Severe paraneoplastic hypoglycemia due to a non-islet cell tumor in a patient with an advanced gastrointestinal stromal tumor

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Abstract

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumors of the gastrointestinal tract, mainly localized in the stomach. Most GIST derive from mutations in tyrosine kinase receptors (KIT) or platelet-derived growth factor receptor-α (PDGFRA). GISTs are rarely associated with paraneoplastic hypoglycemia caused by non-β-cells tumor. This syndrome, defined non-islet cell tumor hypoglycemia (NICTH), arises from excess tumor production of insulin-like growth factor. We describe a 67-year-old female with severe NICTH secondary to an advanced and metastatic GIST.

Introduction

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal malignant tumors of the gastrointestinal tract (GI). Compared to the other tumors they are rare, accounting for 1-2% of all gastrointestinal neoplasms. GIST can develop anywhere in the GI tract, most commonly in the stomach (60%) and the small intestine (30%), and less frequently in the colon, rectum and esophagus. A few cases (<5%) are found in different sites within the abdominal cavity, especially in the mesentery, omentum, and retroperitoneum. The reported incidence of GIST is about 10 cases per million inhabitants/year in Europe. Clinical manifestations depend on the tumor location, size, and growth pattern. About one in four GISTs are asymptomatic and are incidentally discovered during endoscopic examination or abdominal computer tomography (CT) scan for other disorders. Symptomatic patients present with weight loss, abdominal pain, gastrointestinal bleeding or bowel perforation. At the time of diagnosis about half of patients have advanced disease with metastases.

Non-islet cell tumor hypoglycemia (NICTH) is a rare paraneoplastic syndrome caused by non-β-cells tumors. The clinical feature are recurrent fasting hypoglycemia, associated with normal or decreased levels of insulin and insulin-like growth factor (IGF1), and elevated insulin-like growth factor-2 (IGF2). NICTH has been associated with mesenchymal and epithelial tumors including...
hepatocellular carcinoma, lymphoma, fibrosarcoma, nerve sheath tumors, hemangiopericytoma, and thyroid carcinoma. The association of NICTH with GIST is rare and only fifteen cases have been identified in the review of literature covering the past 16 years. However, before the diagnostic immunohistochemical analysis in the ‘80s, GITS were often misdiagnosed as abdominal leiomyoma or leiomyosarcoma and many of those associated with NICTH showed histological features which could represent GISTs.

We present a case of severe NICTH secondary to an advanced and metastatic GIST.

**Case Report**

A 67-year-old female patient was admitted to the Internal Medicine ward complaining of diffuse pain in the upper abdomen that had lasted three weeks, not associated with meals. She reported an undetermined weight loss during the previous month despite usual food intake. The patient had a long history of hypertension well controlled with medications, and a positive family history for colon and gastric cancer (parents).

On admission, her vital signs were within normal limits. The physical examination revealed abdominal tenderness with a palpable mass in the right upper quadrant. Laboratory tests showed normal values of fasting glycaemia, hemoglobin, white blood cells count, renal and adrenal function, liver enzymes, fibrinogen, prothrombin time, and thyroid function tests. Increased values of C-reactive protein (104, normal up to 5), and cancer antigen CA 125 (291, normal up to 35) and NSE (22.5, normal up to 16) were also observed.

An abdominal ultrasound, contrast enhanced computed tomography (CT) scan and magnetic resonance imaging of the abdomen revealed multiple lobulated peritoneal and mesenteric masses of varying sizes, with necrotic areas (Figure 1). There were also multiple sub-diaphragmatic and perihepatic lesions measuring from few millimeters to 3-4 cm, the largest 13x8 cm, extending in the Morison’s pouch. The stomach wall was thickened in the cardia, fundus and great curvature regions. Multiple lobulated masses with the same characteristics were observed in the lower
abdomen, close to the small bowel, without signs of obstruction. A scan of the thorax showed moderate bilateral pleural effusion and small non-calcified soft tissue nodules in the breast. No pathological finding was observed with upper gastrointestinal tract endoscopy and colonoscopy.

On the fourth day the patient developed fasting autonomic and neuroglycopenic symptoms and signs consistent with severe hypoglycemia, with blood glucose lower than 1.1 mmol/L (20 mg/dl) and rapid resolution after glucose infusion. Further episodes of hypoglycemia occurred in the following days requiring treatment with continuous intravenous infusion of glucose, corticosteroids, and glucagon. During these episodes the patients remained fully conscious and awake, even when blood glucose fell below 1.6 mmol/L (30 mg/dl).

Insulinoma or NICTH were suspected. An endocrine laboratory test showed low values of insulin (0.4 microUI/ml, normal 2.6 – 25), C-peptide (0.1 ng/ml, normal 1.1 – 4.4), growth hormone (0.12 ng/ml, normal 0 – 10) and insulin-like growth factor-1 (IGF1, 86 ng/ml, normal for age 81 – 200).

An ultrasound-guided fine needle biopsy of the largest abdominal mass was performed. The biopsy specimen was stained with hematoxylin and eosin for microscopic examination.

Histopathology showed spindle-shaped and epithelioid cells, growing in the form of fascicles, palisades, and whorls, including large cells with hyperchromatic nuclei, marked diffuse cellularity and nuclear palisading with 1-2 mitoses at 10x magnification (Figure 2).

Immunohistochemical analysis was carried out using monoclonal antibodies on an automated staining system (Benchmark Ultra, Roche Ventana). Neural-like differentiation was shown by the expression of neuron-specific enolase (MRQ55 clone) and Vimentin (V9 clone). Stem-cell growth factor receptor (CD117) and receptor tyrosine kinase (c-KIT) were positive in 60% of the neoplastic cellular population (Figure 3). These findings were compatible with the histological diagnosis of GIST.

Based on the pathology findings, treatment with the tyrosine kinase inhibitor imatinib, 400 mg/day, was started. One week later, despite intensive medical support, the patient became comatose and died two days later.
Discussion

As a general rule, tumor-associated hypoglycemia may be due to a tumor producing an excess of insulin, such as pancreatic insulinoma, or due to destruction of the liver and adrenal glands by massive tumor infiltration or the production of substances interfering with glucose metabolism, such as insulin-receptor antibodies or secretion of IGF1. However, in the setting of decreased insulin and IGF1 levels with normal hepatic and adrenal function, the tumor-associated hypoglycemia suggests the diagnosis of paraneoplastic NICTH, ruling out insulinoma and IGF1-producing tumors. Hypoglycemia due to NICTH is thought to derive from tumor secretion of IGF2 associated with a greater proportion of the incompletely processed high-molecular-weight precursor (pro-IGF2 or “big” IGF2). In normal individuals “big” IGF2 account for about 20% of the total IGF2, whereas in patients with NICTH 80% of IGF2 are circulating as “big” IGF2. Both IGF1 and IGF2 are mainly produced by the liver and share structural similarities with insulin. Although their concentration is about 100 times that of insulin, they are almost completely bound to IGF-binding protein-3 (IGFBP3) and an acid-labile subunit, resulting in a biologically inactive ternary complex. Like the other hormones, their physiological activity is mediated by the free hormone, hence IGFs do not induce significant hypoglycemia. Tumor-derived “big” IGF2 has high affinity for insulin receptors but binds poorly to its binding protein because of its excessive molecular weight, thus remaining free unbound or forming a smaller binary complex. Unlike a ternary complex, the small binary complex and the free form may cross through the capillary wall reaching the cells surface and activating the insulin receptors. Big IGF2 is about four times more biologically active than IGF2. This results in persistent insulin-like activity leading to hypoglycemia due to inhibition of glycogenolysis and gluconeogenesis, decreased lipolysis and increased peripheral glucose utilization. Both hypoglycemia and a direct inhibitory effect of “big” IGF2 at the pancreas level decrease insulin secretion. This results in the up-regulation of insulin receptors, causing increased insulin sensitivity. In addition, “Big” IGF2 suppresses the secretion of
pituitary growth hormone (GH), thus decreasing the synthesis of IGF1 and IGFBP3.\textsuperscript{31,35}

In the present patient, IGF2 and “big” IGF2 were not measured because diagnostic tests are not widely available. Furthermore, while the tumor secretion of “big” IGF2 is increased in the majority of patients with NICTH, the concentration of IGF2 may be increased or even normal.\textsuperscript{21,30,36} Therefore, measuring IGF2 levels does not provide meaningful results in the diagnosis of NICTH. The other laboratory tests such as the reduction of both insulin and IGF1, along with reduced C-peptide and GH, support the hypothesis that “big” IGF2 was responsible for the sustained hypoglycemia in this patient.

In some cases, the GIST-associated hypoglycemia is not caused by “big” IGF2 but may be attributed to the metabolic effects of neoplastic malnutrition, hepatic and renal dysfunction, and sepsis.\textsuperscript{37} Our patient had normal hepatic and renal function, and no sign of infection or malnutrition.

In the present patient the tumor was detected before the occurrence of hypoglycemia which is the presentation in about half of the patients, whereas hypoglycemia is the onset of disease in the others.\textsuperscript{15} Although the paraneoplastic manifestation of NICTH in GIST is rare, when it occurs the tumor is advanced or metastatic.\textsuperscript{38}

Most GIST derive from the interstitial cells of Cajal which are pacemaker cells involved in the contractile activity of the GI tract.\textsuperscript{39,40} The pathology of GISTs consist of three morphological patterns, including spindle cell (70%), epithelioid (20%), and the mixed type (10%). These features are not specific to GIST but may overlap with other tumors of the GI tract. Because the cells of Cajal are modified smooth muscle cells with a neural function for peristaltic contraction, the microscopic and ultrastructural appearance of GIST may have mixed features of smooth muscle and nerve sheath cells. Therefore, immunohistochemical stains are used to confirm a suspected diagnosis. GIST should be considered in the differential diagnosis of mesenchymal or epithelioid tumors involving the liver, pancreas and pelvic cavity. In the present case, the GIST was thought to derive from the stomach and histologically comprised spindle-shaped and epithelioid cells positive for KIT.
Immunohistochemistry studies have demonstrated that the receptor tyrosine kinase KIT, also known as stem-cell growth factor receptor or CD117, is essential for the development of interstitial cells of Cajal. More than 95% of GISTs are positive for KIT (CD117) protein staining. About 90% of GIST have mutations of KIT and a smaller proportion have mutation of platelet-derived growth factor receptor-α (PDGFRA), a close homologue of KIT. These mutations result in oncogenic kinase activation that can cause uncontrolled cells proliferation leading to a stromal tumor. Hence, expression of KIT or PDGFRA is a crucial diagnostic marker for GIST. However, a small subset of GISTs do not have detectable KIT or PGDFRA mutation.

The treatment of localized disease is based on surgical removal of the tumor mass. Resection is not always possible in extensive metastatic disease. GISTs are resistant to conventional chemotherapy and only slightly sensitive to radiotherapy. However, a class of tyrosine kinase inhibitors, such as imatinib, and sunitinib and regorafenib as second line medication, was introduced in the early 2000s and is currently used to treat metastatic disease and in the adjuvant treatment of KIT-positive tumors.

Conclusions
Although the association of NICTH with GIST is rare, the occurrence of sustained hypoglycemia with low levels of insulin and IGF1 can be a paraneoplastic manifestation of an underlying tumor, especially a GIST. The identification of GIST has considerable clinical relevance because KIT-selective tyrosine kinase inhibitors have been proved effective in the tumor adjuvant treatment.

References


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Figure 1. Non-contrast MR images acquired using the Dixon technique. (A) axial “water only” sequence showing multiple soft tissue peritoneal localizations adjacent to the anterior, lateral and posterior margin of the right lobe of the liver (arrows). (B) on a more caudal level, axial “in-phase” sequence depicts peritoneal localizations adjacent to the posterior and medial margin of the VI segment of the liver and a retroperitoneal localization adjacent to the superior pole of the right kidney (arrows). In the same examination contrast enhancement and restricted diffusion within the walls of the body of the stomach were noticed (not shown).
Figure 2. Hematoxylin and eosin stain showing multiple palisade cells indicative of neural differentiation.

Figure 3. Immunohistochemical analysis showing CD117/c-KIT immunoreactivity.