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VCA Clinical Consults

What's Your Diagnosis?

PATIENT HISTORY

SIGNALMENT: "Norm" is a 10.5 year old neutered male Labrador Retriever. Weight 70.5 lb/31.8 kg.

PERTINENT PAST HISTORY: "Norm" has generally been a very healthy dog with no chronic medical issues. He has received all routine health care as recommended by his primary care veterinarian. He is current on vaccinations and monthly preventatives. He eats a commercial adult maintenance dog food.

CURRENT HISTORY: "Norm" was presented to his primary care veterinarian for evaluation of increased water consumption and urination. His owners had been noticing frequent urinary accidents in the house. His physical examination was reported as unremarkable although he had lost 2 pounds since his visit 6 months prior. A minimum database including CBC, chemistry panel, thyroid and urinalysis was performed. See **Table 1** for abnormalities.

"Norm" was diagnosed with IRIS Stage 2 chronic renal disease and due to the presence of proteinuria and glucosuria a urine culture was submitted. Results were negative for microbial growth. The owner was instructed to collect individual urine samples for 3 consecutive days. The urine was submitted for a pooled urine protein:creatinine ratio (UPCR) which was positive at 2.2. "Norm" had multiple blood pressure readings performed on different days in order to substage his renal disease. All readings were within normal limits.

GLUCOSURIA IN A LABRADOR RETRIEVER—

Fanconi's and more!

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TABLE 1.
"NORM'S" LABORATORY ABNORMALITIES

WBC (ref. range: 4,900-17,600/uL)	22,452
Neutrophils (ref. range: 2,940-12,670/uL)	18,240
Monocytes (ref. range: 130-1,150/uL)	1,856
Blood glucose (ref. range: 63-114 mg/dL)	**89 - normal**
Potassium (ref. range: 4.0-5.4 mmol/L)	3.5
Phosphorus (ref. range: 2.5-6.1 mg/dL)	4.0
BUN (ref. range 9-31 mg/dL)	33
Creatinine (ref. range: 0.5-1.5 mg/dL)	1.9
Urine specific gravity	1.012
Urine protein (ref. range: negative)	1+
Urine glucose (ref. range: negative)	2+ (500 mg/dL)
Sediment	negative

While proteinuric renal disease is quite common in dogs, the leukocytosis and glucosuria remained an interesting finding and "Norm's" primary care veterinarian referred him for an Internal Medicine consult for further evaluation and imaging.

INTERNAL MEDICINE EXAMINATION

"Norm" was evaluated two weeks later. On examination, he was bright, alert, well hydrated and in good body condition. He was noted to have mild edema in the ventral neck region. His heart rate was normal at 100 but his heart sounds were a bit muffled and heard more caudally in the thoracic cavity than expected. His lung sounds were mildly decreased. Abdominal palpation was unremarkable. The remainder of his examination—including neurologic, retinal and rectal evaluations—was within normal limits.

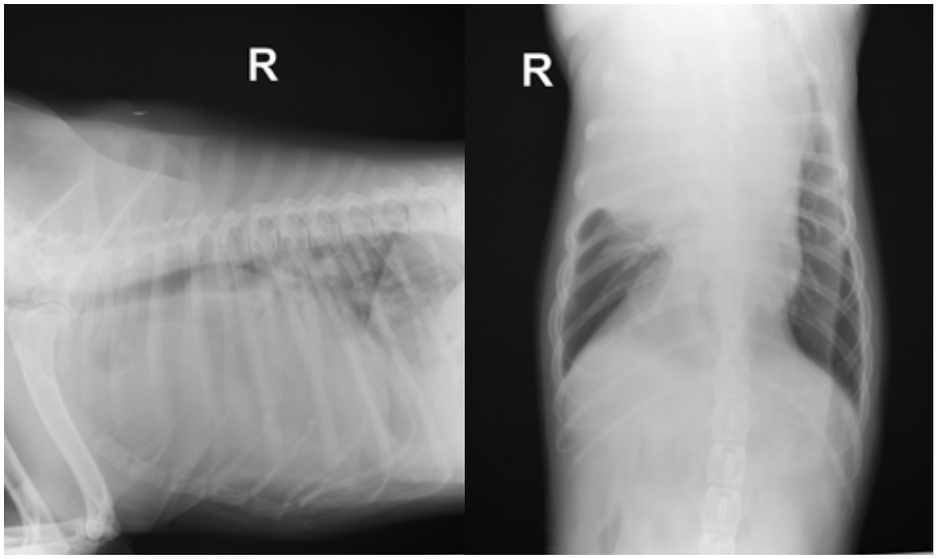
Glucosuria accompanying renal disease can occur with several disorders including leptospirosis, Fanconi's syndrome, Fanconi's-like syndrome associated with jerky treat toxicosis, copper storage disease (commonly identified in the Labrador Retriever breed), medication usage (NSAIDs, gentamicin, etc.) and others. The owner confirmed "Norm" had significant leptospirosis risk as they live in a wooded area and he has access to wildlife and puddles/ponds. The owner also reported "Norm" receives rawhides and chicken jerky-style treats daily and sometimes multiple times daily.

Recheck bloodwork was performed which revealed progressive azotemia (BUN 45, creatinine 2.2), worsening hypokalemia (3.1 mmol/L) and ongoing decline of phosphorus (3.0 mmol/L). His urine was still isosthenuric with proteinuria and progressive glucosuria (3+ glucose) and mild ketonuria (1+). This was thought to be consistent with tubular damage and possible Fanconi's-like syndrome. "Norm" still had a significant leukocytosis characterized by neutrophilia and monocytosis.

PCR evaluation for *Leptospira* was performed on both blood and urine. Serum was held for leptospirosis MAT testing if the PCR was negative. PCR was negative on both blood and urine so serum was submitted for antibody evaluation to *Leptospira* and was also negative.

Thoracic radiographs were recommended to evaluate "Norm's" slightly muffled and displaced heart sounds (see **Figure 1**). These films revealed a large cranial thoracic mass displacing his heart caudally within the thoracic cavity. This cranial mediastinal mass was considere to be the cause of his neutrophilia and monocytosis as well as his ventral neck edema.

FIGURE 1



An abdominal ultrasound was recommended to evaluate both his renal architecture as well as for the presence of underlying neoplasia given the thoracic radiograph findings. Ultrasound revealed the kidneys to have mildly hyperechoic cortices but no pelvic dilation or other abnormalities. The remainder of the abdominal structures were normal. A brief thoracic ultrasound revealed a very large (>10 cm) right sided complex heterogeneous thoracic mass originating from the cranial mediastinum. There was no pleural effusion noted.

A fine needle aspirate of the cranial mediastinal mass was performed. Cytology revealed a small mature lymphocyte population suggestive of a thymoma. Remarkably, "Norm" had no respiratory or other clinical signs associated with his large cranial mediastinal mass. Indeed it had been a coincidental finding during the workup of chronic renal disease and glucosuria.

"Norm's" owners were counselled to discontinue feeding jerky treats as Fanconi's-like syndrome continues to be associated with this toxicosis and was suspected to be the cause of his renal disease and glucosuria. The hope was to stabilize "Norm's" chronic renal disease prior to thoracotomy for suspected thymoma. A renal diet was started and benazepril was added for management of the proteinuria.

"Norm" was rechecked in 2 weeks. Bloodwork was improved with BUN 38, creatinine 1.5, K 3.8, PO4 4.5, usg 1.025, 1+ proteinuria and 1+ glucosuria. A recheck (3 day collection) UPCR was 1.1. His blood pressure remained normal. Therapy was continued and "Norm" was evaluated two weeks later by a board certified surgeon.

"Norm" underwent thoracotomy for cranial mediastinal mass resection. The mass was invasive into the mediastinal tissue and parietal pleura of the right middle and cranial lung lobes. The mass was also attached to the thoracic wall and extended to the right side of the heart. The sternal lymph node was moderately enlarged. A large portion of the mass was necrotic and poorly encapsulated. Approximately 80% of the mass could be resected. The enlarged sternal node was removed and submitted for histopathology. "Norm" had a thoracostomy tube placed. Histopathology revealed an invasive thymoma (see **Table 2**) with no evidence of metastasis.

TABLE 2.
"NORM'S" CRANIAL MEDIASTINAL MASS HISTOPATHOLOGY

Examined is tissue from a 10 year old castrated male Labrador Retriever dog named Norm.

Slide 1; Lymph node: One section is examined. There are multiple prominent lymphoid follicles. Within medullary sinuses are large numbers of hemosiderophages.

Slides 2-6; Mediastinal mass: Fifteen sections are examined. Most of the tissue is composed of a highly cellular neoplasm. Neoplastic cells are polygonal to occasionally spindloid and are arranged in small nests, trabeculae and sheet-like arrangements with a collagenous stroma. Neoplastic cells often have distinct cell margins, eosinophilic and granular to vacuolated and clear cytoplasm with round to oval nuclei, stippled chromatin and 1-2 nucleoli. There is moderate anisocytosis and anisokaryosis. There are 2 mitotic figures within 10 random 400x fields. Neoplastic cells are interspersed with small lymphocytes. Multifocally scattered within the neoplasm are small to large foci of necrosis.

Microscopic Diagnoses:
- Lymph node: Draining hemorrhage
- Mediastinal mass: Thymoma (see comment)

Comments:
A cytokeratin immunohistochemical stain exhibits positive cytoplasmic immunoreactivity which is diagnostic for thymoma. No further tests are pending.

DIAGNOSIS

Acquired Fanconi's syndrome – associated with jerky treat toxicosis

Stage III invasive thymoma

DISCUSSION

Detailed discussions of Fanconi's syndrome and thymoma are beyond the scope of this article and the reader is referred to the listed references.

Jerky treat toxicosis

From 2007 through the end of 2015, the FDA received 5,200 complaints of illness associated with the consumption of chicken, duck or sweet potato jerky treats. The reports involve more than 6,200 dogs, 26 cats, three people and include more than 1,140 canine deaths. Although numbers have declined in recent years, there are still cases being reported.

The majority of complaints involve chicken jerky (treats, tenders and strips) but others include duck, sweet potato and treats with chicken or duck jerky wrapped around dried fruits, sweet potatoes, yams or rawhide. The illnesses and deaths reported are most often, but not always, linked to jerky pet treats sourced from China. ***Clinical Note: Pet owners should be aware that manufacturers are not required to list the country of origin for each ingredient used in their products. Although a product may be labelled "Made in USA," individual ingredients may be sourced elsewhere.*** About 60% of reports are for gastrointestinal illness (with or without elevated liver enzymes), 30% relate to kidney or urinary signs and the remaining 10% of cases involve a variety or other signs including convulsions, tremors, hives and skin irritation. ***Clinical Note: Jerky treat ingestion should become a standard inquiry for any patient affected by gastrointestinal and/or renal disease.***

The FDA's jerky treat toxicosis investigation has revealed an unexpected number of acquired Fanconi's syndrome cases and these cases are referred to as Fanconi's-like syndrome (FLS). Fanconi's syndrome (FS) is a rare inherited kidney disease typically seen in certain breeds (i.e., Basenji). Patients affected by Fanconi's syndrome have a proximal renal tubular defect which leads to inadequate resorption of many urine constituents such as glucose, amino acids, bicarbonate, sodium, calcium, phosphate, lactate, ketones, carnitine, water and uric acid. The abnormal glucose reabsorption by the proximal renal tubule leads to glucosuria and osmotic diuresis resulting in the dramatic polyuria and polydipsia which is so typical of the disorder. Depending on the severity of the tubular lesions, FS progresses at a variable rate to renal tubular acidosis, chronic renal failure and renal papillary necrosis which may eventually result in death of the affected dog.

Since 2007 more than 360 of the affected dogs reported to the FDA have had glucosuria with normoglycemia which are the hallmarks of FS. Since 2012, 263 dogs have had specific urine testing for markers of FS and 214 have tested positive. ***Clinical Note: This urine metabolic screening is readily available at PennGen and affected dogs will usually reveal generalized aminoaciduria and lactic aciduria (in addition to the glucosuria and ketonuria).*** The FDA continues to monitor FLS positive dogs to determine how long markers of FLS stay in the urine after discontinuation of jerky treats. 71% of dogs retested approximately 4 months after the initial positive results continued to have confirmed FLS.

Frustratingly, the toxic mechanism or ingredient in jerky treats has not been identified. The FDA has subjected 530 jerky treat samples (from pet owners) plus 450 unopened retail samples to a number of different tests (see **Table 3**) to no avail. Fortunately most dogs diagnosed with FLS associated with jerky treat toxicosis usually improve or recover completely with appropriate veterinary care and removal of the jerky treats from the diet. Persistent chronic renal failure is possible.

Other causes of acquired Fanconi's syndrome are listed in **Table 4** and must be considered in any patient affected by Fanconi's-like signs.

TABLE 3.
FDA JERKY TREAT TESTING

Pathogenic bacteria (*Salmonella, Clostridium,* Shigatoxin, etc.)
Metals or elements (arsenic, cadmium, lead, etc.)
Markers of food irradiation
Pesticides
Antibiotics (both approved and unapproved sulfonamides, quinolones, tetracyclines)
Antivirals (amantadine, etc.)
Mold and mycotoxins
Rodenticides
Radioactivity
Biogenic amines
Illegal dye agents
Nephrotoxins (ethylene glycol, hydrocarbons, melamine, etc.)
Miscellaneous chemicals

Table taken from FDA website Jerky Pet Treats Annual Update:
https://www.fda.gov/AnimalVeterinary/SafetyHealth/ProductSafetyInformation/ucm360951.htm#do

At this time, the FDA statement to pet owners regarding jerky pet treats is as follows: *"Jerky pet treats are not required as part of a complete and balanced diet for your pet. If you choose to feed jerky pet treats, watch your pet closely. Signs that have been reported in association with jerky pet treats may occur within hours to days of feeding the jerky treat products are decreased appetite, decreased activity, vomiting, diarrhea (sometimes with blood or mucus), increased water consumption and/or increased urination. Severe cases may be diagnosed with pancreatitis, gastrointestinal bleeding, and/or kidney failure or the resemblance of Fanconi syndrome.*

If you believe your pet has become ill from consuming a jerky pet treat, please provide us with valuable information by reporting it electronically through our Safety Reporting Portal or to your local FDA Consumer Complaint Coordinator. In addition to your contact information, your pet's symptoms, and medical records, the one piece of information we most often lack is the lot number of the jerky treat product. If we have the lot numbers, we can identify whether particular lots triggered more complaints, trace products back to specific manufacturing facilities, and identify lots for testing. While we still want to hear from you even without the lot number, this information can help our investigation immensely."

The FDA advises veterinarians who are reporting cases of suspected jerky pet treat-related illness to include the following information:

- *How long the owner has been feeding the treat*
- *What else the pet has been eating (all treats, human food, and pet food), including how much is given daily of all items*
- *Bloodwork values, especially for liver and kidney*
- *Urinalysis results*

The FDA also requests in the letter that veterinarians obtain a urine sample (10 ml if possible) from dogs or cats that may have illness associated with jerky pet treats and freeze it for testing for FLS. This testing will allow the FDA to get a better idea of how many of the suspected cases involve FLS and whether or not the pets display symptoms of kidney or urinary disease therapy with survival times of 1 to 3 years.

TABLE 4.
CAUSES OF ACQUIRED FANCONI'S SYNDROME

Leptospirosis
Gentamicin administration
Primary hypoparathyroidism
Copper storage hepatopathy
Various heavy metal toxicoses
Jerky treat toxicosis
Idiopathic

TABLE 5.
MEDIASTINAL MASSES

NEOPLASTIC MASSES	NON-NEOPLASTIC MASSES
Lymphoma	
Thymoma	
Chemodectoma	
Ectopic thyroid carcinoma	
Metastatic carcinoma	
Rib or sternal sarcoma	Branchial cysts
Hemangiosarcoma	Cysts of pleural, thymic or lymphatic origin
Lipoma/liposarcoma	Fungal and other granulomas
Lymphangioma	
Lymphagiosarcoma	
Histiocytic tumors	
Parathyroid adenocarcinoma	
Osteosarcoma	

Thymoma

The two most common mediastinal tumors are lymphoma and thymoma. Less common types of mediastinal neoplasia and non-neoplastic mediastinal lesions are listed in **Table 5.** Thymomas originate from neoplastic thymic epithelium. They are classified histologically as differentiated epithelial, lymphocyte-rich or clear cell. Thymomas can be invasive (malignant) or non-invasive (benign) and the invasiveness predicts prognosis. Invasive thymomas can invade into all surrounding tissues such as the vena cava, pericardium and thoracic wall. Thymomas rarely metastasize.

Thymomas generally affect older animals (average age of 9 years) and no genetic or environmental causes have been identified. German Shepherd Dogs, Labrador Retrievers and Golden Retrievers are over-represented breeds.

The history and physical examination of dogs affected by thymoma can be unremarkable or patients may have signs referable to respiratory

embarrassment such as coughing, tachypnea, dyspnea or exercise intolerance. As with "Norm," decreased lung sounds are common.

Paraneoplastic syndromes frequently accompany thymoma. Up to 40% of dogs with thymoma have signs of myasthenia gravis and therefore may present with generalized muscle weakness, dysphagia or regurgitation related to megaesophagus. Hypercalcemia has been reported and affected patients may experience weakness, polyuria, polydipsia or signs of renal failure. Other paraneoplastic syndromes accompanying thymomas include exfoliative dermatitis, mycocarditis, third degree AV block and polymyositis. ***Clinical Note: Acquired Fanconi's syndrome has never been reported as a paraneoplastic syndrome associated with thymoma.***

Like "Norm," patients with very large and/or invasive masses may have pre-caval syndrome which results in facial, neck and/or forelimb swelling due to obstruction of venous and/or lymphatic drainage.

The minimum database is often normal in affected dogs, although lymphocytosis or hypercalcemia may be noted. ***Clinical Note: Dogs with large parenchymal (benign or malignant) masses (e.g., pulmonary, spleen, liver, etc.) often have leukocytosis characterized by neutrophilia and monocytosis due to necrotic regions within the lesions. Dogs with unexpected leukocytosis should always have screening imaging performed!*** Thoracic radiography is critical for the diagnosis of a cranial mediastinal mass and pleural effusion is a frequent finding. Megaesophagus and aspiration pneumonia may be found if myasthenia gravis is a complicating feature. Cytology is often of limited usefulness and it can be difficult to differentiate lymphoma from thymoma. Fine needle aspirates from thymomas usually reveal small mature lymphocytes rather than the epithelial component of the tumor. Flow cytometry can be performed to help differentiate lymphoma from thymoma.

Surgery is the treatment of choice for thymomas. Large thymomas should be removed via thoracotomy; however, smaller more encapsulated thymomas can sometimes be resected successfully via thoracoscopy. CT scans are usually recommended in patients with cranial mediastinal masses for surgical planning. CT is useful for demonstrating the invasiveness of thymoma in dogs. A fairly recent CT study of dogs with thymoma revealed enlarged lymph nodes in 15% and pulmonary metastasis in 5%. Invasion into the vena cava was seen in 15% of cases. 88% of dogs with thymoma were considered to be surgically resectable based on CT results. With complete surgical excision of a thymoma the average survival time is 635-790 days. The one year survival is 64% and 3 year survival is 42%. Thymoma recurrence is often treated surgically a second (or more times) and survival times of 3-5 years from the first surgery can be achieved.

If a thymoma is deemed not surgically resectable, radiation therapy should be considered as thymomas respond quite well to radiation therapy with a 75% response rate. Although a complete response to radiation therapy is possible, a partial response is far more typical and can slow disease progression and decrease pleural effusion associated with the neoplasm. The median survival time of 248 days was achieved in one study.

"NORM'S" TREATMENT

At the time of suture removal from his thoracotomy, repeat bloodwork was performed. "Norm's" azotemia had improved further (BUN 25, creatinine 1.3), electrolytes were within normal limits and no glucosuria or proteinuria were noted. This was additional support that "Norm" had suffered Fanconi's-like syndrome associated with jerky treats consumption. The renal diet and benazepril were discontinued.

"Norm" was referred for an oncology consultation to address the residual thymoma. As thymomas are generally slow growing tumors and "Norm" was doing so well post-operatively, the oncologist recommended ongoing monitoring of "Norm" with close observation of clinical signs and periodic thoracic radiography (q 3 months) to assess growth of the thymoma. If significant re-growth were to occur or "Norm" develops clinical signs of respiratory disease, a second surgery or radiation therapy at that time was stated as the best option.

"Norm" has been followed 3 months post-op with no residual chronic renal disease or significant regrowth of his thymoma.

REFERENCES

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US FDA Jerky Pet Treats Annual Update, 2/23/18

https://www.fda.gov/AnimalVeterinary/SafetyHealth/ProductSafetyInformation/ucm360951.htm#do

CLINICAL ASSESSMENT

1 Which of the following is not considered a cause of glucosuria in dogs?

a. Diabetes mellitus
b. Leptospirosis
c. Fanconi's syndrome
d. Phenobarbital
e. Gentamicin

2 Thymomas are readily diagnosed on cytologic examination. **True or False?**

3 Treats labelled "Made in USA" are safe sources of jerky treats. **True or False?**

4 Which of the following is/are hallmarks of Fanconi's and Fanconi's-like syndrome in dogs?

a. Glucosuria with normal blood glucose
b. Aminoaciduria
c. Ketonuria
d. Chronic renal failure
e. All of the above

5 Fanconi's-like syndrome associated with jerky treat toxicosis is usually a fatal disease in dogs – similar to the inherited form of the disease. **True or False?**

6 There is a confirmatory blood test for Fanconi's-like syndrome associated with jerky treat toxicosis. **True or False?**

7 Paraneoplastic syndromes are rare with thymomas. **True or False?**

8 Which of the following is not a paraneoplastic syndrome associated with thymoma?

a. Hypercalcemia
b. Exfoliative dermatitis
c. Myasthenia gravis
d. Fanconi's
e. AV block

9 Definitive treatment of thymoma with surgical resection will not necessarily result in resolution of the paraneoplastic syndrome. **True or False?**

10 Thymomas can be very large and are often quite locally invasive neoplasms. The long term prognosis for thymoma is quite poor. **True or False?**

CLINICAL ASSESSMENT ANSWERS:

1. **d. Phenobarbital.** Glucosuria is a hallmark of diabetes mellitus as well as certain renal diseases such as leptospirosis, Fanconi's syndrome, Fanconi's-like syndrome associated with jerky treat toxicosis, copper storage disease, and certain medication usage (gentamicin, etc.). Phenobarbital has not been associated with glucosuria.
2. **False.** Fine needle aspirate cytology is often of limited usefulness and it can be difficult to differentiate lymphoma from thymoma. Fine needle aspirates from thymomas usually reveal small mature lymphocytes rather than the epithelial component of the tumor. Flow cytometry can be performed to help differentiate lymphoma from thymoma.
3. **False.** Most of the illnesses and deaths (but not all) reported from jerky treat toxicosis were linked to jerky pet treats sourced from China. Pet owners must be aware that manufacturers are not required to list the country of origin for each ingredient used in their products. Although a product may be labelled "Made in USA," individual ingredients may be sourced elsewhere.
4. **E. all of the above.**
5. **False.** Fortunately most dogs diagnosed with FLS associated with jerky treat toxicosis usually improve or recover completely with appropriate veterinary care and removal of the jerky treats from the diet. Persistent chronic renal failure is possible.
6. **False.** There is a DNA blood test available for screening Basenji's for the inherited defect of Fanconi's syndrome. PennGen offers a urine metabolic screening test to detect aminoaciduria, lactic aciduria as well as glucosuria and ketonuria associated with jerky treat toxicosis.
7. **False.** Thymomas frequently have associated paraneoplastic syndromes.
8. **D. Fanconi's.** Fanconi's syndrome has never been associated with thymomas.
9. **True.**
10. **False.** Although locally invasive, thymomas rarely metastasize and are generally amenable to surgical excision. The average survival time treated with surgery alone is 635-790 days with a one year survival of 64% and 3 year survival of 42%.