Chapter 7
Acromegaly and Diabetes Mellitus: Special Considerations

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Case Presentation

A 49-year-old man with a history of bipolar disorder, diabetes mellitus type 2 (DM2), hypertension, and hyperlipidemia presented to the hospital with psychosis and profound functional decline. The endocrinology team was consulted when he was noted to have random blood glucose of 526 mg/dL and 2+ urine ketones.

The patient reported a 10-year history of DM2 without any known complications. His blood glucose had been poorly controlled in recent months due to medication nonadherence in the setting of his psychiatric illness with an outpatient hemoglobin A1c (HbA1c) > 14%. He also reported the gradual worsening of his glycemic control over several years despite uptitration of antihyperglycemic agents by his primary care physician. His medication regimen at the time of admission was metformin, pioglitazone, canagliflozin, and dulaglutide. Family history was notable for a mother with DM2 but no other endocrine diseases.

On exam, his body mass index (BMI) was 30.2 kg/m^2 with blood pressure 134/87 mm Hg and pulse 94 beats per minute. The patient was noted to have frontal bossing, mandibular prognathism, macroglossia,

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L. B. Nachtigall (ed.), *Pituitary Tumors*,
https://doi.org/10.1007/978-3-319-90909-7_7

soft tissue swelling of the hands, and acanthosis nigricans of the posterior neck. Upon further questioning, he indicated that he had noted coarsening of his facial features, enlargement of his hands and feet, headaches, and increased diaphoresis over at least 10 years. However, he interpreted these signs and symptoms of acromegaly in the context of his psychiatric illness, believing that they were manifestations of a "curse" that had been placed upon him by his wife's family.

Given the patient's poor glycemic control with impaired insulin secretion as evidenced by 2+ urine ketones, he was started on a combination of short- and long-acting insulin that was increased to 100 units per day. Metformin was continued, but the patient's other antihyperglycemic agents were stopped to avoid polypharmacy. Serum insulin-like growth factor 1 (IGF-1) was 620 ng/mL (normal, 52–328 ng/mL), which was 3.7 standard deviations above his age- and sex-adjusted mean. All other hormonal axes were within normal limits. Pituitary magnetic resonance imaging (MRI) showed a 3 cm sellar and suprasellar mass consistent with a pituitary macroadenoma that displaced the optic chiasm and invaded the right cavernous sinus. Diffuse calvarial thickening also was noted. Formal visual field testing demonstrated bitemporal hemianopsia.

My Management

(a) Transsphenoidal surgery by an experienced pituitary surgeon was recommended in order to debulk tumor in the setting of optic chiasm displacement.
(b) Postoperatively, blood glucose was closely monitored with insulin dose reductions made accordingly.
(c) A first-generation long-acting somatostatin analog (octreotide LAR) was recommended in order to control residual tumor postoperatively.
(d) Blood glucose was closely observed in the context of octreotide therapy initiation as levels may rise or fall.

Assessment and Diagnosis

DM2 is a complication of acromegaly that is associated with an increased risk of cardiac disease [1] and mortality [2]. Concurrent diabetes also poses unique considerations for clinicians in terms of diagnosis and management of acromegaly.

The reported prevalence of DM2 in acromegaly has been highly variable with estimates ranging from 16 to over 50% [3, 4]. Patients with acromegaly have been shown to be at a higher risk of DM2 than the general population or non-acromegalic individuals with traditional diabetes risk factors [3, 5]. Increased BMI [5, 6], older age [5, 6], and family history of DM2 [6] all have been associated with impaired glucose tolerance in acromegaly, as in the general population. Longer pituitary disease duration [5] and higher IGF-1 (rather than GH) [6, 7] also predict disturbances in glucose homeostasis. In our patient, hyperglycemia may have been an early manifestation of GH excess since the onset of his DM2 dates back to when his acromegaly symptoms began. Additionally, the gradual rise in IGF-1 as his tumor grew over time may have accounted for the progressive deterioration of his glycemic control in recent years. His susceptibility to DM2 was likely further enhanced by his personal history of obesity (BMI 30.2 kg/m^2) and his family history of DM2. Notably, the endocrine consult team had been called to manage hyperglycemia, which led to the evaluation for acromegaly. Acromegaly should be considered in the differential diagnosis of disturbed glucose homeostasis and has been discovered incidentally in 0.6% of hospitalized patients with DM2 [8].

GH excess in acromegaly leads to DM2 by creating a state of insulin resistance. In a study using hyperinsulinemic-euglycemic clamp, acromegalic patients were shown to have defects in both hepatic and extrahepatic insulin action [9]. Extending these findings, GH was later shown to antagonize downstream mediators of insulin signaling including phosphoinositide (PI) 3-kinase [10]. GH also indirectly impairs insulin action by bringing about a rise in free fatty acids through the stimulation of lipolysis [11]. While insulin resistance is the primary disturbance in acromegaly, hyperglycemia only develops when pancreatic β cells can no longer keep up with the increased demand to secrete insulin. Several studies have shown that insulin

resistance is similar among acromegalic patients irrespective of DM2 status, whereas a decline in β cell function was a distinguishing feature among individuals with prediabetes and diabetes [6, 12]. At the time of his hospital presentation, our patient had evidence of impaired β-cell function as evidenced by positive urine ketones although formal testing of insulin secretion (e.g., C-peptide) had not been obtained.

While IGF-1 is the preferred screening test for acromegaly [13], cases of acromegaly in the setting of poorly controlled DM2 have been described in which IGF-1 was falsely within the normal range. In these patients, IGF-1 subsequently rose to an abnormal value only once glycemic control was achieved with insulin therapy [14, 15]. For patients in whom IGF-1 is equivocal, GH suppression with oral glucose tolerance testing (OGTT) may be assessed [13]. However, an oral glucose load in diabetic individuals may fail to cause normal GH suppression such that false-positive results may occur [13, 16]. An OGTT also may be contraindicated for safety reasons among individuals with chronic hyperglycemia [17], and there is insufficient data to support the reliability of the OGTT to suppress GH while on insulin. Despite these considerations, our patient had a clearly elevated IGF-1, prompting his pituitary MRI without the need for further hormonal testing.

Management

Acromegalic patients with comorbid DM2 often experience improved glycemic control following treatment of GH excess. Transsphenoidal surgery by an experienced surgeon is the treatment of choice in acromegaly for macroadenomas with local mass effect [13]. In one longitudinal study, 51% of acromegalic patients with baseline impaired glucose tolerance or DM2 experienced normalization of glucose homeostasis following surgical cure. In this study, individuals whose blood glucose derangements persisted had the most impaired β-cell function preoperatively [18]. Given the rapid decline in GH levels with surgery, close monitoring of blood glucose is required to avoid hypoglycemia, particularly in those receiving insulin or antihyperglycemic agents that may require dose adjustment.

While polyuria following resection of a pituitary adenoma commonly is attributed to diabetes insipidus (DI) [19], the differential diagnosis for postoperative diuresis in a diabetic acromegalic patient is broad. Resolution of soft tissue edema (i.e., diuresis of third-space fluid) is common following surgical control of acromegaly; a negative fluid balance on postoperative day 2 is predictive of a lower postoperative GH level [20]. Poor glycemic control due to surgical stress and/or the administration of intraoperative steroids also may result in polyuria. Thus, in acromegalic patients with comorbid DM2, concurrent sodium and glucose should be measured at regular intervals postoperatively, and signs/symptoms of DI besides polyuria should be assessed prior to the administration of desmopressin.

For patients in whom surgery is not appropriate or who have persistent disease despite surgical intervention, medical therapy with somatostatin analogs or the growth hormone receptor anatgonist is the treatment of choice [13]. The first generation somatostatin analogs (octreotide LAR and lanreotide) target somatostatin receptor subtype 2 and to a less extent receptor subtype 5 that are present in the pituitary and pancreas. Thus, though these agents may improve glucose homeostasis by reducing GH excess, they alternatively may exacerbate blood glucose levels by suppressing insulin secretion. Reassuringly, in a large meta-analysis of acromegalic patients, while fasting insulin decreased significantly with somatostatin analog treatment, marginal increases in fasting blood glucose and HbA1c were not significant. On the other hand, among the subset of patients with baseline DM2 or impaired glucose tolerance, glycemic control was noted to worsen in 25% of individuals [21].

Pasireotide is a second-generation somatostatin analog with affinity primarily for somatostatin receptor subtype 5 that may be used as an alternative to first-generation agents. In addition to inhibiting insulin secretion [22], pasireotide has been shown to reduce the secretion of glucagon-like peptide-1 (GLP-1) [23]. In a phase III clinical trial among medically naïve patients with acromegaly, long-acting pasireotide was associated with more hyperglycemic events (29% vs. 8%) and new diagnoses of DM2 (19% vs. 4%) compared to long-acting octreotide [24]. Another phase III study of pasireotide

in acromegalic patients inadequately controlled on first-generation somatostatin analogs found that individuals with baseline DM2 or prediabetes were at increased risk of hyperglycemia-related adverse events compared to those with normal glucose tolerance [25]. Pegvisomant, a human GH receptor antagonist, has been shown to have more favorable effects on glucose homeostasis and may be an alternative for patients who develop progressive hyperglycemia in response to somatostatin analogs [13].

In acromegalic patients with comorbid DM2, glycemic control should be optimized prior to the initiation of somatostatin analog therapy, particularly in those who are high risk or who will receive pasireotide. Metformin has been recommended as the first-line agent to treat pasireotide-related hyperglycemia in patients with Cushing's disease [26]. A mechanistic study in healthy controls also has suggested that glucagon protein-1 (GLP-1) receptor agonists and dipeptidyl peptidase (DPP-4) inhibitors may be particularly efficacious to treat hyperglycemia on pasireotide, perhaps since these agents specifically target the GLP-1 pathway [22].

Outcome

Our patient's elevated IGF-1 and macroadenoma on pituitary imaging were diagnostic of acromegaly. Given displacement of the optic chiasm, surgery was recommended as the first-line treatment option. However, in the context of the patient's recent psychiatric hospitalization, he was reluctant to undergo surgery and instead preferred medical therapy in the short term. Octreotide LAR 20 mg IM monthly was initiated. His blood glucoses were controlled prior to the initiation of therapy and were monitored following treatment initiation without a change in his insulin requirement.

One month after hospital discharge, the patient consented to and underwent transsphenoidal surgery with uncomplicated removal of sellar tumor. Residual tumor was noted in the right cavernous sinus on postoperative MRI. Pathology demonstrated pituitary adenoma that stained positive for GH with a Ki-67 proliferation rate of 0.5%. Somatostatin analog therapy was held for approximately two months following surgery to determine the bioactivity of residual disease at

which time IGF-1 was 520 ng/mL (z-score 3.2). Accordingly, octreotide LAR was reinitiated at 30 mg IM monthly. Following three doses, IGF-1 partially downtrended to 407 ng/mL (z-score 2.5), and octreotide LAR was further uptitrated to 40 mg IM monthly. Three months later (7 months postoperatively), IGF-1 was 298 ng/mL (z-score 1.7), suggesting biochemical control on maximal octreotide therapy.

In the days following surgery, the patient experienced a noticeable diuresis with no hyperglycemia or change in serum sodium or thirst, consistent with mobilization of third-space fluid. The patient's blood glucose was monitored closely, and his insulin was downtitrated from 100 to 40 units daily within the first postoperative month. Following the reinitiation of octreotide, he experienced a marked reduction in headaches, diaphoresis, and soft tissue swelling that paralleled the biochemical improvement in his IGF-1. Insulin was further downtitrated and then discontinued while on maximum-dose octreotide, and DM2 subsequently was managed with metformin alone. With IGF-1 within the normal range, HbA1c was 6.9%.

In summary, control of GH excess in our patient corresponded to a remarkable reduction in his insulin resistance. Accordingly, despite the high dose of insulin that he needed preoperatively, insulin therapy was no longer required once biochemical control was achieved. As expected, our patient's DM2 did not resolve entirely with acromegaly treatment given that he had evidence of baseline β-cell dysfunction on initial presentation.

Clinical Pearls and Pitfalls

- DM2 is a common complication of acromegaly that is associated with heart disease and increased mortality.
- Acromegaly should be considered in the differential diagnosis of DM2, in the appropriate clinical context.
- Risk factors for impaired glucose tolerance in acromegaly include older age, increased BMI, family history of DM2, longer disease duration, and higher IGF-1.
- Poorly controlled DM2 may complicate the workup of acromegaly by leading to IGF-1 false negatives and OGTT false positives.

- Surgical or medical treatment of acromegaly may result in a reduction in insulin resistance such that decrease or discontinuation of antihyperglycemic agents may be appropriate.
- Somatostatin analogs, particularly pasireotide, may paradoxically worsen glycemic control despite improving GH excess.
- Postoperative polyuria in an acromegalic patient with comorbid DM2 may represent diabetes insipidus, diuresis of third-space fluids, or hyperglycemia.
- Pretreatment β-cell dysfunction predicts persistent abnormalities in glucose homeostasis despite acromegaly cure.

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