

A Case of Gastrointestinal Stromal Tumor with Hyperinsulinemic Hypoglycemia

King-Fair Hall, MD; Chia-Li Lin¹, MD; Tsung-Hsi Wang², MD; Rung-Ho Chang³, MD; Han-Ming Chen⁴, MD, PhD

Gastrointestinal stromal tumor (GIST) is an uncommon malignant tumor that has recently been drawn to the attention of clinicians because of the protean clinical spectrum, endocrinological pathogenesis, aggressive metastatic features, poor prognosis, oncogenic tyrosine kinase receptor mutation and its brilliant revolutionized inhibitor imatinib. However, very few cases of GIST and hypoglycemia have been reported worldwide and they are usually associated with normal or low insulin levels. Here, we report on a rare case of GIST with postabsorptive hypoglycemia, extraordinary hyperinsulinemia and low insulin-like growth factor I (IGF-I). Its unusual neurological presentation made its diagnosis very difficult. After a complete resection, the symptoms diminished. We point out the unusual endogenous hyperinsulinism, clinical features and postulate possible mechanisms. (*Chang Gung Med J* 2008;31:107-11)

Key words: hypoglycemia, gastrointestinal stromal tumor, insulin-like growth factor I, non-islet cell tumor with hypoglycemia

Gastrointestinal stromal tumor (GIST) is the most common intestinal mesenchymal tumor. Its annual incidence in European countries is reported as 1-15 cases in one million of the general population⁽¹⁾ and is similar in Asian countries, being 1.68-1.96 per 100,000 people.⁽²⁾ The most frequent locations are the stomach (39% to 72.3%) and the small intestines (17% to 30%).⁽²⁻⁴⁾ The clinical spectrum of GIST is protean and fascinating. Gastrointestinal bleeding is the most common manifestation.⁽⁵⁾ However, hypoglycemia is also rarely associated with it. Only a few cases of GIST with hypoglycemia (GISTH) have been presented in different areas.⁽⁶⁻⁹⁾ They were encountered with lower insulin-like growth factor I (IGF-I) serum levels, normoinsulinemia or hypoinsulinemia, and high IGF-II levels. The latter finding was speculated to be the causative mechanism of the

clinical hypoglycemia and led to the GISTH cases being discussed under the topic of non-islet cell tumor with hypoglycemia (NICTH).

In this report, we present a case of GISTH with lower IGF-I but hyperinsulinism inducing hypoglycemia. To our knowledge, GISTH with hyperinsulinism has not yet been reported in the literature.

CASE REPORT

An 80-year-old man was admitted to the neurological department due to episodic nocturnal mental change. He had attacks with psychotic features, including splitting, knocking the bedside, scolding his wife and delusions of persecution, especially at night. The patient was initially diagnosed in the outpatient department as having dementia with seizures

From the Department of Neurology; ¹Department of Gastroenterology; ²Department of Pathology; ³Department of Radiology; ⁴Department of Surgery, Ten-Chan General Hospital, Taoyuan, Taiwan.

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Correspondence to: Dr. Han-Ming Chen, Department of Surgery, Ten-Chan General Hospital, No. 155, Yanping Rd., Zhongli City, Taoyuan County 320, Taiwan (R.O.C.) Tel.: 886-3-4629292 ext. 28811; Fax: 886-3-4343050; E-mail: ming1838@yahoo.com

for several months. No oral hypoglycemic agents were prescribed in the medication record. Physical examination was unremarkable. During the first night of hospitalization, the patient had hypoglycemia of 33 mg/dl during an attack. He was immediately given a bolus of four ampoules of 500 g/L dextrose solution and a continuous infusion of 100 g/L dextrose solution. Several minutes later, the patient was fully oriented with blood glucose elevated to 203 mg/dl. However, he had several similar confusional episodes, and interdigestive and night fasting hypoglycemia (also referred to as postabsorptive hypoglycemia) were noted. The serum insulin and C-peptide levels during the typical clinical Whipple's triads were later reported as 37.2 μ IU/ml (normal range: 0.00 – 15.6 μ IU/ml) and 12.2 ng/ml (normal range: 0.78-1.89 ng/ml), respectively. However, the serum levels for thyroid, parathyroid, adrenal, growth and prolactin hormones were all within normal limits. The abdominal ultrasonogram revealed a tumor on the posterior wall of the stomach.

Abdominal computed tomography (CT) showed a well-demarcated solid tumor about $5.5 \times 7.5 \text{ cm}^2$ in the posterior stomach surrounded by the pancreas tail and the gut; no regional lymph node metastasis was revealed (Fig. 1). During surgical exploration, the tumor was found to be firmly adhered to the left liver and spleen. Involvement of the esophagogastric junction was also noted. The patient underwent total



Fig. 1 One cut of the abdominal computed tomography revealed a well-defined oval lesion (indicated with *) about $5.5 \times 7.5 \text{ cm}^2$ hiding on the stomach posterior wall. It is shown adhered to the spleen and pancreas tail on this film.

tumor resection by proximal subtotal gastrectomy, splenectomy and partial hepatectomy. Under microscopic examination with hematoxylin and eosin (HE) stain, the tumor was composed of hypercellular spindle cells arranged in fascicles and whorls (Fig. 2). Immunohistochemical study showed tumor cells positive for CD117 (Fig. 3) and CD34, focally positive for smooth muscle actin, and negative for desmin and S-100 protein. These findings indicated the diagnosis of GIST.

The insulin, C-peptide and IGF-I levels were rechecked 2 days and 1 week after surgery. The insulin levels before surgery and 2 days after surgery were 37.2 μ IU/ml and 6.6 μ IU/ml, respectively. The C-peptide levels before surgery, 2 days after surgery

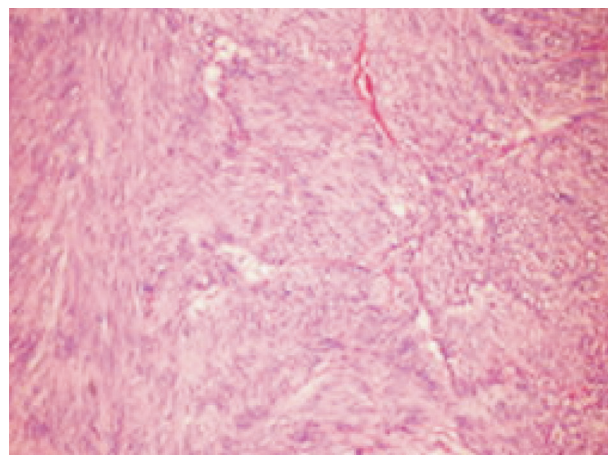


Fig. 2 Light microscopy (x40) showing hypercellular spindle cells arranged in fascicles and whorls.

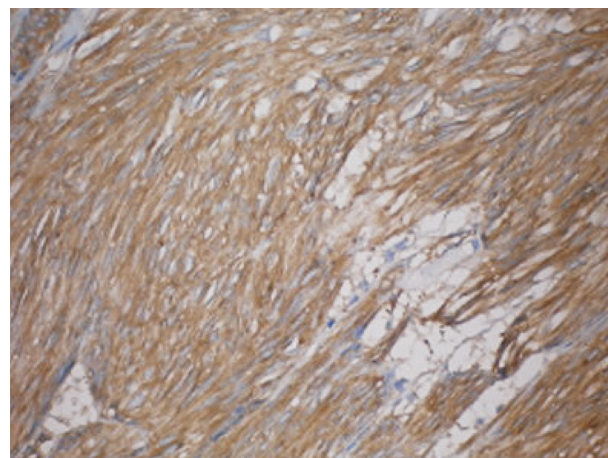


Fig. 3 Immunohistochemical study (x100) showing tumor cells positive for CD117.

and 1 week after surgery were 12.12 ng/ml, 1.94 ng/ml and 1.27 ng/ml, respectively. The IGF-1 levels (normal range for ≥ 60 years of age: 78-258 ng/ml) before surgery, 2 days after surgery and 1 week after surgery were 30.8 ng/ml, 48.7 ng/ml and 78.5 ng/ml, respectively. Two weeks after surgery, the patient was discharged from hospital with a fasting serum glucose level of 80 mg/dl and no further confusional episodes. Positron emission tomography (Fig. 4) revealed no residual tumor or distant metastasis two months after surgery.

DISCUSSION

Tumor induced hypoglycemia is an uncommon condition. The most familiar occurrence is due to insulinoma that arises from pancreatic or extrapancreatic islet cells. Other cell types, such as mesenchymal, epithelial or hematopoietic, may also cause hypoglycemia. To differentiate their different endocrinological characters from islet cell tumors, pathologists usually place them in the category of NICTH. Cases of NICTH have been mostly found in the gastrointestinal system, such as the liver or stomach, and sporadically in the chest, kidney, and adrenal and prostate gland.⁽¹⁰⁾ GIST is one kind of gastroin-

testinal mesenchymal tumor that presents rarely with hypoglycemic symptoms. Only sporadic case reports have been presented worldwide.⁽⁶⁻⁹⁾ These cases of GISTH may be regarded as one kind of NICTH.

The pathogenesis of NICTH is not clear. The causative mechanisms include insulin-like growth factor II or its high-molecular-weight precursor named big IGF-II,⁽¹⁴⁾ multiple liver metastases, bulking tumor or, rarely, autoimmunity.⁽¹¹⁾ Diagnosis of NICTH is based on the low serum insulin level, low serum concentrations of IGF-I and IGF binding protein-III (IGFBP-III) in combination with elevated concentrations of pro-IGF-II. However, not all cases of NICTH have consistent findings. Firstly, the levels of IGF-II in some NICTH cases were found to be normal.^(7,12,13) Hizuka found only 13 of his 44 patients had high IGF-II levels.⁽¹⁰⁾ Secondly, although there is a greater chance of high serum IGF-II levels if big IGF-II is present, this was not confirmed in another report by Kato.⁽¹⁴⁾ IGF-II serum levels were 3 times higher during the patient's hypoglycemic course but most of the positive immunohistologically stained (monoclonal anti-IGF-II antibody) gastric tumor tissue had only a few cells that stained positive for pro-IGF-II. Thirdly, Seckl presented a similar case to ours where NICTH caused profound hypoglycemia.⁽¹¹⁾

Obviously, the laboratory findings of this case did not fulfill the "classic" diagnostic criteria for NICTH. Diagnosis of NICTH is questionable and made this patient a "novel" case with rare clinical findings. There are also several extraordinary findings when the previously reported GISTH patients and our case are compared.⁽⁶⁻⁹⁾ Our case had lower levels of IGF-I but high serum levels of insulin and c-peptide. Furthermore, the hypoglycemic symptoms in most GISTH cases, which have normoinsulinism or hypoinsulinism, disappear one or two days after surgery. In our case, the hyperinsulinism diminished considerably 2 days after surgery and fasting hypoglycemic episodes no longer occurred. A whole body nuclear scan was performed and ruled out hot spots representing metastasis or residual tumor.

It is very difficult to explain the hyperinsulinism and hypoglycemia in our case by the homeostatic pathophysiology of IGF, growth hormone and insulin, since we did not check the IGF-II levels. We speculate that our different hyperinsulinemic hypoglycemia laboratory data might be due to the clinical

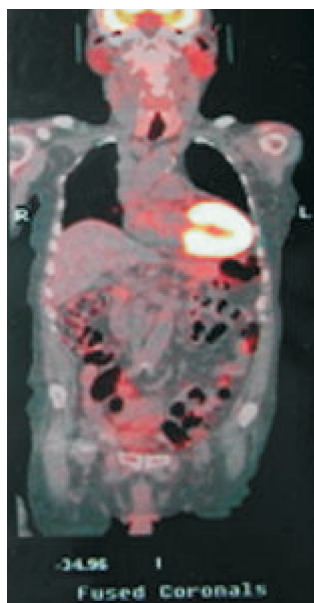


Fig. 4 Fused coronal positron emission tomography with [^{18}F] fluorodeoxyglucose tracer revealing neither residual tumor nor liver metastasis.

stage, as our patient was in the early phase of GISTH and the previous patients were mostly in the metastatic stage.⁽⁶⁻⁹⁾ However, more case analyses should be undertaken to prove that hyperinsulinism or hypoinsulinism are course-dependent.

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胃腸道基質瘤合併高胰島素血性低血糖症

何競輝 林家立¹ 王宗熙² 張榮和³ 陳漢明⁴

胃腸道基質瘤是一種不常見的胃腸道惡性腫瘤，其多變之臨床表現、內分泌學之病因病理、惡性轉移的變化、不良的預後及在腫瘤學上之基因突變，都有其特別之處。臨床上極少基質性瘤是以低血糖表現。我們將在此做一病例之報告，為一胃腸道基質瘤合併高胰島素血性低血糖症，其臨床上甚為罕見地以神經學症狀表現。(長庚醫誌 2008;31:107-11)

關鍵詞：低血糖，胃腸道基質瘤，類胰島素生長因子，非胰島細胞瘤合併低血糖症

天晟醫院 神經內科，¹腸胃道內科，²病理科，³放射診斷科，⁴外科

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通訊作者：陳漢明醫師，天晟醫院 外科。桃園縣320中壢市延平路155號。Tel.: (03)4629292轉28811; Fax: (03)4343050; E-mail: ming1838@yahoo.com