Case Series

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Acquired Fanconi syndrome in four cats treated with chlorambucil

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Abstract

Case series summary Fanconi syndrome (FS) is well described in humans and dogs, but has not been reported in cats. This case series describes four cats with acquired FS. On the basis of clinical signs and intestinal biopsies, all cats were initially diagnosed with alimentary lymphoma or inflammatory bowel disease. Treatment with chlorambucil and corticosteroids was started at standard doses, based on published protocols. Within 2–26 months of the start of treatment, glucosuria, despite normoglycemia, was identified incidentally on routine biochemical screening; FS was diagnosed with urine metabolic assays, confirming aminoaciduria and glucosuria in all four cases. Neither polyuria nor polydipsia were noted in any case, and only 1/4 cats had any clinical signs at the time of diagnosis. Partial or complete resolution of FS was seen in 3/4 cases within 3 months of discontinuing chlorambucil therapy.

Relevance and novel information This is the first case series to document acquired FS in the cat, and the first to suggest a possible association between chlorambucil and acquired FS. Cats treated with chlorambucil should be monitored for the development of glucosuria, and discontinuation of chlorambucil should be considered if FS is identified. Further study into the association between chlorambucil and acquired FS in cats is warranted.

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The proximal renal tubule is responsible for the majority of glomerular filtrate reabsorption, and is the only point of reabsorption for many solutes, including amino acids and organic acids, filtered proteins, glucose and phosphate.[1] Fanconi syndrome (FS) is a dysfunction of the proximal tubule, resulting in variable excretion of glucose, amino acids, uric acid, ions and electrolytes.[2,3] Both idiopathic and acquired forms of FS have been described in the dog,[4–9] in addition to a familial form reported in Basenjis and several other breeds.[4,10] In dogs and humans, acquired FS has been associated with medications, infectious and systemic diseases, certain food additives and toxins, among other causes.[5,7–9,11–13] Recently, large numbers of cases of acquired FS have also been reported in dogs exposed to jerky pet treats.[9,14,15] To our knowledge, there are no published reports of FS in cats.

This case series describes the development of acquired FS in four cats, 2–26 months after the start of treatment for infiltrative intestinal diseases with chlorambucil and other drugs. In 3/4 cases, FS partially or completely resolved after cessation of chlorambucil treatment.

Case series description

Case 1

A 13-year-old, 2.96 kg female spayed domestic shorthair cat was presented in May 2009 for evaluation of chronic vomiting, polyphagia, hyperactivity and weight loss. Complete blood count (CBC), serum biochemistry and total thyroxine (T4) obtained at the local veterinarian 2 weeks prior to presentation showed no significant findings. Endoscopic biopsies of the duodenum were obtained, and histopathology showed moderate-to-marked lymphoid infiltrates with scattered plasma cells, suggestive of early low-grade lymphoma. Treatment with prednisone (Prednisone; Qualitest Pharmaceutical) 5 mg (1.7 mg/kg) orally q24h and chlorambucil (Leukeran; Aspen) 2 mg orally twice weekly was started (Table 1). Two months into treatment the medications were adjusted to increase patient compliance and address persistent vomiting: oral prednisone was changed to a compounded, transdermal formulation of prednisolone at an increased dosage of 10 mg (3.3 mg/kg q24h), while chlorambucil was changed to a compounded, oral liquid at the same dose.

The patient was re-evaluated for weight loss 18 months after initial presentation. Follow-up CBC, serum

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Table 1 Signalment, disease, treatments, development of acquired Fanconi syndrome (FS) and outcome in four cats treated with chlorambucil

	Case 1	Case 2	Case 3	Case 4
Age (y)/signalment	13/DSH Fs	13/DSH MC	12/DSH Fs	8/Persian MC
Intestinal disease diagnosis	Suspected low-grade alimentary lymphoma vs IBD	Low-grade alimentary lymphoma	Low-grade alimentary lymphoma	IBD
Chlorambucil dosage	2 mg orally twice weekly	2 mg orally three times weekly	2 mg orally three times weekly	2 mg orally twice weekly
Chlorambucil compounded?	Yes	No	Yes	Yes
Steroid formulation(s) and dosage(s) used during chlorambucil treatment period*	Prednisone 5 mg orally q24h, prednisolone 10 mg transdermally q24h, prednisolone 10 mg orally q24h	Prednisolone 10 mg orally q24h	Prednisolone 10 mg orally q24h, dexamethasone 1 mg orally q24h, budesonide 1 mg orally q24h	Budesonide 1 mg orally q24h, methylprednisolone acetate 20 mg intramuscularly
Other medications used during chlorambucil treatment period†	None	Mirtazapine, oxytetracycline ophthalmic	Cobalamin	Metronidazole, metoclopramide, lysine, idoxuridine, moxifloxacin, famciclovir, alendronate, mirtazapine, amoxicillin-clavulanate, robenacoxib, buprenorphine
Time to identification of glucosuria (months)	26	7	2	5
Time to diagnosis of FS (months)‡	27	7	4	5
Chlorambucil discontinued	Yes	Yes	Yes	Yes
Time to resolution of FS (partial/complete)	Not resolved after 1 week	3 months (unknown, no follow-up urine assay)	6 weeks (complete)	2 months (partial)
Case outcome after FS diagnosis	Euthanized after 9 months (suspected to be unrelated to FS)	Died after 6 months (suspected to be unrelated to FS)	Alive after 10 months	Alive after 6 months

*See text for duration and timeline of administration
†See text for drug dosages, duration and timeline of administration
‡Time of urine metabolic assay submission
DSH = domestic shorthair; Fs = female spayed; MC = male castrated; IBD = inflammatory bowel disease; y = years

biochemistry, ionized calcium, total T4 and urinalysis (UA) showed hypercalcemia (total calcium 11.7 mg/dl, reference interval [RI] 8.2–10.8 mg/dl; ionized calcium 1.39 mmol/l, RI 1.16–1.35 mmol/l), lymphopenia (432/µl, RI 1200–8000/µl) and proteinuria (2+, RI negative) with a urine specific gravity (USG) of 1.056 (RI 1.015–1.060). Idiopathic hypercalcemia was diagnosed 2 months later on the basis of a persistent ionized hypercalcemia (1.64 mmol/l, RI 1.16–1.34) with normal parathyroid hormone (4 pg/ml, RI 4–25 pg/ml), the lack of significant findings on abdominal ultrasound and the absence of consistent clinical signs. Twenty-two months after starting treatment, transdermal prednisolone was changed back to oral administration of a compounded liquid at the same dosage (10 mg q24h) owing to the uncertain absorption and bioavailability of the transdermal formulation.

The patient was clinically well 26 months after starting chlorambucil. Follow-up CBC, serum biochemistry and UA showed resolution of the hypercalcemia, but a new finding of glucosuria (1+, RI negative) with normoglycemia (123 mg/dl, RI 64–170 mg/dl). Urine metabolic assay performed 1 month later was consistent with FS (Table 2). Treatment was continued with compounded oral prednisolone and chlorambucil, and follow-up diagnostics 4 months after diagnosis of FS documented

Table 2 Results of urine metabolic assays in four cats treated with chlorambucil*

	Ketones	Cystine	Amino acids	Organic acids	Carbohydrates
Case 1	–	Slight (+)	Severe generalized	Moderate lactate	Severe glucose
Case 2	–	–	Mild generalized	Moderate lactate	Severe glucose
Case 3 – initial	–	–	Moderate generalized	Normal: negative lactate	Severe glucose
Case 3 – follow-up†	–	–	↑ Glutamine ↑ Taurine	Normal: negative lactate	–
Case 4 – initial	–	–	Moderate generalized	Moderate lactate	Moderate glucose
Case 4 – follow up†	–	–	Moderate generalized	Normal: negative lactate	–

*All assays performed at the University of Pennsylvania School of Veterinary Medicine PennGen Laboratories
†See text for timeline of follow-up after discontinuation of chlorambucil in cases 3 and 4
– = negative; + = positive

persistent glucosuria (1+, RI negative) with normal serum chemistry, including blood glucose (139 mg/dl, RI 64–170 mg/dl). All medications were continued at this time.

The patient was re-evaluated for progressive weight loss, decreased appetite and vomiting 8 months after the diagnosis of FS (35 months after starting chlorambucil treatment). Over the next month diagnostic testing, including CBC, serum biochemistry and abdominal ultrasound, showed no significant findings. Clinical signs were attributed to refractory or progressive intestinal disease, and treatment was changed from chlorambucil to lomustine. One week after lomustine administration the patient was presented for anorexia, progressive vomiting and collapse. Repeat evaluation showed elevated liver enzymes (aspartate aminotransferase [AST] 213 IU/l, RI 10–100 IU/l; alanine aminotransferase [ALT] 252 IU/l, RI 10–100 IU/l; alkaline phosphatase [ALP] 148 IU/l, RI 6–102 IU/l), hyperbilirubinemia (2.8 mg/dl, RI 0.1–0.4 mg/dl), marked electrolyte abnormalities (hyponatremia 137 mEq/l, RI 145–158 mEq/l; hypokalemia 2.7 mEq/l, RI 3.4–5.6 mEq/l; hypochloremia 89 mEq/l, RI 104–128 mEq/l), normoglycemia (131 mg/dl, RI 64–170 mg/dl), alkalosis (pH 7.51, RI 7.27–7.42), hyperlactatemia (5.4 mmol/l, RI 1.1–3.5 mmol/l), normal venous bicarbonate level (22, RI 17–22), glucosuria (3+, RI negative), ketonuria (2+, RI negative) and bilirubinuria (2+, RI negative) with a USG of 1.021 (RI 1.015–1.060). Abdominal ultrasound showed moderate ascites and diffusely thickened small intestines. The patient was euthanized the following day owing to progressive obtundation and lack of response to treatment.

Case 2

A 13-year-old, 4.0 kg male castrated domestic shorthair cat was evaluated in July 2011 for a 6 month history of weight loss with recent-onset vomiting, lethargy and decreased appetite. CBC, serum biochemistry and UA revealed a marked leukocytosis characterized by a severe neutrophilia (52,720/µl, RI 2500–8500/µl; bands 659/µl, RI 0–150/µl), lymphocytosis (8567/µl, RI 1200–8000/µl), monocytosis (2636/µl, RI 0–600/µl) and eosinophilia (1318/µl, RI 0–1000/µl), mild hyperglycemia (210 mg/dl, RI 64–170 mg/dl) and proteinuria (2+, RI negative) with a USG of 1.070 (RI 1.015–1.060). Histopathology of full-thickness jejunal biopsies showed small cell, low-grade lymphoma. Treatment was started with chlorambucil (Leukeran; Aspen) 2 mg orally three times weekly, prednisolone (PrednisTab; Butler Schein) 10 mg (2.5 mg/kg) orally q24h and mirtazapine 3.75 mg (0.9 mg/kg) orally every 2–3 days (Table 1). Within 4 weeks the mirtazapine was discontinued and prednisolone was changed to a compounded liquid formulation at the same dose. The only additional medication used was a 2 week course of oxytetracycline hydrochloride ophthalmic ointment (Terramycin; Pfizer) for conjunctivitis that developed 4 months into treatment.

Seven months after starting chlorambucil the patient was evaluated for recent-onset lethargy and decreased appetite. CBC, serum biochemistry and UA revealed a lymphopenia (572/µl, RI 1200–8000/µl), normoglycemia (124 mg/dl, RI 64–170 mg/dl), proteinuria (2+, RI negative) and glucosuria (2+, RI negative) with a USG of 1.057 (RI 1.015–1.060). Urine metabolic screening was consistent with FS (Table 2).

Over the next month both progressive lymphoma and/or FS secondary to a drug reaction (chlorambucil) were considered possible causes for persistent weakness and inappetence. Treatment was therefore changed from chlorambucil to lomustine; prednisolone was continued, alternately as compounded liquid or commercially prepared tablets, based on the owners' preference. Follow-up 1 month later documented persistent glucosuria (3+, RI negative) with normoglycemia (143 mg/dl, RI 64–170 mg/dl), but 3 months after discontinuing chlorambucil the glucosuria had resolved. At that time, however, an ileocolic mass was identified on abdominal ultrasound, and cytology of the mass showed an expanded lymphoblast population consistent with high-grade alimentary lymphoma. Treatment with l-asparaginase and a CHOP-based chemotherapy protocol (cyclophosphamide,

doxorubricin, vincristine and prednisolone) was started but discontinued 1 month later owing to a lack of response. The cat died at home 2 months after the diagnosis of high-grade lymphoma.

Case 3

A 12-year-old, 3.5 kg female spayed domestic shorthair cat was presented in October 2013 for a 2 year history of weight loss with intermittent vomiting and diarrhea. A CBC, serum biochemistry, total T4 and UA were within normal limits, with the exception of proteinuria (2+, RI negative) with a USG of 1.045 (RI 1.015-1.060). Two months later duodenal biopsies were obtained endoscopically, which revealed low-grade, small cell lymphoma. Treatment was started with compounded liquid prednisolone 10 mg (2.9 mg/kg) orally q24h, compounded liquid chlorambucil 2 mg orally three times weekly and cobalamin 250 µg subcutaneously once weekly (Table 1).

Two months after starting medication the patient was clinically well. Follow-up diagnostics showed a mild anemia (hematocrit 28%, RI 29–48%), lymphopenia (720/µl, RI 1200–8000/µl), elevated blood urea nitrogen (46 mg/dl, RI 14–36 mg/dl), proteinuria (2+, RI negative) and glucosuria (2+, RI negative) with a USG of 1.063 (RI 1.015–1.060); blood glucose was normal (124 mg/dl, RI 64–170 mg/dl). At that time prednisolone was discontinued, and compounded dexamethasone liquid (1 mg [0.23 mg/kg] orally q24h) started to minimize sodium and water retention in light of a newly auscultated cardiac gallop rhythm. Further cardiac evaluation was declined. Two months later (4 months after starting chlorambucil) the patient continued to be asymptomatic, but follow-up evaluation showed persistent glucosuria (3+, RI negative) and proteinuria (2+, RI negative) with normoglycemia (160 mg/dl, RI 64–170 mg/dl). Urine metabolic screening was consistent with FS (Table 2).

Treatment with dexamethasone and chlorambucil was initially maintained; however, over the next 3 months the cat developed marked corticosteroid adverse effects, including severe, bilateral carpal laxity; suspect diabetes mellitus (blood glucose 229, RI 64–170); and newly elevated liver enzymes (AST 166 U/l, RI 10–100 IU/l; ALT 338 IU/l, RI 10–100 IU/l; ALP 176 IU/l, RI 6–102 IU/l). UA at the time showed persistent glucosuria (3+, RI negative) and proteinuria (1+, RI negative) with a USG of 1.068 (RI 1.015–1.060). Corticosteroid treatment was then changed from dexamethasone to budesonide (1 mg orally q24h). Follow-up 3 weeks later (9 months into treatment with chlorambucil) showed normoglycemia (125 mg/dl, RI 64–170 mg/dl) and resolution of all liver enzyme elevations other than ALP (120, RI 6-102 IU/l), but persistent glucosuria (2+, RI negative).

Although the patient was doing well clinically, chlorambucil treatment was changed to cyclophosphamide after 9 months owing to possible chlorambucil-induced FS; treatment with budesonide was continued. Six weeks later follow-up urine screening confirmed resolution of FS (Table 2). At the time of writing, the patient is clinically stable, 14 months after diagnosis with alimentary lymphoma and 3 months after resolution of acquired FS.

Case 4

An 8-year-old, 3.98 kg male castrated Persian cat was presented in April 2014 for chronic vomiting, decreased appetite and lethargy. Prior medical history included polycystic kidney disease; an intestinal eosinophilic fibrosclerosing granuloma, diagnosed 7 years prior and treated continuously since with budesonide 1 mg orally q24h, metronidazole 35 mg (8.8 mg/kg) orally q24h and intermittent metoclopramide 0.7 mg (0.2 mg/kg) orally as needed; chronic conjunctivitis/rhinitis secondary to herpesvirus, treated for 2 years with lysine 250 mg orally q12h and intermittent courses of idoxuridine ophthalmic 1 drop in both eyes q48h, moxifloxacin ophthalmic 1 drop in both eyes q48h and famciclovir 62.5 mg (15.7 mg/kg) orally q24h as needed; and idiopathic hypercalcemia treated for 1 year with alendronate 12.5 mg (3.1 mg/kg) orally once weekly. On presentation, CBC, serum biochemistry, total T4 and UA showed a mild hypertriglyceridemia (224 mg/dl, RI 25–160 mg/dl), lymphopenia (885/µl, RI 1200–8000/µl), eosinophilia (1357/µl, RI 0–1000/µl) and trace proteinuria (RI negative) with a USG of 1.037 (RI 1.015–1.060). Endoscopic biopsies of the stomach revealed polyploid adenomatous mucosal hyperplasia with erosion and ulceration and mixed, prominently eosinophilic lamina proprial hypercellularity with minimal atypia. Duodenal histopathology showed a mild plasmacytic lamina proprial infiltrate, mild villous edema and mild villous widening. A single injection of methylprednisolone acetate 20 mg (5 mg/kg) intramuscularly was given immediately after endoscopy owing to the patient's deterioration in spite of budesonide treatment. Based on the histopathology and clinical decline, compounded liquid chlorambucil 2 mg orally twice weekly and mirtazapine 0.75 mg (0.2 mg/kg) orally q24–48h were started the following month for refractory inflammatory bowel disease (Table 1). Budesonide was also restarted at this time. One month into treatment, UA performed at routine follow-up was normal except for trace proteinuria (RI negative).

Two months after starting chlorambucil the patient was evaluated for a 1 week history of behavior change that began after professional grooming. Physical examination revealed a 2.5×10 cm region of alopecia with erythema, ecchymoses superficial ulceration and hemorrhagic crusting over the right caudal dorsum. The area was surgically debrided and closed primarily. Histopathology showed focally extensive, full-thickness, epidermal ulceration and necrosis. The close temporal

proximity to grooming, acute behavior change and histopathology strongly suggested thermal injury. The patient was treated postoperatively with amoxicillin-clavulanate (Clavamox; Zoetis) 62.5 mg (16 mg/kg) orally q12h for 10 days, robenacoxib (Onsior; Novartis Animal Health) 6 mg (1.5 mg/kg) orally q 24h for 3 days and buprenorphine 0.06 mg (0.015 mg/kg) orally q8h for 3 days.

Within 5 months of starting chlorambucil the patient's clinical signs of intestinal disease were well controlled. Follow-up CBC, serum biochemistry and UA showed normoglycemia (117 mg/dl, RI 64–170 mg/dl), lymphopenia (910/µl, RI 1200–1800/µl), eosinophilia (1260, RI 0–1200/µl), proteinuria (1+, RI negative) and glucosuria (2+, RI negative) with a USG of 1.043 (RI 1.015–1.060). Urine metabolic screening was consistent with FS (Table 2). Chlorambucil was discontinued at the time of diagnosis owing to concern of an association with FS; all other medications were continued. Two months later, follow-up urine screening showed partial resolution of FS (Table 2). At the time of writing the patient remains clinically stable and non-azotemic, 11 months after first receiving chlorambucil and 6 months after diagnosis with FS.

Discussion

While the proximal renal tubule reabsorbs the vast majority of total glomerular filtrate, it is the single site of reabsorption of multiple solutes, including glucose, phosphate, amino acids and organic acids, and filtered proteins.[1] FS is the result of a defect in the proximal renal tubule, resulting in variably impaired reabsorption of solutes, including glucose, amino acids, lactic acid, uric acid, filtered proteins, bicarbonate, phosphate, sodium, potassium and water. Clinical signs can range from mild to severe, and include polyuria, polydipsia, dehydration, weight loss and poor haircoat.[2,3] Glucosuria in the face of normo- or hypoglycemia is one of the most common findings and prompts further investigation. While the type and severity of reabsorptive defects vary, diagnosis of FS is made with urine assays documenting combinations of glucosuria, lactic aciduria, generalized amino aciduria and phosphaturia.[3,5,16]

In dogs and humans, both heritable and acquired forms of FS are described. Reported causes of acquired FS include numerous medications (antibiotics [penicillins, degraded tetracyclines, aminoglycosides], salicylates [aspirin], antiepileptics [valproate], chemotherapeutics [streptozotocin, ifosfamide, cisplatin, mercaptopurine], tyrosine kinase inhibitors [imatinib mesylate], antiretrovirals [adefovir, tenovir]), Chinese herbs, food additives (4-pentenoate) and heavy metals (lead, mercury, cadmium), among other causes.[5–9,11–15,17] Systemic diseases, including leptospirosis, proximal renal tubular acidosis, copper storage hepatopathies, primary hypoparathyroidism, amyloidosis and multiple myeloma, have also been implicated.[7–9] Ingestion of pet jerky treats from China has been associated with large numbers of cases of acquired FS over the past decade, although the causative agent remains unknown.[9,14,15] Acquired FS may be transient or resolve partially if the inciting cause is removed, but in many cases it persists or progresses to renal failure.[3,5] To our knowledge there are no published reports of acquired FS in cats. In the USA, 24 cats have been reported to the US Food and Drug Administration as becoming ill after eating jerky pet treats, but none of the published data describe these cats as developing FS.[15]

Chlorambucil is a nitrogen mustard derivative and alkylating agent, used as both an immunosuppressive and antineoplastic agent. In cats it is most commonly used in the treatment of alimentary lymphoma, but it has also been reported for treatment of other inflammatory, immune-mediated and neoplastic diseases.[18–23] The most common reported adverse effects of chlorambucil are gastrointestinal toxicity and myelosuppression.[18] In humans, rare side effects include neurotoxicities, dermal reactions and interstitial lung disease.[24–26] Of these, only a reversible myoclonic neurotoxicity has been documented in a single case report of a cat.[24]

In the present study, all cats were diagnosed with either low-grade alimentary lymphoma or inflammatory bowel disease on the basis of consistent clinical signs and intestinal biopsies. Treatment was initiated with corticosteroids and chlorambucil at standard doses,[27] and additional medications were used as needed for symptomatic treatment or comorbid disease(s). The described cats developed glucosuria despite normoglycemia within 2–26 months of starting treatment, and in all cases a diagnosis of acquired FS was confirmed with urine metabolic screening performed at the University of Pennsylvania School of Veterinary Medicine PennGen Laboratories. Given the rarity of FS in cats, a common etiology was considered likely. Jerky treat ingestion was initially considered but ruled out on the basis of a lack of history of exposure in all cases. Chlorambucil was then identified as the only medication common to all four patients. Further support for chlorambucil as the causative agent was given by the partial or complete resolution of FS in 3/4 cases within 3 months of discontinuation of chlorambucil.

Other drugs used during the course of treatment were also considered as possible causative agents. All the cats were concurrently treated with corticosteroids, but these were considered unlikely causative agents as multiple different drugs (prednisone, prednisolone, methylprednisolone, dexamethasone and budesonide) and drug formulations were used between the cases. Furthermore, in 2/4 cases partial or complete resolution of FS was seen in spite of continuation of steroid treatment. Of the other

drugs used during treatment, only case 4 received a medication (amoxicillin-clavulanate) previously associated with acquired FS;[6] this was considered less likely to be causative given the short treatment course used and the subsequent partial resolution of FS after discontinuation of chlorambucil.

In this case series, 3/4 cats were treated with compounded, liquid formulations of chlorambucil, and all cats received at least one compounded medication during the treatment period. The use of specialty compounded formulations was based upon owner preference to increase patient compliance via improved palatability and/or ease of administration. Potential risks in the use of compounded medications include preparation errors (contamination, mathematical mistakes) and changes to the drug's stability, potency or absorption when re-formulated from a commercially made product.[28,29] Oral absorption of chlorambucil is documented in approval studies on the commercially prepared tablets and can likely be extrapolated to oral suspensions, but 100% bioavailability of the drug in those suspensions is not assured.[29] Furthermore, limited data are available on its stability in solution. Early studies of chlorambucil in aqueous suspensions showed rapid decomposition, with a potency <90% after 7 days, even when refrigerated.[30] No published data exist as to the stability of chlorambucil in oil-based suspensions. Beyond-use dates are provided by individual pharmacies, ideally on the basis of internal testing of specific formulations. In the absence of such data, the beyond-use date for any compounded medication is assigned as the lesser of 6 months or 25% of the time remaining of the approved drug's expiration.[29] In the described cases, prescriptions were refilled every 5–20 weeks, making it possible that drug activity was decreased at some time points of administration. Additionally, although limited in number, the majority of stability studies support that failures of compounded medications result in decreased product potency or bioavailability.[29] These studies therefore also suggest that the described patients could have been treated with less chlorambucil than prescribed. Finally, because of the significant time periods between patient treatment and the compounding of medications through different pharmacies for each patient, variables internal to the compounding process (errors in preparation and differences between suspensions) were considered less likely contributors to the development of FS in these cats. None of these risk factors, however, can be completely excluded. Although 1/4 cats (case 2) received only commercially formulated chlorambucil, it is possible that the use of compounded medication may have increased the risk of FS in the other cases.

Infectious and systemic diseases have also been associated with the development of acquired FS.[7–9] All the patients in this case series were treated for infiltrative gastrointestinal disease: two were diagnosed with low-grade alimentary lymphoma, one with suspected low-grade alimentary lymphoma and one with refractory inflammatory bowel disease. In the latter two cases it is possible that a diagnosis of alimentary lymphoma was missed on endoscopic biopsy,[31] and that intestinal neoplasia led to acquired FS in all four cases. However, standard treatment for alimentary lymphoma is not considered curative;[27] with a persistent inciting cause we would not expect resolution of acquired FS.[8]

Contrary to recent reports of acquired FS in dogs secondary to jerky pet treat ingestion,[7,9] none of the cats described in this case had a history of polyuria or polydipsia. It is possible that this clinical sign was masked by concurrent corticosteroid administration or that the disease was identified early in its course. Only case 2 had any clinical signs when FS was diagnosed. These signs were initially attributed to progressive intestinal disease but could have been due to the presence of FS. However, at the time of resolution of glucosuria, the cat was diagnosed with high-grade alimentary lymphoma and was refractory to further treatment, suggesting that any clinical signs attributable to FS were limited. Finally, although many dogs with idiopathic FS progress to azotemia,[5] at the time of writing none of the reported cases had evidence of chronic renal damage. In the described cases, however, 2/4 (cases 1 and 2) died within 9 months of diagnosing FS, and 1/4 (case 4) showed complete resolution within 2 months of diagnosis. No conclusions can be made about the long-term sequelae of acquired FS in cats based on this small case series.

Given the widespread use and number of reports detailing the treatment of cats with chlorambucil, the authors were surprised that neither glucosuria nor FS have been previously reported as an adverse effect. It is possible that practitioners have not routinely performed follow-up UAs at the same time as standard blood tests when monitoring treatment, and therefore the syndrome would be missed. Alternatively, it is possible that in recent years changes have been made to the manufacturing process of brand-name chlorambucil (Leukeran; Aspen), the only commercially made product available in the USA. Finally, the dramatic increase in the use of compounded medications – including chlorambucil – in veterinary medicine over the past 15 years may have increased the risk of this rare syndrome in cats.[29] However, no conclusions explaining the lack of historical record can be drawn from this study.

Conclusions

The four cats in this case series all developed FS after starting treatment for infiltrative intestinal disease with standard doses of chlorambucil and corticosteroids. Clinical signs of FS were absent, or, when present, were either misinterpreted as or masked by the primary

intestinal disease or concurrent medication. Three of four cases had partial or complete resolution of FS within 3 months of the discontinuation of chlorambucil. Monitoring of chlorambucil-treated cats for the development of glucosuria and discontinuation of chlorambucil should be considered in cats that develop acquired FS. Further studies are warranted to support an association between cats treated with chlorambucil and the development of FS, and to determine the prevalence, risk factors and progression of acquired FS in these cases.

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