Successful Multimodal Treatment of an IGF2-Producing Solitary Fibrous Tumor With Acromegaloid Changes and Hypoglycemia

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Doege–Potter syndrome with acromegaloid facial changes is extremely rare. Uncooked cornstarch along with glucocorticoids have been used as supportive care in patients with non–islet cell tumor hypoglycemia (NICTH). Preoperative embolization of hepatic solitary fibrous tumors (SFT) with NICTH has yielded unsatisfactory results. Herein we present the case of a 61-year-old man with a 3-month history of severe frequent hypoglycemic episodes and acromegaloid facial changes. During a spontaneous hypoglycemia (26 mg/dL), laboratory values showed a hypoinsulinemic pattern with low levels of GH, IGFPB3, and an IGF2/IGF1 ratio of 8.5:1. Cross-sectional imaging revealed a large (16 × 13 × 11 cm) hepatic tumor, and cytology was consistent with SFT. A preoperative right portal embolization was performed in an effort to induce normal remnant liver hypertrophy to allow for safe tumor resection. After the procedure, uncooked starch treatment followed by prednisone was started, achieving complete remission of hypoglycemic episodes in the preoperative setting. He subsequently underwent partial hepatectomy. The histologic diagnosis was compatible with a potentially malignant SFT. The patient had an excellent outcome with complete remission of hypoglycemia, improvement of facial acromegaloid changes, and no further evidence of disease. To our knowledge, this is the first case of a patient with Doege–Potter syndrome with acromegaloid facial changes induced by a potentially malignant liver SFT, treated successfully with a multimodal approach consisting of uncooked cornstarch, low-dose prednisone, preoperative embolization, and complete surgical resection. The use of cornstarch and low-dose glucocorticoids may be an adequate treatment in advance of undergoing surgery.

Non–islet cell tumor hypoglycemia (NICTH) is a rare paraneoplastic syndrome usually found in association with IGF2-producing mesenchymal tumors. Rarely, acromegaloid facial changes have been reported, likely secondary to the stimulation of insulin and IGF1

receptors. Uncooked cornstarch along with glucocorticoids have been used in NICTH as supportive care [1]; also, preoperative embolization of hepatic solitary fibrous tumors (SFT) has been performed, albeit with unsatisfactory results [2].

We report a case of a 61-year-old man with acromegaloid changes and severe hypoglycemia due to a hepatic IGF2-producing large SFT, successfully treated with right portal vein embolization, uncooked cornstarch, and low-dose prednisone, prior to surgical resection. Informed consent for publication was obtained from the patient.

1. Case Presentation

A 61-year-old man presented with a 3-month history of episodic disorientation, incoherent speech, erratic behavior, and diaphoresis, associated with decreased blood glucose levels (<30 mg/dL). These symptoms would remit following intake of carbohydrate-rich foods; however, episodes increased in frequency, and he was eventually found unconscious before his transfer to our institution. Upon admission, capillary blood glucose measurements ranged from 31 to 53 mg/dL, and he was hospitalized to determine the etiology of the hypoglycemic disorder.

Physical examination highlighted facial changes characterized by coarse facial features, seborrheic keratoses, skin tags, rhinophyma, prominent nasolabial sulci, frontal bossing, and pachyderma [Fig. 1(B)]. During a spontaneous hypoglycemic episode, laboratory tests revealed blood glucose of 26 mg/dL, with low levels of insulin, C-peptide, proinsulin, and β-hydroxybutyrate (Table 1).

Growth hormone concentration was 0.008 ng/mL (range, 0 to 3 ng/mL), IGF2 was 673 ng/mL (range, 333 to 967 ng/mL), IGF1 was 78.88 ng/mL (range, 17 to 206 ng/mL), the IGF2/IGF1 ratio was 8.62:1, and IGF-binding protein (IGFBP3) was 2.1 µg/mL (range, 3.2 to 6.6 µg/mL). A circulating oral hypoglycemic agents screen, insulin autoantibodies, and anti-insulin receptor antibodies were negative. Renal, liver, adrenal, and thyroid function tests were all normal.

A cross sectional abdominal CT scan showed a large (16 × 13 × 11 cm) hypodense lesion in the right hepatic lobe, with minimal heterogeneous contrast enhancement [Fig. 1(D)]. There was no evidence of metastatic disease and tumor markers (AFP, CA19-9, and CEA) were negative.

The patient was maintained on a 50% glucose IV infusion at a 15 to 35 mL/h rate, along with a carbohydrate-rich diet five times per day; hypoglycemia occurred predominantly when periods without oral intake exceeded 6 hours.

A percutaneous ultrasound-guided liver biopsy was performed. Cytology results suggested a fusiform and epithelioid tumor, compatible with a SFT. A total hepatic volume of 1174 cm^3 with a parenchymal normal remnant of 348.7 cm^3 (19.6%) was calculated. Therefore, a presurgical right portal embolization aiming to induce hypertrophy of the normal liver remnant, prior to tumor resection, was deemed necessary [Fig. 2(A)].

After embolization, uncooked cornstarch treatment was started (2 mg/kg every 6 hours) followed by 10 mg/d prednisone in an effort to control refractory hypoglycemia. These treatments allowed for normal glucose concentrations.

Six weeks after the portal embolization, a CT scan showed liver remnant hypertrophy (533.2 cm^3, 30%) and he was readmitted for surgical intervention. He had a difficult airway management owing to macroglossia and hypertrophy of laryngeal tissues. During the right hepatectomy, after clipping the right suprahepatic vein, the patient had sustained hyperglycemia requiring insulin administration (preclipping glycemia of 50 to 90 mg/dL, postclipping glycemia of 190 to 298 mg/dL).

The patient was discharged without complications. Histopathological analyses confirmed an SFT (14.5 × 10.5 × 9 cm) with clear margins at 0.2 cm [Fig. 2(B)], 5% necrosis, and a high proliferation rate of 8 to 10 mitotic figures per high-power field. There was no lymphovascular or perineural invasion. Immunohistochemistry showed positive staining with antibodies against CD34, Bcl2, and CD99 and negativity for TLE1, EMA, and CK. The Ki-67 proliferation rate was 15% [Fig. 2(C)].

The surgical outcome was excellent and facial acromegaloid changes improved on a short postoperative follow-up period (5 months), with complete remission of hypoglycemia [Fig. 1(C)]. IGF2 levels and the IGF2/IGF1 ratio have trended down, and levels of IGFBP3 and GH have increased
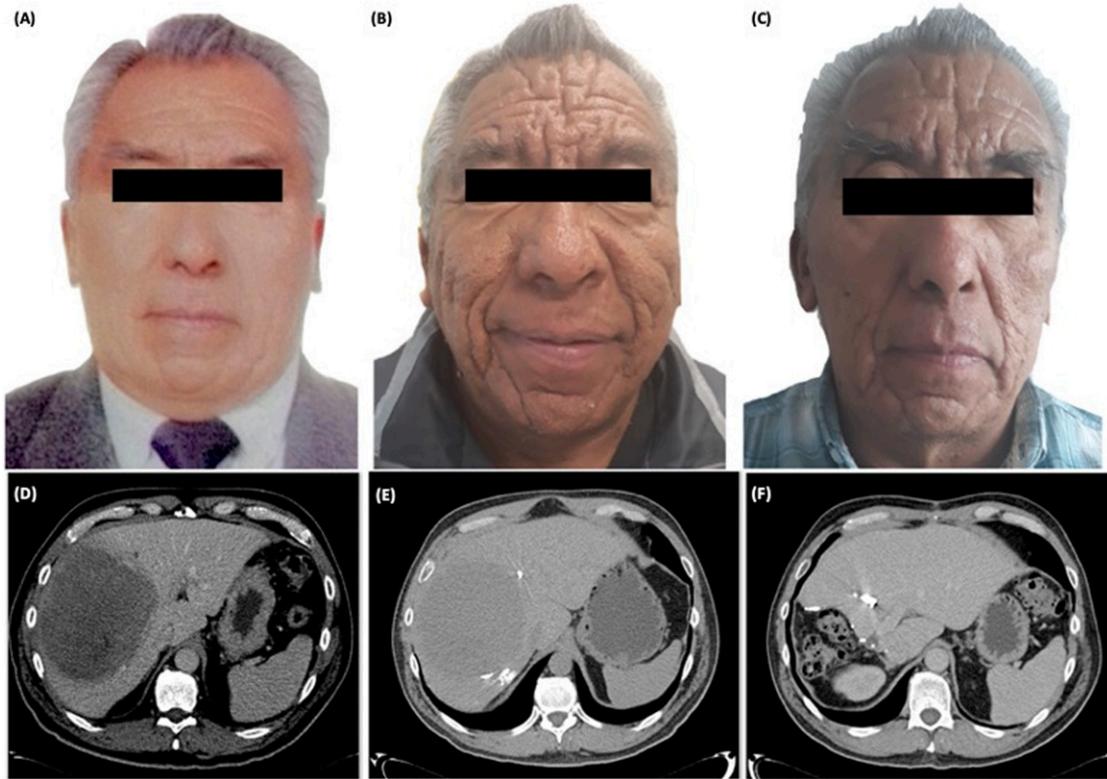
Figure 1. (A) Baseline photograph before chief complaint started (~1 y earlier). (B) Acromegaloid facial features at clinical presentation: coarse facial appearance, seborrheic keratoses, skin tags, rhinophyma, prominent nasolabial sulci, frontal bossing, and pachyderma. (C) At 4 mo after surgery, the acromegaloid changes had improved. (D) A cross-sectional enhanced CT scan at diagnosis showed a round hypodense hepatic lesion with minimal heterogeneous enhancement. (E) A nonenhanced CT scan at 6 wk after embolization exhibited peripheral hyperdensity. (F) A CT scan at 4 mo postsurgery showed complete tumor resection and normal liver remnant hypertrophy.

[Fig. 3]. At follow-up the CT scan showed complete surgical tumor resection, a further increase of the remaining normal liver volume (1066.4 cm^3), and no evidence of metastases [Fig. 1(F)].

2. Discussion

We present the case of a patient with non–islet cell-dependent hypoglycemia, associated with a large SFT (Doege–Potter syndrome) and severe acromegaloid changes, treated successfully with preoperative medical and interventional approaches followed by surgical resection.

Few cases of IGF2-producing tumors have been shown to cause coarse facial features, similar to those observed in patients with acromegaly. In a recent review of six NICTH cases by Jannin *et al.* [3] acromegaloid changes were reported in two of six patients (both with SFT). Moreover, scarce data exist regarding posttreatment remission of acromegaloid facial features [4]. In a review of 71

Table 1.   Results of Laboratory Test During a Spontaneous Hypoglycemic Episode

| Glucose (mg/dL)	Insulin (µU/mL)	C-peptide (nmol/L)	Proinsulin (pmol/L)	β-Hydroxybutyrate (mmol/L)	Glucose Increase After Glucagon (mg/dL)	Circulating Oral Hypoglycemic Agents	Anti-Insulin Antibodies	IGF2 (ng/mL)	IGF1 (ng/mL)
26	0.25	<0.05	<0.5	0.03	108	Negative	Negative	673	78.8
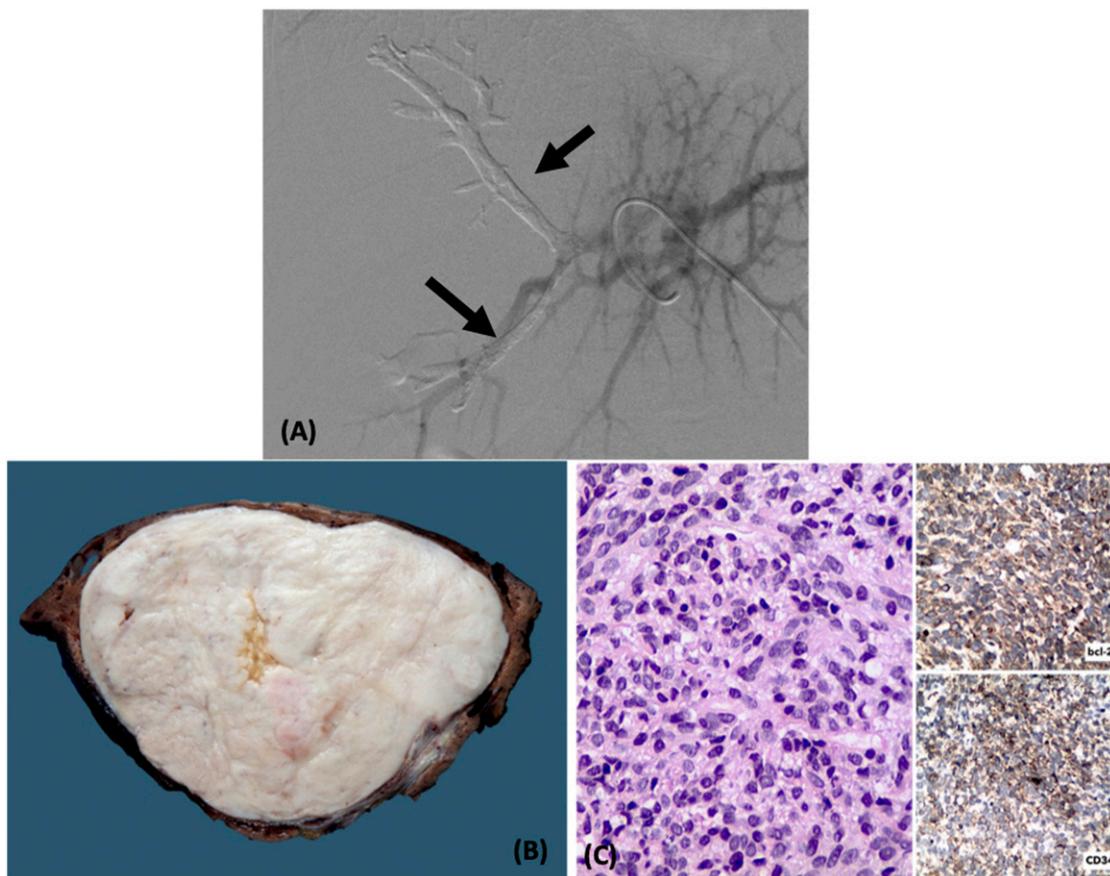
Figure 2. (A) Right portal vein embolization; the arrows indicate the absence of contrast in the anterior and posterior branches of the right portal vein. (B) Macroscopic tumor of 14.5 × 10.5 × 9 cm, 2000 g, solid, lobulated, well delineated, white with yellow areas, and located at 0.2 cm of the surgical margin. (C) Microscopically in the hematoxylin and eosin stain the tumor had a high proliferation rate of 8 to 10 mitotic figures per high-power field (400× magnification) and positive immunostaining with antibodies anti-CD34 and -Bcl2.

cases of Doege–Potter syndrome by Han *et al.* [5], two patients with acromegaloid changes were described, one with improvement of facial changes after therapy. Dutta *et al.* [6] reported five cases with NICTH and two with regression of acromegaloid changes following therapy. Lastly, one case of NICTH with acromegaloid facial and acral involvement showed substantial improvement of acromegaloid changes 1 week after treatment, with further improvement at a 1-year follow-up [4].

The differential diagnosis of acromegaloid features without GH/IGF1 excess (pseudoacromegaly or acromegaloidism) can be challenging. A variety of entities should be considered, such as pachydermoperiostosis, severe insulin resistance, familial mandibular prognathism, and acromegaloid changes secondary to chronic intake of phenytoin and/or minoxidil [3].

Although our patient had pachyderma (cutaneous thickening), he had no evidence of digital clubbing or hyperhidrosis, which constitute the three main features of pachydermoperiostosis, a rare genetic disease found in association with *HPGD* mutations, with an autosomal recessive inheritance [7].

Other types of skin lesions such as rhinophyma and seborrheic keratoses are widely described in the literature in association with these tumors. Despite this, the pathophysiology of acromegaloid changes has not been fully understood, but it could relate to IGF2-mediated stimulation of IGF1-related receptors and subclasses of insulin-related receptors [8]. Normally, mature IGF2 is mainly produced by the liver; nonetheless, it is also secreted by most tissues [9]. In our patient, acromegaloid changes were so prominent that they conditioned a difficult airway intubation prior to surgery, but they showed a relatively rapid improvement during follow-up [Fig. 1(C)].
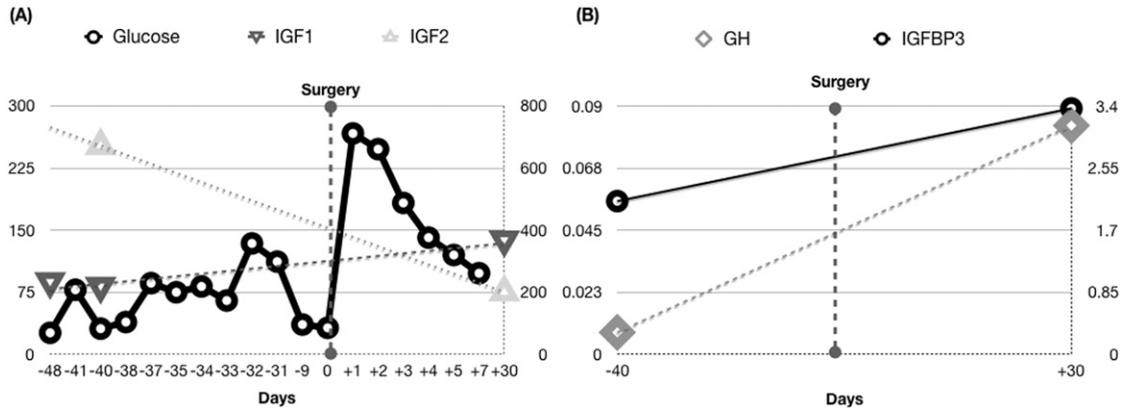
Figure 3. (A) Glycemic variability, with persistent initial hypoglycemia, transient transoperative hyperglycemia, and remission of the hypoglycemic episodes after surgery. The dashed lines represent the linear trends of IGF1 and IGF2 concentrations, and the bold line represents the serum glucose level. (B) GH (dashed line) and IGFBP3 (bold line) concentrations increased from baseline preoperative values (linear trends).

The IGF system [10] entails two IGF ligands (IGF1/2) and two IFG receptors (IGF1R and IGF2R). IGF1 is under endocrine control (GH mediated), whereas IGF2 is relatively independent of GH and is produced in an autocrine/paracrine fashion. IGF1/2 are structurally and functionally related to insulin, and most of the biological actions of IGFs are likely mediated via the IGF1 receptor, which is structurally homologous to the insulin receptor (IR). The IRs have two isoforms [IRA, preferentially expressed in fetal tissues and in some malignancies, and IRB in endocrine target tissues (muscle, liver, fat)]. IGF2 has high and low affinity for IRA and IRB, respectively, with a predominant mitogenic effect and, to a lesser extent, with insulin-like metabolic effects. IGF2 also binds to IGF2 receptor and hybrid receptors (IGF1 receptor–IRA/B). The hypoglycemic effects of IGFs are ~10-fold weaker than those of insulin, and normal concentrations of IGFs in humans are ~1000-fold higher than insulin ones. However, >90% of IGFs are bound to transport proteins (IGFBPs) in normal conditions. Of the six IGFBPs isoforms, IGFBP3 is the most abundant and binds >95% of IGFs. Most (~75%) IGFs circulate in ternary high–molecular mass complexes (150 kDa; IGF plus IGFBP3 plus acid-labile subunit ALS), incapable of crossing capillaries. A minority of IGFs circulate as binary complexes (IGF–IGFBP2/3; ~45 kDa) and <1% as free IGFs, with both being capable of crossing capillary membranes with ultimate biologic activity.

In the setting of a NICTH, IGF1 is usually low, whereas IGF2 can be normal or high or even low. Actually, most of the NICTH cases do not show high levels of total IGF2, similar to our patient [10]. Tumors of patients with NICTH have been shown to express high concentrations of IGF2 mRNA. Moreover, the posttranslational processing of pro-IGF2 is abnormal, with a higher proportion of incompletely processed forms (>60% *vs* ~15% in healthy subjects) consisting of larger non-glycosylated proteins [IGF2 with a 21–amino acid extension of the E-domain (pro-IGF2E)], likely due to insufficient enzyme processing in the context of high amounts of pro-IGF2 being produced by neoplastic cells. "Big-IGF2" seems to have properties that do not allow the formation of ternary high–molecular mass complexes, is biologically active, and has equal affinity for IGFBPs as does the fully processed IGF2, capable of forming binary complexes with eventual biologic activity due to increased bioavailability of free IGF2 that binds to IFG1R and IRs, thereby promoting glucose consumption by peripheral tissues. Hypoglycemia is further favored by a GH decrease that leads to diminished ALS, IGF1, and IGFBP3 levels, as well as decreased hepatic glucose production.

Although serum total IGF2 can be normal in NICTH, the pro-IGF2/IGF2 and IGF2/IGF1 ratios may be elevated [11]. The IGF2/IGF1 ratio is considered a marker of high IGF2 concentration; a ratio of ~3:1 is normal, and in most IGF2-producing tumors the ratio is >10:1 [12].

In our case, the occurrence of spontaneous symptomatic hypoinsulinemic hypoglycemia, increased IG2/IGF1 ratio (8.5:1), suppression of GH and IGFBP3, and the associated clinical features made IGF2-mediated hypoglycemia the most likely etiology.

SFTs are uncommon neoplasms, mostly found in the pleural space. However, these tumors have been reported to occur in other locations, including the retroperitoneum, soft tissues of the limbs, head, neck, and abdominal cavity, although the liver is rarely involved [13]. Currently, <100 cases of SFT of the liver have been reported in the literature [14], and only 5, including our case, are IGF2 producers [15].

NICTH treatment can be difficult and multiple treatment modalities are usually needed. Embolization therapy has been reported in five cases of SFT; in four of these cases hypoglycemia did not improve and tumor atrophy was not achieved [5]. One case described the treatment of a metastatic SFT with hepatic radioembolization (using 90Y-labeled glass microspheres) with satisfactory response in both hypoglycemia and tumor size [16]. In a case of a hepatic SFT with malignant transformation to fibrosarcoma, the tumor was embolized 6 weeks preoperatively in an attempt to induce hypertrophy of the contralateral lobe, with unsatisfactory results [2]. In the current case, owing to the small calculated liver remnant, the same type of procedure was performed in an effort to induce normal liver hypertrophy and thus assure normal hepatic function after tumor resection. This was achieved successfully without complications, with a postoperative normal liver function.

Another treatment modality that has been employed is the use of somatostatin analogs. A case of an intra-abdominal hemangiopericytoma causing hypoglycemia was effectively treated with a continuous somatostatin infusion [17]. Nonetheless, in two other cases somatostatin-based therapy was unsuccessful. One was a pleural SFT expressing somatostatin receptors, in which the use of maximal doses of octreotide did not improve hypoglycemia, but was subsequently treated effectively with a combination of GH and glucocorticoids [18]. The other case was a gastric adenocarcinoma producing big-IGF2; octreotide failed to control hypoglycemia, whereas prednisolone (2 mg/kg) and enteral feeding averted new serious events [19].

The use of uncooked cornstarch has been used for fasting hypoglycemia in glycogen storage diseases at a dose of 1.5 to 2.5 g/kg body weight every 4 to 6 hours [20]. Some have used prednisone for treatment of NICTH (30 mg or higher [21, 22]). To our knowledge, there is only one previous case reporting treatment with uncooked starch for a NICTH along with low-dose prednisone (20 mg/d) [1]. Our patient received uncooked cornstarch and prednisone (10 mg/d) before tumor resection, with complete remission of hypoglycemia during ambulatory follow-up.

The World Health Organization defines some of the histological characteristics of SFT as suggestive of malignancy, including hypercellularity, cytological atypia, tumor necrosis, high mitotic rate ($\geq$4 to 10 per high-power field), and/or infiltrative margins [23, 24]. Others consider Ki-67 >5% as another marker of malignancy [25]. Owing to severity/rapid clinical progression, tumor size, and especially based on histopathological characteristics, we labeled this liver tumor as a potentially malignant SFT, which was completely surgically removed.

To our knowledge, this is the first case report of a patient with acromegaloid facial changes induced by an IGF2-producing SFT of the liver treated successfully with a multimodal approach.

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