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CASE REPORT

Diabetes mellitus secondary to growth hormone-secreting pituitary adenoma

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Abstract

Growth hormone-secreting pituitary adenoma is a common intracranial benign tumor, characterized by excessive production of growth hormone, which leads to acromegaly or giant disease. An abnormal increase in growth hormone can induce glucose metabolism disorder, which is often diagnosed and treated as type 2 diabetes, because of uncontrollable hyperglycemia, delaying the treatment of the primary disease. This paper reports the diagnosis and treatment data of a patient with growth hormone-secreting pituitary adenoma who was first diagnosed as having diabetes, and reviews the related literature to facilitate a better understanding of the disease.

Abbreviations:

GHPA	- growth hormone-secreting pituitary adenoma
GH	- growth hormone
IAA	- insulin autoantibody
MRI	- magnetic resonance imaging
IGF-1	- insulin-like growth factor-1
LH	- luteinizing hormone
PRL	- prolactin
ACTH	- adrenocorticotropic hormone
FSH	- follicle-stimulating hormone
TSH	- thyroid stimulating hormone
LCA	- leukocyte common antigen
GFAP	- glial fibrillary acidic protein
Pit1	- pituitary specific transcription factor 1
Tpit	- pituitary cell-restricted t box factor
SF	- splicing transcription factor
PA	- pituitary adenomas

INTRODUCTION

Growth hormone-secreting pituitary adenoma (GHPA) is a common component of functional pituitary adenomas, accounting for about 20% of pituitary adenomas (Iacovazzo *et al.* 2021). It can occur at any age and has an almost equal male-to-female ratio (Qiao *et al.* 2021). It is characterized by excessive secretion of growth hormone (GH). This can cause gigantism in adolescents and acromegaly in adults. GHPA is insidious in its onset, and the symptoms are not obvious in the early stage. As the disease progresses, it gradually involves several organs and systems. It is rarely diagnosed early, and is often misdiagnosed because of various complications, which delays treatment past the optimal window, and increases the risk of operation (Wang *et al.* 2021).

In this paper, we report and analyze a case of GHPA with hyperglycemia who was first diagnosed as having diabetes. We also review the

related literature to facilitate a better understanding of the disease.

METHODS

Ethics

This study was approved by the Ethics Committee of the First Affiliated Hospital of Anhui Medical University, and this patient provided informed consent to participate.

Case report

A 59-year-old male patient with symptoms of dry mouth, polydipsia, polyuria, and gradually blurred vision, without any obvious cause lasting 8 months, which had been exacerbated over the previous 2 weeks, was seen at the First Affiliated Hospital of Anhui Medical University on March 17, 2021. This was accompanied by fatigue, chest tightness, shortness of breath, no headache or dizziness, no excessive food and hunger, no fear of heat, no sweating, or palpitations, etc. Prior visiting our hospital, he consulted a clinician at the People's Hospital of Feidong County, Anhui Province, and was found to have elevated fasting glucose (venous blood glucose 8.0 mmol/L) but was not given special treatment. Two weeks before hospitalization, the above symptoms of the patient had been exacerbated. In order to seek further diagnosis and treatment, he was hospitalized in the outpatient Department of Endocrinology of our hospital. His fasting blood glucose was 20.9 mmol/L, and glycosylated hemoglobin A1c was 13.9%. Accordingly, he was admitted to our department with the diagnosis of "diabetes".

The patient reported being in good health in the past and denied a family history of similar diseases and other genetic diseases. Physical examination on admission showed blood pressure of 130/82 mmHg, body mass index of 26.7 kg/m^2, thick lips, a large tongue, protruding nasolabial groove, protruding eyebrow arch and zygomatic bone, a wrinkled forehead, sense of facial tightness, and enlarged protrusion of the mandible. The dorsum of both hands and feet were broad and thick, the ends of the hands and toes were hypertrophic, and his skin was thick. The bilateral thyroid gland showed I degree enlargement, had a soft texture, and no thyroid nodule could be palpated. No abnormality was found in the rest of the body.

Blood biochemistry investigations revealed that fasting blood glucose concentration was 18.7 mmol/L (reference: 3.9–6.1 mmol/L), total cholesterol level was 5.96 mmol/L (reference: 2.30–5.20 mmol/L), triglyceride level was 1.91 mmol/L (reference: 0.56–1.70 mmol/L), low density lipoprotein level was 3.61 mmol/L (reference: 1.20–3.30 mmol/L), and thyroid peroxidase antibody level was 65.70 U/ml (reference: 0–60 U/ml). The fasting insulin level was 8.5 mIU/ml, and the two hours postprandial insulin level was 35.5 mIU/ml. Glutamic acid decarboxylase antibody and insulin autoantibody (IAA) tests were negative (Table 1).

Thyroid B-ultrasound showed diffuse thyroid lesions with multiple mixed echoes in both lobes of the thyroid (TI-RADS 3 grade). Color Doppler ultrasonography of cervical vessels indicated the formation of plaque in the right subclavian artery. The symmetry of bipedal sensory threshold decreased.

The patient was initially diagnosed with diabetes mellitus (type to be determined), hyperlipidemia, and thyroid nodules upon admission. The patient was given "degludec insulin once a day + aspart insulin three times a day (basal + bolus mode)," combined with oral "acarbose 100 mg tid + metformin 0.5 g tid" as intensive hypoglycemic therapy. However, blood glucose levels were poorly controlled: fasting blood glucose fluctuated at 9.8–16.9 mmol/L, and postprandial blood glucose fluctuated at 12.8–20.6 mmol/L.

Given the patient's typical appearance of acromegaly (with obvious changes in comparison of photos taken over the last 3 years) and his poor results with intensive

Tab. 1. Blood biochemistry investigations

Indicators	Results	References
FBG (mmol/L)	18.7	3.9–6.1
TC (mmol/L)	5.96	2.30–5.20
TG (nmol/L)	1.91	0.56–1.70
LDL-C (mmol/L)	3.61	1.20–3.30
TPOAb (U/ml)	65.70	0.00–60.00
FINS (mIU/ml)	8.5	3.0–25.0
2h-INS (mIU/ml)	35.5	15.0–125.0
GAD-Ab	negative	negative
IAA	negative	negative

Notes: FBG, fasting blood glucose; TC, total cholesterol; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; TPOAb, thyroid peroxidase antibody; FINS, fasting insulin; 2h-INS, two hours postprandial insulin level; GAD-Ab, glutamic acid decarboxylase antibody; IAA, insulin autoantibody.

Tab. 2. Pituitary function test

Indicators	Results	References
GH (ng/mL)	30.30	0.06–5.00
ACTH (pg/ml)	17.10	0.00–46.00
T3 (nmol/L)	1.10	1.01–2.96
T4 (nmol/L)	88.00	55.40–161.25
TSH (μIU/ml)	1.862	0.38–4.34
PRL (ng/mL)	7.32	1.80–20.30
FSH (mIU/ml)	12.440	23.00–116.30
LH (mIU/ml)	2.200	15.90–54.00
IGF-1 (ng/mL)	246.00	48.00–209.00

Notes: GH, growth hormone; ACTH, adrenocorticotropic hormone; T3, triiodothyronine; T4, thyroxin; TSH, thyroid stimulating hormone; PRL, prolactin; FSH, follicle-stimulating hormone; LH, luteinizing hormone; IGF-1, insulin-like growth factor-1

hypoglycemic therapy, the possibility of pituitary tumor could not be ruled out. Magnetic resonance imaging (MRI) of the pituitary gland showed that the bottom of the sella turcica was sunken, and an irregular nodular shadow was seen in the sellar and suprasellar region, with a slightly longer T1 signal and equal T2 signal. The signal was nevertheless uniform, and a contrast-enhanced scan showed mild enhancement with a clear boundary. The size of the lesion was about 22.1 × 19.2 × 18.1 mm. The pituitary stalk was deviated to the right, and the optic chiasm was displaced upward (Figure 1). Visual field examination showed a bilateral temporal visual field defect. A pituitary function test showed that the GH level was 32.37 ng/ml (reference: 0.06–5.00 ng/ml), insulin-like growth factor-1 (IGF-1) level was 362.15 ng/ml (reference range: 48–209 ng/ml), while other anterior pituitary hormone levels were normal (Table 2). The results of a 24-hour cortisol rhythm test in blood indicated the presence of a circadian rhythm of cortisol within normal levels (Table 3).

According to the patient's history, signs, and auxiliary examinations, the pituitary occupancy was considered to have GHPA. Thus, he was transferred to the Department of Neurosurgery of our hospital and underwent endoscopic GHPA resection under general anesthesia. The next day, postoperative recheck identified that GH level was 3.98 ng/ml, IGF-1 level was 199.56 ng/ml, and fasting glucose level was 7.11 mmol/L (same hypoglycemic therapy as before surgery). The postoperative pathology report indicated that the morphological subtype of his adenoma was the sparsely granulated growth hormone tumor. Immunohistochemical staining of adenoma cells showed Syn (+), CKp (paranuclear +), GH (+), while LH (luteinizing hormone), PRL (prolactin), ACTH (adrenocorticotropic hormone), FSH (follicle-stimulating hormone), TSH (thyroid stimulating hormone), LCA (leukocyte common antigen), GFAP (glial fibrillary acidic protein), P53, Pit1(pituitary specific transcription factor 1), Tpit (pituitary cell-restricted t box factor), and SF (splicing transcription factor) all tested negative, and the number of Ki67-positive cells was 2% (Figure 2).

Examination 1-month postoperatively revealed a GH level of 2.24 ng/mL, IGF-1 level of 197 ng/mL; total cholesterol level of 3.76 mmol/L, triglyceride level of 0.49 mmol/L, and low-density lipoprotein cholesterol level of 2.33 mmol/L. Insulin aspart injection and metformin were stopped immediately after the operation, and subcutaneous injection of insulin degludec 4 U/day combined with acarbose 50 mg tid were used for hypoglycemic therapy. Fasting blood glucose levels were 5.3–6.8 mmol/L, while 2-h postprandial blood glucose levels were 7.3–11.5 mmol/L. Pituitary MRI showed postoperative changes, with no significant occupying lesions remaining. The changes in fasting blood glucose, growth hormone, and insulin-like growth factor during the course of the disease are shown in Figure 3.

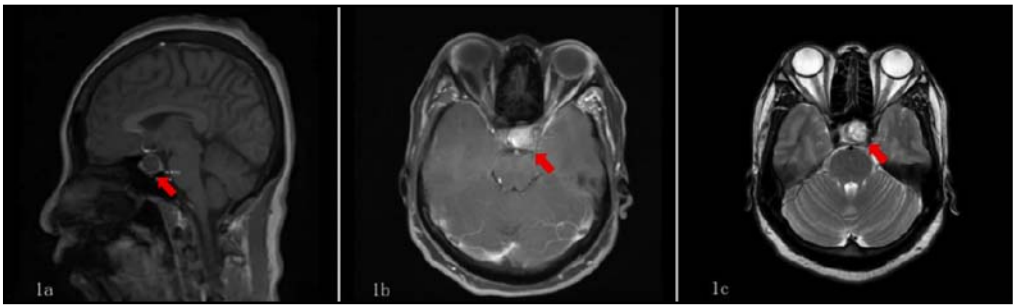

Fig. 1. Pituitary gland magnetic resonance images (sagittal + axial).
a. T1-enhanced sagittal position.
b. T1-enhanced axial position.
c. T2 axial position.

Tab. 3. Results of 24-hour cortisol rhythm test

Indicator	Times	Results	References
Cortisol (μg/dl)	8:00	12.76	5.00–25.00
	16:00	8.63	2.50–12.50
	24:00	3.15	1.85–8.23

DISCUSSION

Pituitary adenomas (PA) are common, indolent, benign intracranial neoplasms, with an incidence of about 5 cases per 100,000 population per year (Daly & Beckers, 2020). Based on clinical phenotype and hormone expression, they are classified into seven morphofunctional types: lactotroph tumor, somatotroph tumor, thyrotroph tumor, corticotroph tumor, gonadotroph tumor, null cell or immunonegative tumor, and plurihormonal tumors (Trouillas *et al.* 2020). Adenomas of different cell origins usually result in the corresponding hypersecretory syndrome, due to overproduction of the hormone by the tumor, and macroadenomas (≥ 10 mm) usually oppress the parasellar tissue, which may affect important vascular and neural structures, with resultant visual-field defects and headaches (Melmed, 2020). Among them, GHPA usually results in an abnormal increase in GH level, leading to significantly elevated IGF-1 levels (Colao *et al.* 2019). Patients with GHPA manifest with gigantism if the tumor develops before epiphyseal closure, or acromegaly if it develops after epiphyseal closure. The appearance of acromegaly varies but is characteristic, and includes but is not limited to acral overgrowth, deformity of facial features, soft tissue swelling, increased sweating, arthralgias, jaw prognathism, menstrual disturbances, erectile dysfunction, and hyperglycemia (Vilar *et al.* 2017). About 29%–45% of patients with GHPA have impaired glucose tolerance, and 20%–35% have diabetes (He *et al.* 2019). GH and IGF-1 contribute to glucose metabolism disorders by promoting lipolysis, decreasing glucose utilization, and inducing increased gluconeogenesis in the liver (Colao *et al.* 2004). In addition, GH, as an insulin receptor antagonist, leads to an increase in blood glucose (Carrasco *et al.* 2010; Hage *et al.* 2021).

Although acromegaly involves characteristic physical manifestations and significant complications, its course is slow and insidious, and the changes are often ignored (Syro *et al.* 2015). The early symptoms of this patient were not obvious until symptoms such as fatigue, polydipsia, and polyuria, caused by hyperglycemia, appeared. On examination after admission, the patient was found to have a typical acromegaly appearance, and when questioned about his medical history, the patient reported noticing gradually changes, such as coarse facial features and hypertrophy of the ends of his hands and feet, 3 years earlier, but had thought that it was due to aging and did not pay the changes much attention. By this time, the enlarged tumor had resulted in compression symptoms, disordered glucose metabolism, and multi-system involvement. Insulin resistance is common in patients with GHPA. Mori *et al.* (2013) reported that nine of twenty patients with GHPA had impaired glucose tolerance and two had diabetes mellitus patterns and founded that serum IGF-I levels were significantly correlated with insulin resistance in patients with GHPA. Pan *et al.* (2021) reported a case

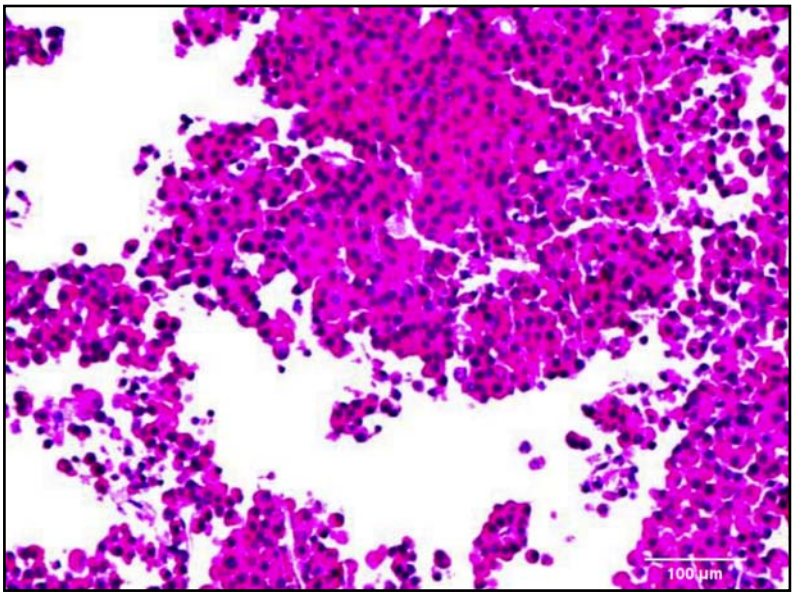

Fig. 2. Pathological changes in pituitary tumor after operation (hematoxylin and eosin staining, ×200)

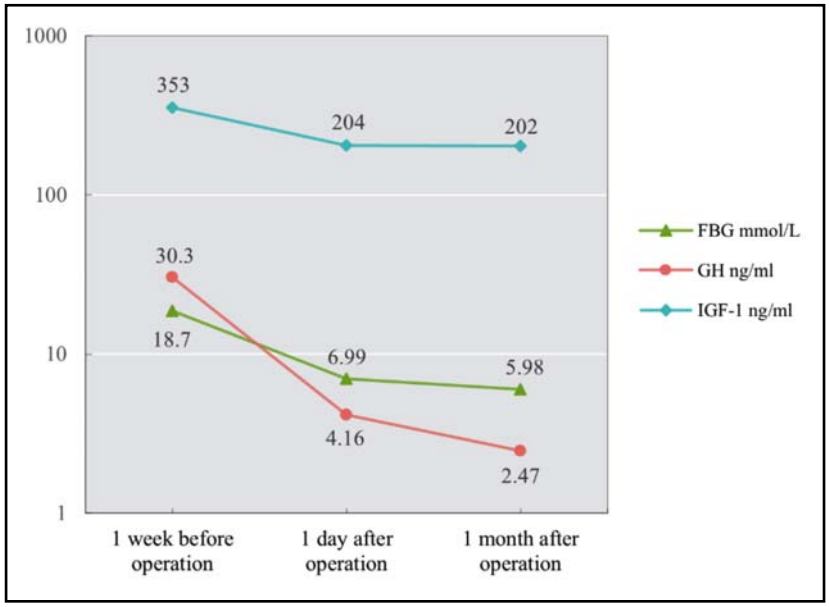

Fig. 3. Changes in fasting blood glucose, growth hormone, and insulin-like growth factor-1. FBG, fasting blood glucose; GH, growth hormone; IGF-1, insulin-like growth factor-1.

of GHPA patient with insulin resistance caused by long-term abnormal secretion of growth hormone, which led to metabolic syndrome and impaired glucose and lipid metabolism, and finally the patient developed diabetic ketoacidosis and acute pancreatitis induced by pituitary adenoma stroke. In our report, we observed this patient was proved to have diabetes and insulin resistance, which is in accordance with findings by other studies. However, Moradi *et al.* (2019) reported a case of pseudoacromegaly related to the selective post-receptor defect in insulin signaling, and the case also presented with acromegaly and insulin resistance, which should be differentiated. Chen *et al.* (2007) has reported that the dosage of insulin in such patients can reach 300 U/day. Thus, decreasing insulin resistance and increasing insulin sensitivity is the key to treatment. After giving the patient degludec insulin (20 U/day) and aspart insulin (8 U tid, 44 U/day in total) and adding metformin to reduce insulin resistance, the patient's blood glucose decreased as compared to earlier, but still did not reach the reference standard. Kasuki *et al.* (2019) have been reported that, when acromegaly is complicated by hyperglycemia, the function of multiple systems will be impaired as the disease progresses, which can significantly increase the mortality of patients. A 44 year old Japanese male patient with GHPA, after 10 years missed diagnosis, the pituitary adenoma became unresectable due to the aggressive growth into adjacent tissues, and developed severe hyperglycemia and multiple organ dysfunction (Nishihama *et al.* 2020). The above studies support our view that timely diagnosis and standardized treatment are of great significance for the prognosis of GHPA patients.

Once the disease is diagnosed, it is mainly treated by operation. Transsphenoidal microsurgical resection of pituitary tumors has the advantages of reduced trauma, fewer complications, mild postoperative reaction, and rapid recovery, and is the first choice for the treatment of GHPA, with significant implications for reducing postoperative hormone levels, acromegaly, and improving patients' prognosis (Cardinal *et al.* 2020). The patient was fully informed and communicated about his condition and then underwent radical surgery, which was obviously effective. On the day after the operation, GH levels had decreased from 32.37 ng/ml to 3.98 ng/ml, IGF-1 had decreased from 362.15 ng/ml to 199.56 ng/ml, and fasting blood glucose had decreased from 9.8–16.9 mmol/L to 7.11 mmol/L, without adjustment of the hypoglycemic regimen. Although GH rapidly returned to normal levels and IGF-1 gradually decreased after the operation, insulin combined with oral drugs was still needed to reduce blood glucose levels. This is because, although the insulin resistance caused by hyperfunction of the GH/IGF-1 axis was gradually relieved after surgical resection of the pituitary growth hormone tumor, the patient's chronic hyperglycemic state has caused islet β-cells to fail, and atrophy (Li *et al.* 2016) - which means glucose metabolism cannot be fully recovered in a short time after the cause of insulin resistance was removed (Li *et al.* 2019). One month later, the hypoglycemic regimen of the patient has been simplified to "degludec insulin (4 U/day) and acarbose tablet (50 mg tid)," and it was monitored that his blood glucose levels remained stable. His visual acuity was significantly improved, and the sense of facial tightness was less than that before operation. The postoperative clinical manifestations of this patient are consistent with other reports (Mori *et al.* 2013; Pan *et al.* 2021).

Pathologically, the pituitary adenoma in this patient was a sparsely granulated growth hormone tumor, which suggested more invasive lesions and a proclivity for recurrence (Dineen *et al.* 2017). Consequently, the patient was instructed to undergo follow-up with

regular review. In addition, the patient had high blood lipids combined with carotid plaques before the operation, which may have been caused by the decrease in lipoprotein lipase activity in the blood due to excess GH, and the increase in hepatic low-density lipoprotein-cholesterol expression (Vázquez-Borrego *et al.* 2021). Additionally, elevated triglycerides can accelerate the decline of islet β-cell function and further aggravate insulin resistance. Thus, this group of patients need to start lipid-regulating therapy in time.

In summary, this case emphasizes that the onset of acromegaly caused by GHPA is usually slow, and it often takes decades from the onset to the development of the typical clinical manifestations, which makes it difficult to detect GH tumors in the early stages. The incidence of the disease is relatively low. Moreover, as with our case, patients often go to hospital because of chronic complications that are associated with GHPA, which results in misdiagnosis and missing the optimal window for treatment. In a clinical context, clinicians should pay attention to medical history collection and physical examination, need to be vigilant to diabetes of unknown cause that is difficult to control, and should consider secondary factors.

CONCLUSIONS

In patients with rough skin, enlarged hands and feet, a protruding eyebrow arch, thick nose and lips, coarse voice, and decreased vision, GPHA should be considered, to avoid underdiagnosis and misdiagnosis. Surgical treatment is the first choice for GHPA, and close attention should be paid to the status of patients before, during and after operation, while appropriate follow-up is also required.

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CONFLICT OF INTEREST STATEMENT

We have no financial interests in this manuscript and no affiliations (relationships) to disclose.

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