported (86, 87).

Autoantibodies to insulin or its receptor 'Tumor autoimmune hypoglycemia'

The syndrome of autoimmune hypoglycemia is an uncommon cause of hypoglycemia characterized by elevated levels of insulin in the presence of either anti-insulin antibodies (insulin autoimmune syndrome, Hirata disease) or anti-insulin receptor antibodies (type B insulin resistance) (88, 89, 90). Autoimmune hypoglycemia has also been related to tumor hypoglycemia (13, 90, 91). In this case, anti-insulin antibodies or anti-insulin receptor antibodies are produced by the tumor (13). Both conditions are usually associated with inappropriately elevated insulin and they can lead to fasting hypoglycemia, postprandial hypoglycemia, or both (90). Several tumors have been associated with autoimmune hypoglycemia, among them are multiple myeloma (13, 92), chronic myelomonocytic leukemia (90), and Hodgkin's disease (91).

Other tumor-related factors

Tumor hypoglycemia may be due exclusively to increased glucose consumption by the tumor mass and/or its metastases, as well as in those with massive liver tumor infiltration (93, 94, 95, 96, 97). Among these tumors are hepatocellular carcinoma (95, 96), meningioma (93, 94), non-Hodgkin's lymphoma (98, 99), and pheochromocytoma (97). Excessive tumor glucose consumption can become manifested through functional tests such as ^{18}F-2-fluoro-2-deoxy-D-glucose positron emission tomography/CT (^{18}F-FDG–PET/CT), showing remarkable glucose uptake in the tumor with reduced physiologic uptake in other organs (97). On other occasions, the tumor can infiltrate and destroy different organs, such as the pituitary or adrenal glands, resulting in hypopituitarism or primary adrenal insufficiency, respectively, giving rise to the development of secondary hypoglycemia (100).

Conclusion

Tumors are a rare cause of hypoglycemia. TIH is usually due to the tumor hypersecretion of insulin by pancreatic β cell-derived tumors (insulinomas). However, there are other tumors that have the capability of producing hypoglycemia by mechanisms other than the endogenous hyperinsulinism. This diagnostic possibility should be kept in mind because hypoglycemia in this case can manifest as paraneoplastic symptoms of a tumor with a potentially serious prognosis.

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