**CONSIDER THIS CASE**

**An Uncontrolled Diabetic Cat**

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Sugar, a 12-year-old spayed female Maine Coon cat, presented for poorly controlled diabetes and diabetic neuropathy.

**HISTORY**

Sugar was diagnosed with diabetes mellitus 2 years prior to presentation. Initially, her diabetes was moderately controlled on 5 to 6 units of recombinant human protamine zinc insulin (PZI) (40 U/mL; ProZine, bi-vetmedica.com), but over the year prior to presentation the insulin dose had been progressively increased without improvement in glycemic control.

Upon presentation, Sugar was receiving 14 units of recombinant human PZI. The owner was performing blood glucose curves at home, but struggling to maintain Sugar’s blood glucose below 300 mg/dL.

In addition to diabetes mellitus, Sugar had concurrent hypertrophic cardiomyopathy and chronic rhinitis, and persistent polyuria, polydipsia, polyphagia, and weakness.

**PHYSICAL EXAMINATION**

Physical examination revealed a symmetrically muscled cat, weighing 7.7 kg, with a body condition score of 6/9. Sugar had an unkempt hair coat, mild prognathia inferior, and a broad head (Figure 1), and walked with a plantigrade stance (Figure 2). No organomegaly was appreciated, and the cat appeared to have normal mentation.

**LABORATORY ANALYSIS**

Routine complete blood count (CBC), serum biochemical profile, and urinalysis were performed. The primary abnormalities noted on the serum biochemical profile were (Table 1):

- Hyperglycemia
- Mild increase in alanine aminotransferase
- Hyperalbuminemia
- Elevated blood urea nitrogen
- High normal creatinine.

Urinalysis was unremarkable except for glucosuria (> 1000 mg/dL; reference range, negative); urine culture revealed no growth. A blood glucose curve was performed that showed no response to insulin, and all blood glucose values were between 350 to 400 mg/dL.

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**Table 1. Sugar’s Serum Biochemical Profile Abnormalities**

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>RESULT</th>
<th>REFERENCE INTERVAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alanine aminotransferase (IU/L)</td>
<td>96</td>
<td>19-67</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>4.8</td>
<td>2.2-4.6</td>
</tr>
<tr>
<td>Blood urea nitrogen (mg/dL)</td>
<td>41</td>
<td>18-33</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>2</td>
<td>1.1-2.2</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>376</td>
<td>63-118</td>
</tr>
</tbody>
</table>
FIGURE 1. Although subtle, note Sugar’s broad facial features, clubbed paws, and prognathia inferior (A and B). Courtesy Dr. Erica Queen

FIGURE 2. Cat demonstrating the classic plantigrade stance seen with diabetic neuropathy, which is a consequence of poor glycemic control.

Consider These Questions…

1. What are the possible causes of insulin resistance in this patient?
2. Which additional diagnostic tests would you choose to determine a diagnosis?
3. Based on your suspected diagnosis, what therapeutic options are available for Sugar?
DIAGNOSTIC APPROACH

Consider 2 main areas of focus for the poorly controlled feline diabetic patient (Table 2).

<table>
<thead>
<tr>
<th>TABLE 2. Main Areas of Focus: Poorly Controlled Feline Diabetic Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Evaluation of Management</strong></td>
</tr>
<tr>
<td>* Incorrect insulin storage and handling</td>
</tr>
<tr>
<td>* Incorrect insulin administration/technique by owner</td>
</tr>
<tr>
<td>* Incorrect type of insulin (duration of action too long or too short)</td>
</tr>
<tr>
<td>* Incorrect dose (underdose or overdose/Somogyi response)</td>
</tr>
<tr>
<td><strong>2. Evaluation for Concurrent Disease or Drug-Induced Insulin Resistance</strong></td>
</tr>
<tr>
<td>* Endocrine (hyperadrenocorticism, hyperprogesteronism, hypersomatotropism, hyperthyroidism)</td>
</tr>
<tr>
<td>* Infection (periodontal disease/infection, urinary tract infection)</td>
</tr>
<tr>
<td>* Inflammation (chronic pancreatitis, chronic rhinitis, inflammatory bowel disease, stomatitis)</td>
</tr>
<tr>
<td>* Insulin antagonizing drugs (exogenous glucocorticoids, progestins)</td>
</tr>
<tr>
<td>* Neoplasia</td>
</tr>
<tr>
<td>* Obesity</td>
</tr>
</tbody>
</table>

When approaching these patients, carefully:
1. Evaluate case management for inconsistencies and owner handling/techniques
2. Evaluate insulin administered and dose
3. Consider causes of insulin resistance to determine the individual patient’s diagnostic workup.

**Initial Diagnostics**

Make sure to take a thorough history and perform a complete physical examination, CBC, serum biochemical profile, fructosamine, urinalysis, and urine culture. In addition, also review insulin administration and handling with the owner. Perform one or multiple blood glucose curves at home or in hospital to assess response to insulin, insulin dose, and duration of effect. Single blood glucose measurements collected in hospital can help identify hypoglycemia, but should not be used to assess control.

**Additional Diagnostics**

Additional testing to consider, depending on the physical examination and initial diagnostic findings in each individual patient, includes:
* Serum feline pancreatic lipase immunoreactivity
* Total thyroxine

**Low-dose dexamethasone suppression test if physical examination supports a diagnosis of hyperadrenocorticism**
* Insulin-like growth factor-1 (IGF-1)
* Abdominal ultrasound
* Thoracic radiographs.

**Unusual Concurrent Endocrine Diseases**

Evaluate the patient for clinical signs or examination findings consistent with hyperadrenocorticism, such as thin/fragile skin (Figure 3) or pot belly. If hyperadrenocorticism is suspected, the test of choice is a low-dose dexamethasone suppression test, using dexamethasone, 0.1 mg/kg IV. Acromegaly is an uncommon cause of insulin resistance in cats. In a poorly regulated diabetic cat, lack of a typical acromegalic appearance (prognathism, enlarged feet) does not negate the importance of testing for this condition by measuring serum levels of IGF-1 and performing advanced imaging of the brain. See Consider This Disease: Acromegaly, page 48.

**THIS CASE: DIAGNOSIS**

In Sugar’s case, acromegaly was considered a primary differential due to:
* History of poorly controlled diabetes mellitus, with associated polyuria, polydipsia, and polyphagia
* Physical examination findings of mild prognathia inferior and a broad head
* Elevated IGF-1 levels: 2313 ng/mL (303 nmol/L); reference range, 208 to 443 ng/mL

A computed tomography (CT) scan was performed to evaluate whether a mass was present in the pituitary gland. The CT scan demonstrated a homogenously contrast enhancing mass of the pituitary gland. The pituitary mass was slightly irregular, measuring 0.7 cm in diameter (Figure 4).

These findings confirmed a diagnosis of acromegaly—the cause of the severe insulin resistance and poorly controlled diabetes mellitus.

**FIGURE 3. Feline skin lesions consistent with fragile skin syndrome due to pituitary dependent hyperadrenocorticism (A); same skin lesions after 2 months of therapy (B).**
TREATMENT APPROACH
Ideal treatment for acromegaly has not yet been determined. Current treatment options include radiation therapy, surgery (hypophysectomy), or medical management.

Radiation Therapy
Radiotherapy is the current treatment of choice for pituitary tumors. Many cats experience improvement or resolution of diabetes mellitus, although other acromegalic signs, such as prognathism and enlarged feet, often persist. However, this treatment modality is expensive and outcomes are not always successful.

Hypophysectomy
Hypophysectomy is the treatment of choice in humans, and may become the treatment of choice in cats. At this time, transsphenoidal hypophysectomy has been performed in acromegallic cats, but is only offered in a few, very specialized veterinary institutions. Although it is a procedure with significant risks, good outcomes have been reported.

Medical Management
Medical management using somatostatin analogues, which inhibit growth hormone (GH) secretion, has been used with some success in humans. However, this medical approach has been evaluated in acromegalic cats, demonstrating little to no effect.

Monitoring
Regardless of treatment choice, close diabetic monitoring—is necessary to prevent life-threatening hypoglycemia as IGF-1 levels fall and insulin resistance decreases.

THIS CASE: TREATMENT & FOLLOW-UP
Sugar was treated with a definitive radiation protocol: a total dose of 50 Gy was delivered in 20 treatments using a 2-field technique at 2.5 Gy per fraction.

During hospitalization for radiation treatment, blood glucose was monitored closely:
• Sugar’s insulin dose was decreased based on blood glucose monitoring.
• When Sugar was discharged, she was receiving 5 units SC Q 12 H of recombinant human PZI.
• The owner continued to monitor blood glucose at home and, over the next 6 to 9 months, the PZI dose was reduced to 2 units SC Q 12 H.
Consider This Disease: Acromegaly

Acromegaly, also known as hypsomatotropism, is a disease characterized by excess GH, which stimulates increased production of IGF-1 in the liver and other tissues. GH and IGF-1 cause a variety of changes in the body, including organ enlargement and increased proliferation of bone that can be seen visually as jaw enlargement (prognathism) or large paws.2,4,5

Profile
Acromegaly and excess GH are typically caused by a pituitary adenoma. GH has anti-insulin effects, causing increased glucose production in the liver and reducing insulin sensitivity in the body by a variety of mechanisms. When insulin resistance and glucose production cause elevation of serum blood glucose, the animal becomes diabetic. Prevalence of acromegaly in diabetic cats is unknown, but is suspected to be as high as 30% of difficult-to-regulate diabetic cats.4 It is typically seen in elderly male cats.

Diagnostic Approach
In practice, diagnosis of acromegaly is based on:
1. Common clinical signs, including polyuria, polydipsia, and polyphagia—clinical signs associated with diabetes mellitus—as well as weight gain. Neurologic signs may be seen.
2. Physical examination findings, including an enlarged liver and kidneys on abdominal palpation. In more advanced disease, prognathia inferior and enlargement of the head and paws may be noted.
3. IGF-1 levels—considered a sensitive but not specific test.
   - If values are > 1000 ng/mL (131 nmol/L), acromegaly should be suspected, and additional testing, specifically pituitary imaging, is indicated.
   - The "gray" zone is considered 800 to 1000 ng/mL.
   - If acromegaly is suspected, but IGF-1 levels are within reference range (208–443 ng/mL), perform repeat testing in 6 to 8 weeks.
   - IGF-1 levels can be falsely normal if a cat is in an insulin deficient state.2,4,5
4. Intracranial imaging, either by CT or magnetic resonance, which documents a pituitary mass and confirms the diagnosis (because IGF-1 levels are not 100% reliable).

Additional Diagnostics
Additional biomarkers are being evaluated, but limited data are available. GH assays are not readily available—blood sampling has to be very specific to prevent degradation of the hormone, and the assay lacks sensitivity and specificity.

Differentiating Diseases
Pituitary-dependent hyperadrenocorticism can also cause severe insulin resistance and a pituitary mass—diagnostic results also seen in diabetic cats with acromegaly. However, clinical presentation of these diseases is often very different:
- Cats with hyperadrenocorticism typically present with atrophy of the epidermis; fragile, easily torn skin; and progressive weight loss.
- Cats with acromegaly typically gain weight over time and do not develop problems with their skin/hair coats, other than what is expected in a poorly controlled diabetic cat (eg, unkempt hair coat).

One year later, Sugar was re-evaluated:
- Physical examination was unremarkable, except for persistent prognathia inferior.
- CBC, serum biochemical profile, and urinalysis were unremarkable other than mild hyperglycemia (175 mg/dL) but no glucosuria.
- Fructosamine was normal at 315 mcmol/L (reference range, 0–375 mcmol/L).
- IGF-1 was still elevated at 1262 ng/mL (168 nmol/L), but was significantly reduced from original value.
- Contrast CT was repeated and the pituitary mass was decreased in size, measuring 0.3 cm in diameter (Figure 5, page 47).

Based on these findings, Sugar’s radiation therapy was determined to be effective. In addition, due to the appearance that her diabetes was controlled, the PZI dose was reduced to 1 unit SC Q 12 H.

Over the next 2 years, Sugar’s PZI insulin dose was further reduced to 0.5 units SC Q 12 H. Her IGF-1 levels were also followed, and continued to decrease to 855 ng/mL (112 nmol/L) and then 672 ng/mL (88 nmol/L).

PROGNOSIS
Prognosis for cats with uncontrolled acromegaly and poorly controlled diabetes mellitus is poor to guarded; without treatment most cats are euthanized within a few months of diagnosis. However, in cats, such as Sugar, in which the concurrent disease causing insulin resistance is recognized and treated appropriately, a favorable outcome is possible since glycemic control often improves.

THIS CASE: OUTCOME
Sugar died of hypertrophic cardiomyopathy 3 years following diagnosis and radiation treatment for acromegaly. A complete necropsy was performed; pertinent findings included pituitary gland multifocal adenomas (Figure 6) and significant pancreatic islet amyloidosis (Figure 7, page 51), which is characteristic of feline type 2 diabetes. Prognathism inferior was also noted.

FIGURE 6. Gross pathology image of pituitary adenoma found on necropsy, showing a compressive expansile mass. This patient had hemorrhage within the tumor, which made the mass more apparent on gross pathologic evaluation. Sugar’s mass was difficult to appreciate on gross pathology due to changes from radiation therapy and the fragile nature of the postradiation tissue. Courtesy Dr. Silvia Siso
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CBC = complete blood count; CT = computed tomography; GH = growth hormone; IGF-1 = insulin-like growth factor-1; PZI = protamine zinc insulin

References

FIGURE 7. Cross sectional view of Sugar’s pancreas, with significant islet amyloidosis—a characteristic of feline type 2 diabetes. Note it is devoid of endocrine cells and replaced with amphophilic fibrillar material (amyloid). All of Sugar’s islets had this appearance (A). Image of the pancreas in a healthy cat that illustrates normal appearance of an islet of Langerhans, populated with endocrine cells (B).

Courtesy Dr. Steven Kubiski

CBC = complete blood count; CT = computed tomography; GH = growth hormone; IGF-1 = insulin-like growth factor-1; PZI = protamine zinc insulin

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