Cancer is a documented common cause of sickness and debilitation in cats. More recently, it has become obvious that cancer may induce clinical signs not only directly by altering the body’s structure or function but also by indirect means that may actually be more debilitating than the consequences of the primary tumor. These indirect effects are known as paraneoplastic syndromes and are of profound importance to practicing veterinarians because of their devastating effects on cats with cancer. The most common paraneoplastic syndromes in feline medicine are thought to be caused by the production of polypeptide hormones, the most common of which have endocrine-like effects.

Detection of hormones or hormone-like substances that are directly elaborated or indirectly induced by the tumor can be used as markers for the presence of a tumor. Complete workups of each condition are essential to unravel the typically vague clinical signs and subtle findings on physical examination. Therapy should primarily be directed at eliminating the underlying malignancy, although modulation of tumor-induced hormones or hormone-like substances is an attractive alternative.

**ALTERED CALCIUM HOMEOSTASIS**

**Hypercalcemia of Malignancy**

Cancer is an underrecognized cause of hypercalcemia in cats. In one study of 71 cats with hypercalcemia, the three most common diagnoses were neoplasia (n = 21), renal failure (n = 18), and urolithiasis (n = 11). Primary hyperparathyroidism was diagnosed in 4 cats. Lymphoma and squamous cell carcinoma were the tumors identified most frequently. Calcium oxalate uroliths were diagnosed in 8 of 11 cats with urolithiasis.

Hypercalcemia can be an oncologic emergency. The tumors most often associated with the paraneoplastic syndrome of hypercalcemia are squamous cell carcinoma, lymphoma, primary lung tumors, and multiple myeloma, but any neoplastic process has the potential to elevate serum calcium levels. Granulomatous disease, oxalate urolithiasis, and parathyroid tumors are other diagnostic differentials. Parathyroid adenomas have been identified as malignancy-associated causes of hypercalcemia in dogs and cats, but this is not considered a true neoplastic syndrome because parathyroids normally produce parathormone.

Potential causes of hypercalcemia of malignancy include tumor-induced production of:

- Osteoclast-activating factors (OAFs), such as interleukins, tumor necrosis factor, lymphotoxin, colony-stimulating factors, and interferon-γ
- 1,25-Dihydroxycholecalciferol (vitamin D)
- Prostaglandins
- Transforming growth factors
- Parathyroid hormone-related peptide (PTHrP)

The actual cause of hypercalcemia is not as well described in feline patients as in canine or human medicine.

**Clinical Presentation**

Nonspecific clinical signs predominate. Polyuria is not as commonly recognized in cats as in...
other species. Signs can progress from lethargy, anorexia, nausea, and fatigue to dehydration, azotemia, and coma secondary to hypercalcemia-induced renal failure. Decreased sensitivity of the distal convoluted tubules and collecting ducts to antidiuretic hormone (ADH) causes polyuria and secondary polydipsia. Vasoconstrictive properties of calcium decrease renal blood flow and glomerular filtration rate, resulting in degenerative changes, necrosis, and calcification of the renal epithelium. Other clinical signs (e.g., constipation, muscle weakness, central nervous system signs) may arise as a direct effect of the electrolyte abnormality.

**Diagnosis (Figure 1)**

The diagnostic workup should always include a hemogram, biochemical profile, ionized calcium, urinalysis, radiographs, and ultimately bone marrow aspiration and determination of parathormone (PTH) and PTH-rP concentrations. The former is elevated in renal disease and primary hyperparathyroid disease, whereas the latter may be increased in neoplastic disease. PTH-rP appears to be less reliable in cats than in other species, such as dogs. In one study, cats with neoplasia were shown to have a higher serum calcium concentration (13.5 ± 2.5 mg/dl) than cats with renal failure with or without urolithiasis (11.5 ± 0.4 mg/dl). Serum phosphorus concentrations were higher in cats with renal failure than in cats with neoplasia. Despite the fact that the majority of cats with uroliths were azotemic, their serum urea nitrogen (SUN) and creatinine concentrations and urine specific gravity differed from that of cats with renal failure. In essence, cats with renal failure had more advanced signs.

While blood work is important, clinical pathology must be combined with a good history and physical examination to confirm or eliminate the following differentials:

- Laboratory error
- Interpretation error
- Hyperproteinemia due to dehydration (controversial)
- Acute renal failure

**Treatment**

Eliminating the tumor is the first and most important therapy for hypercalcemia of malignancy. Associated clinical signs can range from very mild to a full oncologic emergency. The approach to the treatment of this condition depends on the severity of the clinical signs.

**Figure 1**—The most common differentials and laboratory findings associated with hypercalcemia in cats.

- Vitamin D and calcium toxicosis
- Granulomatous disorders, such as nocardiosis
- Nonneoplastic bone disorders
- Hypoadrenocorticism
- Calcium oxalate urolithiasis
- True hyperparathyroidism

Calcium values must be interpreted in relation to serum albumin and blood pH. The following correction formula accounts for albumin:

\[
\text{Adjusted Calcium (mg/dl)} = \left( \frac{\text{Calcium [mg/dl]} - \text{Albumin [g/dl]}}{3.5} \right) + 3.5
\]

Clinical signs associated with hypercalcemia are intensified when the electrolyte is in the free, ionized fraction, which is increased by acidosis.

Ultimately, it may be difficult to identify malignancy as the cause of hypercalcemia. Laboratory abnormalities that may accompany true hypercalcemia include:

- Elevated SUN
- Normo- or hypophosphatemia
- Hypercalciuria
- Hyperphosphaturia
- Hypernatriuria
- Decreased glomerular filtration rate (determined by exogenous or endogenous creatinine clearance study)
**Mild Hypercalcemia, Minimal Clinical Signs**
- Restore and maintain hydration and ensure calciuresis, especially during anesthesia and surgery.
- Monitor calcium, phosphorus, and creatinine levels until the underlying cause can be identified and eliminated or until the hypercalcemia and subsequent clinical signs progress to the point that additional therapy is required.
- Avoid nephrotoxic drugs.

**Moderate Hypercalcemia, Moderate Clinical Signs**
More aggressive management is indicated in these patients:
- Administer IV saline in volumes that exceed daily maintenance needs (>44–66 ml/kg/day) and result in urine output exceeding 2 ml/kg/hour.
- Consider adding potassium chloride to 0.9% NaCl to prevent potassium depletion (20–30 mEq KCl/L of 0.9% NaCl).
- Repeatedly assess all electrolytes, SUN, and serum creatinine concentrations to determine necessary adjustments of fluid rate, type, and potassium content.
- Monitor patients carefully for signs of overhydration and congestive heart failure. IV administration of 0.9% NaCl effectively expands the extracellular fluid volume, increases glomerular filtration rate, decreases renal tubular calcium reabsorption, and enhances calcium and sodium excretion.
- In refractory cases, administer:
  - Furosemide (2.2–8.8 mg/kg IV or PO bid; often administered concurrently with NaCl to well-hydrated, hypercalcemic patients to prevent calcium reabsorption in the kidneys). This drug is also effective for treating many cases of anuria or oliguria. Furosemide inhibits calcium resorption at the level of the ascending loop of Henle.
  - Prednisone (0.5–1.0 mg/kg PO bid) or any other glucocorticoid to inhibit OAF, prostaglandins, vitamin D, and the absorption of calcium across the intestinal tract. Glucocorticoids are cytotoxic to lymphoma and myeloma cells and therefore should not be used until suspect tissue has been submitted for histology and a diagnosis made. Glucocorticoids may also obscure the extent of the tumor and thus delay diagnosis of the neoplasm and prevent accurate staging and definitive therapy.

**Severe Hypercalcemia, Severe Clinical Signs**
This is considered an oncologic emergency. Briefly, treatment is the same as for moderate hypercalcemia. In addition, the use of such agents as calcitonin, mitomycin, prostaglandin-synthetase inhibitors, bisphosphonates, gallium nitrate, and oral phosphate may be considered to control hypercalcemia.
- Calcitonin (4–8 MRC U/kg SQ) can cause a dramatic, rapid reduction in calcium levels; levels may remain low for days.
- Mitomycin (25 µg/kg IV once or twice weekly given through a newly placed IV line); at higher dosages, this agent has anticancer properties.
- Prostaglandin-synthetase inhibitors.
- Bisphosphonates are being explored for use in treating hypercalcemia of malignancy. Etidronate disodium is the most commonly used member of this class in human medicine. Early work in human patients with severe hypercalcemia and severe clinical signs suggests that bisphosphonates are effective in long-term control of chronic hypercalcemia. Unlike phosphates, which bind calcium in the gastrointestinal tract, bisphosphonates bind to hydroxyapatite in bone and inhibit the dissolution of crystals.
- Gallium nitrate has recently been approved in human medicine for the treatment of hypercalcemia; it appears to inhibit bone resorption by binding to and reducing the solubility of hydroxyapatite crystals.

**Hypocalcemia**
Hypocalcemia secondary to a malignancy or its treatment is much more common in human than feline medicine.

**Clinical Presentation**
Hypocalcemia is a rare complication of bilateral thyroidectomy and inadvertent parathyroidectomy in cats and an uncommon cause of clinical signs related to cancer. Other causes include magnesium deficiency, which can occur because of prolonged intestinal drainage procedures, parenteral hyperalimentation without magnesium supplementation, and severe liver disease. Hypomagnesemia seems to impair the effect of PTH on its target organs, resulting in hypocalcemia. Tumor lysis syndrome may be associated with hypocalcemia secondary to elevated phosphate levels and can result in partial or generalized seizures; this extremely rare (or underrecognized) condition is an oncologic emergency.
Diagnosis
A diagnosis is made based on an MDB4 and ionized calcium and (if indicated) PTH levels.

Treatment1–9
The underlying cause of hypocalcemia should be identified and treated as soon as possible. Cancer-induced hypocalcemia rarely results in clinical signs or requires therapy. If clinical signs are present, calcium should be administered via slow IV (i.e., 1.0–1.5 ml 10% calcium gluconate/kg given over 10–20 min; maintenance therapy, 2 ml/kg given over 6–8 hr) with electrocardiographic monitoring followed by oral calcium supplements (i.e., calcium lactate, 400–600 mg/kg/day divided into three or four doses). Vitamin D supplementation (1,25-dihydroxycholecalciferol, 0.03 µg/kg/day PO) may be indicated to aid calcium absorption.

ALTERED GLUCOSE HOMEOSTASIS

Hypoglycemia
Hypoglycemia (blood glucose <70 mg/dl), an underrecognized and uncommon paraneoplastic syndrome in cats, can cause a variety of clinical signs ranging from generalized weakness to seizures and death.9–13 Insulinoma is the most common malignancy associated with hypoglycemia in cats. Nonlymphoid hepatic tumors are a common cause of hypoglycemia in other species, but this tumor type is not as commonly recognized in cats. Insulinomas produce excessive quantities of insulin, which causes very low blood glucose levels. In contrast, hypoglycemia of extrapancreatic tumors is associated with low to low-normal insulin levels.9–13 Extrapancreatic tumors cause hypoglycemia by secretion of an insulin-like substance, by accelerating the utilization of glucose by the tumor, and by failure of gluconeogenesis and/or glycogenolysis by the liver.9–13 The most common nonmalignant causes of hypoglycemia include hyperinsulinism, hepatic dysfunction, adrenocortical insufficiency, hypopituitarism, extrapancreatic tumors, starvation, sepsis, and laboratory error. Rarely, hypoadrenocorticism secondary to lymphoma infiltration of the adrenal glands can cause hypoglycemia.11

Clinical Signs
Hypoglycemia in cats can result in very subtle clinical signs if the condition progresses very gradually. Acute onset results in overt clinical signs that can include such neurologic signs as weakness, disorientation, behavioral changes, facial twitching, seizures, coma, and death.9–13 These signs generally occur in cats when blood glucose falls below 45 mg/dl. Catecholamines, growth hormone, glucocorticoids, and glucagon are released secondary to hypoglycemia and activate compensatory mechanisms to combat hypoglycemia by promoting glycogenolysis.

Diagnosis
It is not currently possible to identify the mechanism responsible for inducing hypoglycemia associated with many extrapancreatic tumors. Insulin-producing tumors (e.g., insulinomas) may be diagnosed by identifying elevated insulin levels in association with low blood glucose concentrations.1,9–13 Frequent evaluation of glucose and insulin concentrations during a 72-hour fast may be necessary to accurately diagnose insulinoma in some cats. Although quite controversial and certainly not validated in cats, the amended insulin:glucose ratio has been advocated as a method to help diagnose insulin-producing tumors:

\[
\text{Serum Insulin (µU/ml) × 100 \ Amended Serum Glucose Ratio (mg/dl) – 30}
\]

Values above 30 are suggestive of an insulinoma or other insulin-producing tumor. The reality is that abdominal imaging (radiology and ultrasonography) is indicated for any cat with sustained hypoglycemia and hyperinsulinemia of unknown origin; this should be followed by exploratory abdominal surgery and concurrent supportive care (e.g., IV glucose). Diagnostic imaging helps guide the surgeon and eliminate other causes of hypoglycemia (e.g., hepatic abscess).

Treatment
Surgery is the only way to make a definitive diagnosis and eliminate the underlying cause of malignancy-associated hypoglycemia. Metastases are common in most malignant tumors associated with this condition. Therefore surgery may not be curative but is palliative in many cases. If an insulinoma is suspected, partial pancreatectomy may be indicated. Complications include iatrogenic pancreatitis and diabetes mellitus. To minimize damage to the pancreas and reduce the chance of pancreatitis, careful surgical techniques should be employed; preoperative somatostatin treatment is optimal. Medical management of hypoglycemia is essential before, during, and after surgery because of the serious consequences of hypoglycemia and the high metastatic rate of insulinomas.1,9–13

Cats with severe hypoglycemia should be treated with IV administration of 2.5% to 5% dextrose in

4MDB = minimum database; includes CBC, biochemical profile, urinalysis, FeLV/FIV serology, T4 testing, and thoracic radiographs (three views).
Compendium Sustained increased renal frac-
2,7,9 transient diabetes mellitus
It is likely that
Absence of volume depletion
Hypophosphatemia may be
diazoxide may be diffi-
Hyponatremia of extracellular
December 2001
Normal renal, pituitary, thy-
hypoosmolality of plasma
2 urine that is less than maxi-
1046 Small Animal/Exotics
insulin receptor affinity.
management of pancreatic tumors
(cell) carcinoma was diagnosed in a
example, in one study, a functional,
periods of 1 year or more. For
insulin release by membrane stabi-
hydrochlorothiazide (2–4 mg/kg
PO divided bid), with or without
Diagnosis was made on the basis of
SIADH can be caused by
increased expression of ADH from
the pituitary gland or can be a true
paraneoplastic syndrome secondary
to the ectopic production of ADH.
In addition, several drugs (including
chlorpropamide, vincristine,
vinblastine, cyclophosphamide,
opiates, histamine, thiazides, barbi-
turates, and isoproterenol) can
indirectly cause SIADH by poten-
tiating the release of ADH.

Clinical Signs
Most cats with SIADH are clini-
creas was confirmed by biopsy. The
cat died 18 months later, and
necropsy revealed metastases to
regional lymph nodes and liver.
Specimens of the tumor and
metastatic lesions both stained pos-
positively for insulin. In another
report, transient diabetes mellitus
developed after an insulinoma was
removed in a cat but normalized
after 1 week. The cat remained
normal until recurrence of ataxia,
twitching, and hypoglycemia 7
months postoperatively. The
episodes were responsive to admin-
istration of exogenous glucose.
Treatment consisted of pred-
nisolone, which successfully palli-
ated the hypoglycemic episodes for
2 years, at which time the cat died
of unknown causes.

ALTERED SODIUM HOMEOSTASIS
Although the syndrome of inap-
propriate secretion of antidiuretic
hormone (SIADH) is rarely identi-
fied in veterinary medicine, it is
one of the best characterized and
most frequently encountered
ectopic hormone syndromes in
human medicine. It is likely that
SIADH will be identified more
frequently in cats as awareness of
this syndrome grows.

SIADH can be caused by
increased expression of ADH from
the pituitary gland or can be a true
paraneoplastic syndrome secondary
to the ectopic production of ADH.
In addition, several drugs (including
chlorpropamide, vincristine,
vinblastine, cyclophosphamide,
opiates, histamine, thiazides, barbi-
turates, and isoproterenol) can
indirectly cause SIADH by poten-
tiating the release of ADH.

Clinical Signs
Most cats with SIADH are clini-
levels drop to 120 to 125 mEq/L,
however, lethargy and mental dull-
ness may be noted. When they drop
below 115 mEq/L, more dramatic
central nervous system problems
can develop and may progress to
convulsions and coma. When this
occurs, the cat must be treated as a
medical emergency.

Diagnosis
The diagnosis of SIADH is
based on the absence of hypo-
volemia and dehydration and the
following laboratory findings:

- Hypoosmolality of plasma
despite inappropriately concen-
trated urine (high sodium)
- Hyponatremia of extracellular
fluids
- Urine that is less than maxi-
mally dilute
- Absence of volume depletion
- Sustained increased renal frac-
tional excretion of sodium
- Normal renal, pituitary, thy-
roid, and adrenal function
- Hypophosphatemia may be
noted

Spurious or artifactual hypona-
tremia can occur in cats with
marked increases in serum lipids or
serum proteins. In addition, in cats
with marked hyperglycemia, water
can be drawn into the circulatory
system, diluting electrolytes and
caus ing hyponatremia.

Treatment
The treatment of choice for
patients with SIADH is to elimi-
nate the underlying cause. If clin-
ical signs warrant treatment, addi-
tional measures may be helpful.
Water restriction is effective for
mild cases in which the cat can be
carefully monitored for over- or
underhydration. The objective is
to raise the serum sodium level
while restricting water intake to
approximately 66 ml/kg/day.
Demeclocycline antagonizes the actions of ADH on the kidneys and thus causes reversible nephrogenic diabetes insipidus. Possible side effects in humans include nausea, vomiting, skin rashes, and hypersensitivity reactions. Demeclocycline is effective in treating patients with mild to moderate SIADH. Other drugs, such as lithium carbonate and phenytoin, are not as effective. IV hypertonic sodium chloride is generally reserved for patients that have significant clinical signs related to hyponatremia.

REFERENCES


