FELINE ADRENAL DISEASE

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FELINE HYPERADRENOCORTICISM

Rare disease in the cat

Middle to old age cats

Mean = 13.4 years

Range 4 - 18 years

Usually associated with:

Diabetes mellitus — 72/97 cases female

Cutaneous lesions — 74%

FELINE HYPERADRENOCORTICISM

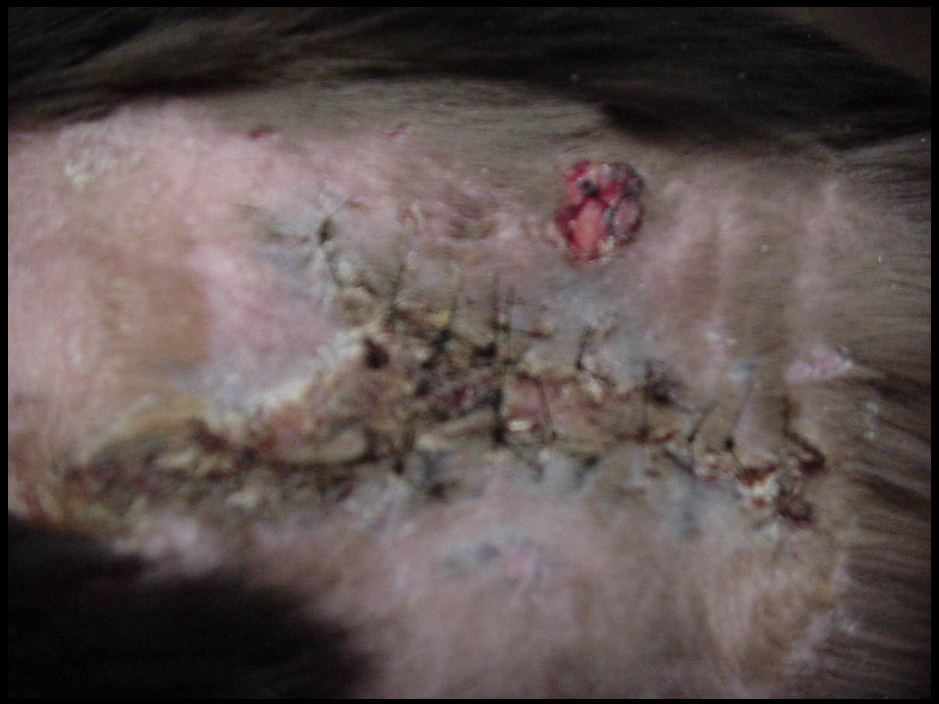
Clinical Signs

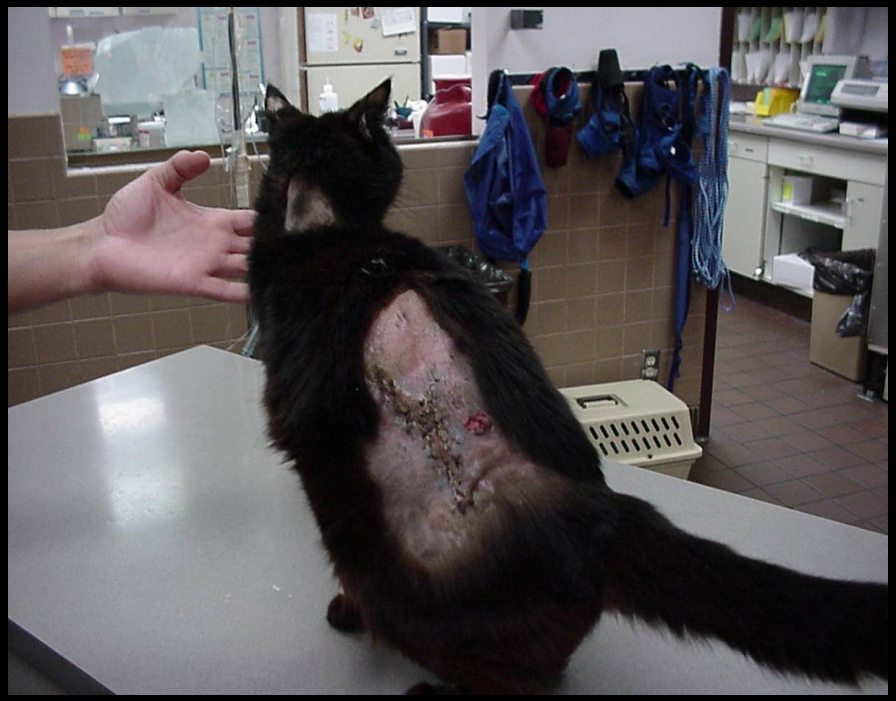
- PU/PD
- Polyphagia
- Diabetes mellitus
- Insulin resistance

Physical Examination

- “Pot-Bellied”
- Hepatomegaly
- Weight gain
- Muscle wasting
- Alopecia
- Thin skin
- Severe ulceration

FELINE ADRENAL DISEASE





FELINE HYPERADRENOCORTICISM

Laboratory Abnormalities

- Hyperglycemia
- Hypercholesterolemia
- Increased SAP (30 %)
  - Reflects underlying diabetes

FELINE HYPERADRENOCORTISM

Laboratory Abnormalities

Stress leukogram is inconsistent

Urine specific gravity > 1.020

UTI's - routine urine cultures

FELINE HYPERADRENOCORTICISM

Endocrinologic Evaluation

- ACTH Stimulation
- Dexamethasone Suppression
- UCCR
- Combined Testing

FELINE HYPERADRENOCORTICISM

Endocrinologic Evaluation

ACTH Stimulation

Cortrosyn

0.125 mg (1/2 vial) IV or

5 ug/kg IV; freeze remainder

Pre and 60 minute post

FELINE HYPERADRENOCORTICISM

Endocrinologic Evaluation

Dexamethasone Suppression Testing

- Cats are not like dogs
- Inconsistent suppression in normal cats
  - with 0.01 mg/kg IV DexNaPO4
- Doses evaluated have ranged from
  - 0.005 - 1.0 mg/kg

FELINE HYPERADRENOCORTICISM

Endocrinologic Evaluation

Dexamethasone Suppression Testing

- Non-adrenal illness
- In PDH the most reliable dose is:
  - 0.1 mg/kg IV with pre, 4 and 8 hour post; 89 % sensitive

FELINE HYPERADRENOCORTICISM

Endocrinologic Evaluation

UCCR

- Likely sensitive though poorly specific
- Can be used to rule-out HAC
- Simple though not easy
- Early morning urine sample

FELINE HYPERADRENOCORTICISM

Endocrinologic Evaluation

Combination Testing

- Dexamethsone suppression (0.1 mg/kg; pre, 2 and 4 hours) followed by an ACTH stimulation test (1 and 2 hours).
- Limitations related to sample times
- No advantage over DST or ACTH alone

FELINE HYPERADRENOCORTICISM

Endocrinologic Evaluation

Differentiating PDH from AT

HDDS

Abdominal US

Plasma ACTH

CT/MRI

FELINE HYPERADRENOCORTICISM

Endocrinologic Evaluation

Differentiating PDH from AT

HDDS

Multiple samples preferred

1.0 mg/kg DexNaPO4 with a pre, 4 and 8 hour post

FELINE HYPERADRENOCORTICISM

Endocrinologic Evaluation

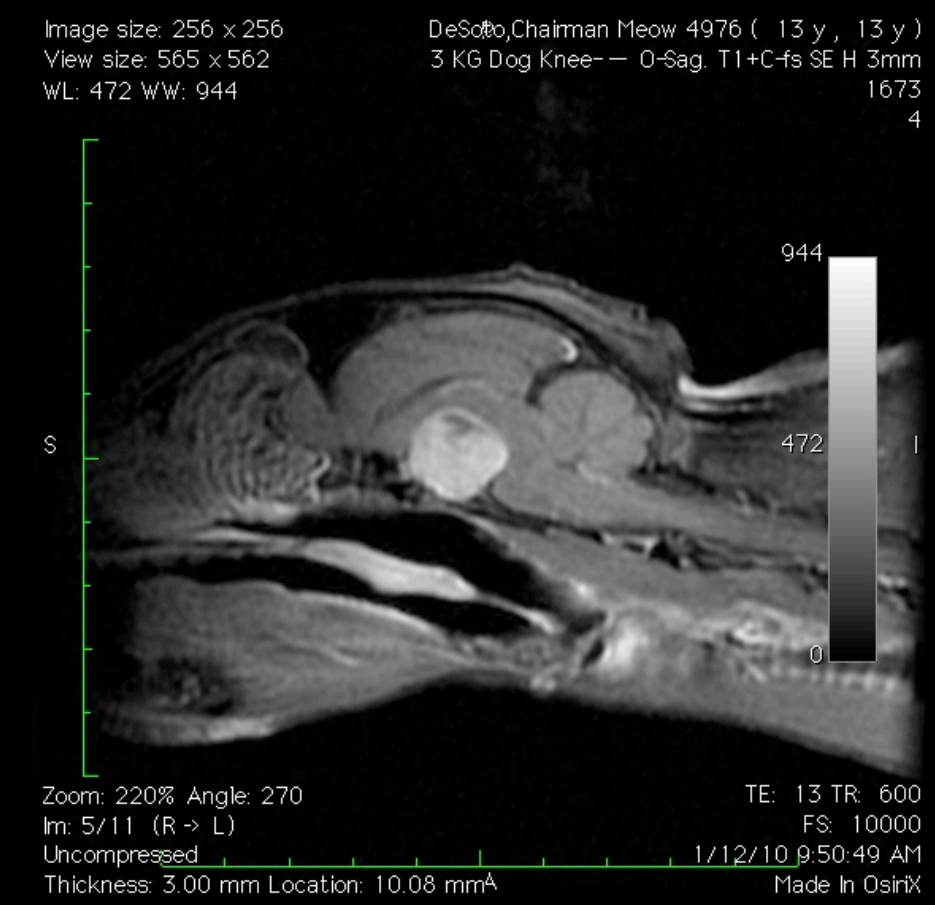
Differentiating PDH from AT

Abdominal US

Abdominal radiographs

Adrenal calcifcation in normal cats

CT or MRI - “silent” lesions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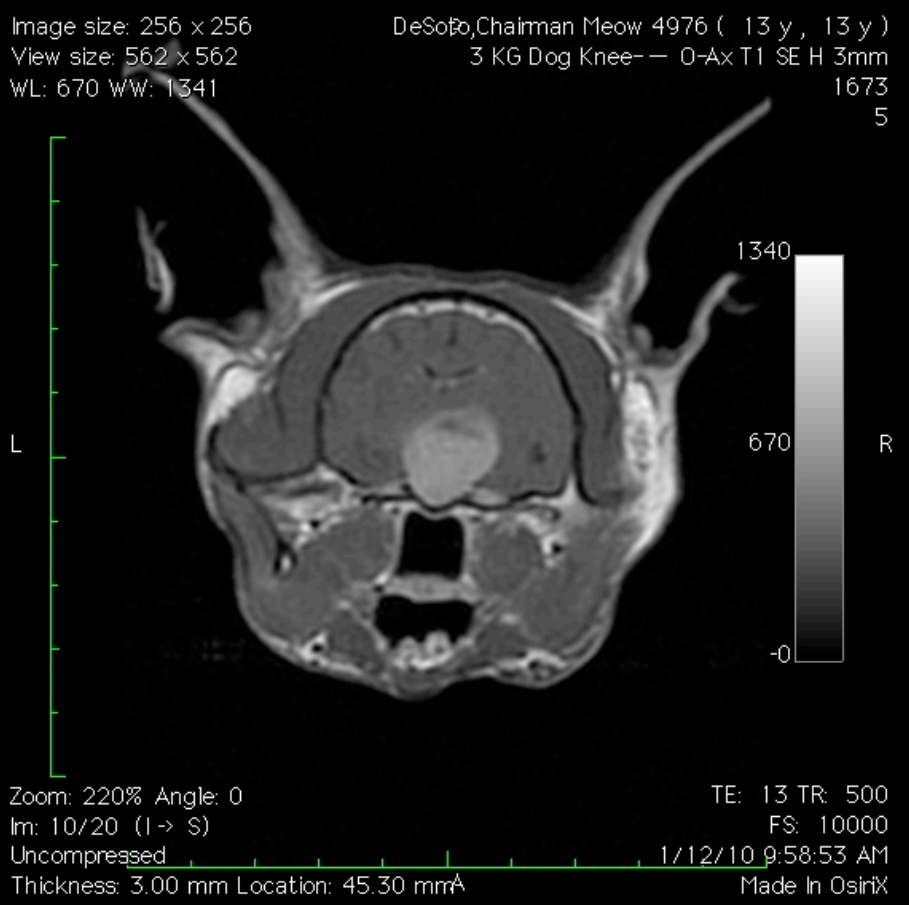
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FELINE HYPERADRENOCORTICISM

Endocrinologic Evaluation

- Differentiating PDH from AT
  - Plasma ACTH
    - Aprotonin tubes
    - Contact laboratory in advance
    - Normal or high = PDH
    - Low values seen in normal cats

FELINE HYPERADRENOCORTICISM

Disease is uncommon

No test is 100 % accurate

Rely on history and PE

Concurrent illness

Dont rely on a single test

Multiple modalities

Endocrinologic

Anatomic

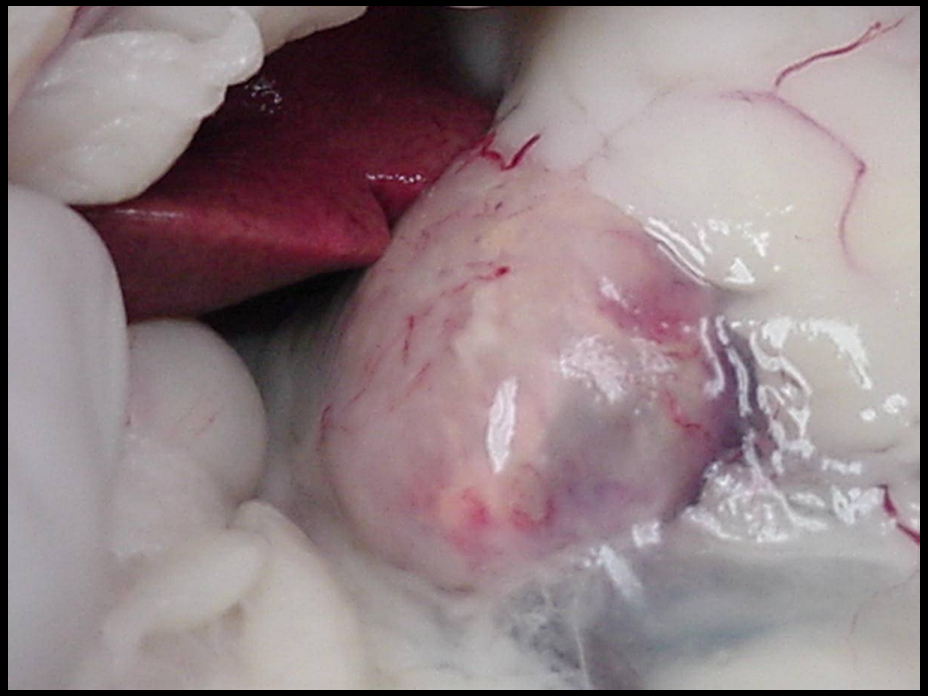
Treatment and prognosis

FELINE HYPERADRENOCORTICISM

Functional Adrenal Neoplasia

- Approximately 24 % (18/74 cases)
- Adenoma = carcinoma
- Treatment is surgical correction
  - Medical therapy prior to surgery
- Prognosis
  - Insufficient data

FELINE HYPERADRENOCORTICISM



FELINE HYPERADRENOCORTICISM

Therapy for Feline PDH

Medical Therapy

- op-DDD (Lysodren)
- Metapyrone (Metopirone)
- Ketoconazole (Nizoral)
- L-Deprenyl (Anipryl)
- Trilostane (Vetoryl; Modrenal)\

FELINE HYPERADRENOCORTICISM

Therapy for Feline PDH

Ketoconazole (Nizoral)

- Oral antifungal agent
- Inhibition of cortisol production
- 15 mg/kg BID
- Side-effects
  - Hepatotoxicity; thrombocytopenia

FELINE HYPERADRENOCORTICISM

Therapy for Feline PDH

Metyrapone (Metopirone)

- Inhibition of cortisol production
- 65 mg/ kg BID to TID
- Monitor with ACTH stim testing
- Questionable long term therapy

FELINE HYPERADRENOCORTICISM

Therapy for Feline PDH

op-DDD (Lysodren)

Similar protocol as in dogs

Supplemental glucocorticoids

Side-effects similar to those in dogs

FELINE HYPERADRENOCORTICISM

Therapy for Feline PDH

L-Deprenyl (Anipryl)

- MAO-B inhibitor
- Safe in cats at 0.5 to 2.0 mg/kg/day
- No data on efficacy in cats with PDH

FELINE HYPERADRENOCORTICISM

We have recently evaluated the safety and efficacy of trilostane therapy (Vetoryl, Dechra Pharmaceuticals) in 15 cats with PDH. Clinical signs (13 of 15 cats) and ACTH stimulation testing results (13 of 15) improved with trilostane therapy. Diabetes mellitus was reported in 9/15 cases. Insulin requirements decreased by 36% within 2 months in 6/9 diabetic cats. Median survival time was 617 days for all cats (range 80-1,278 days).

FELINE HYPERADRENOCORTICISM

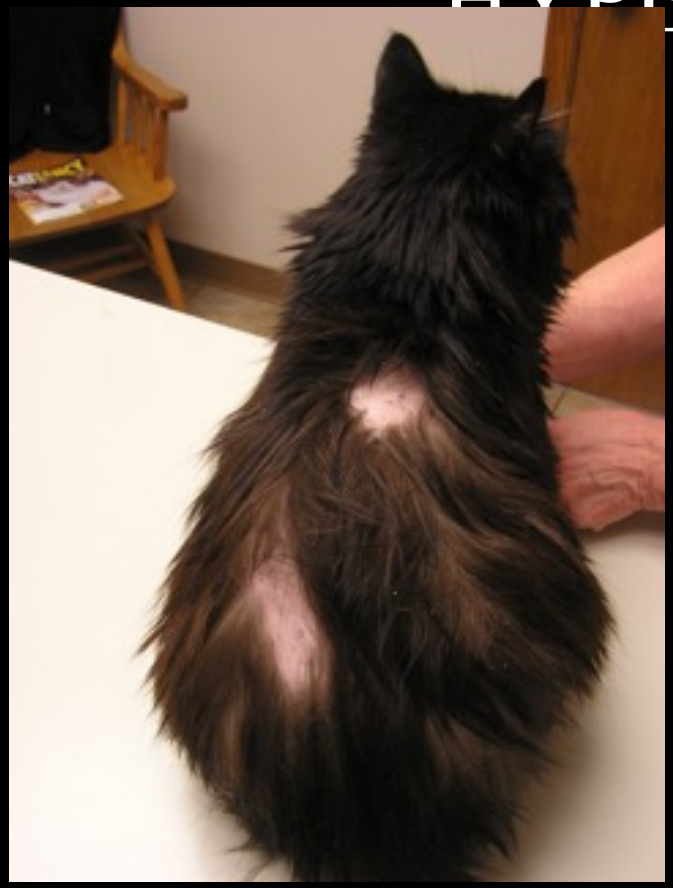
•Complications included weight loss, urinary tract infections, chronic kidney disease, seizures, and recurrent pancreatitis. Hypocortisolemia was documented in 1 case. Cause of death occurred as a result of non-adrenal or non-diabetic illnesses (renal failure, seizures [caused by hypoglycemia or unknown]), or lymphoma.

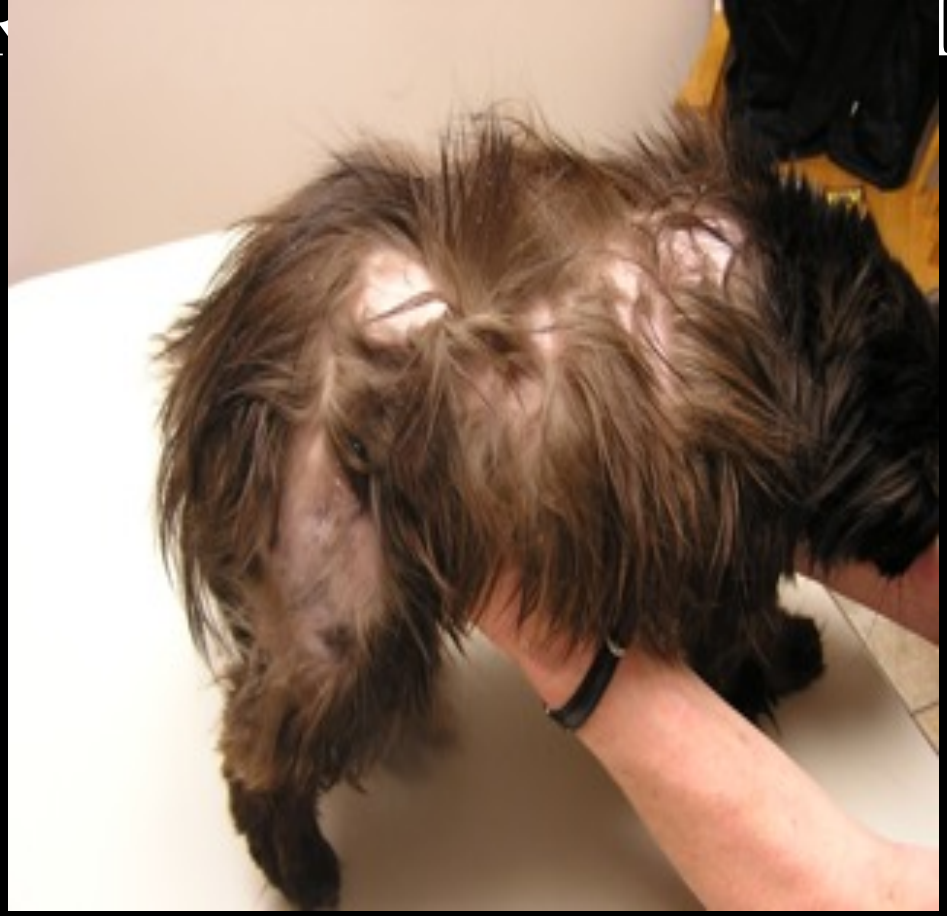
FELINE HYPERADRENOCORTICISM

Trilostane ameliorates clinical signs of HAC in cats, is tolerated well in the long term, and can lead to improved regulation of diabetes. It should be considered first line therapy for cats undergoing medical management of PDH.

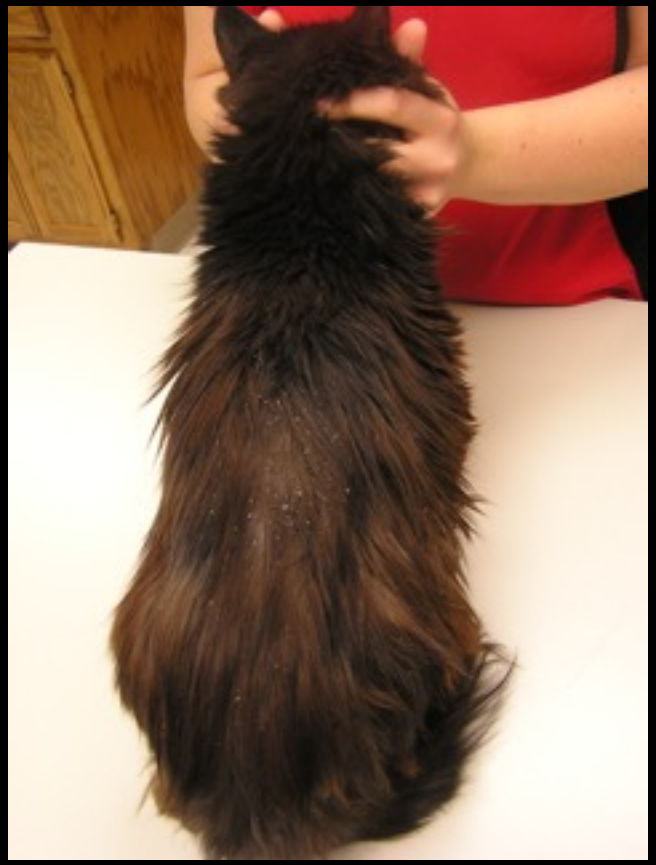
Recommended starting dose is 2-3 mg/kg PO once a day

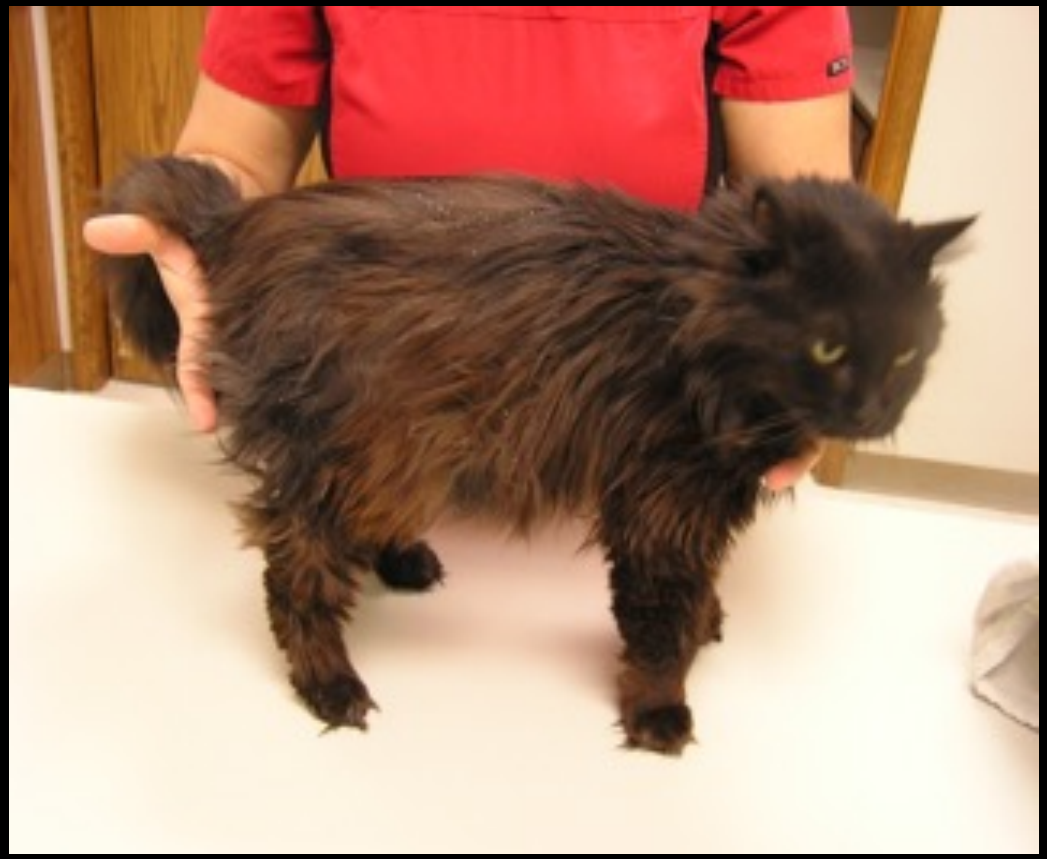
FELINE





FELINE HYPERADRENOCORTICISM



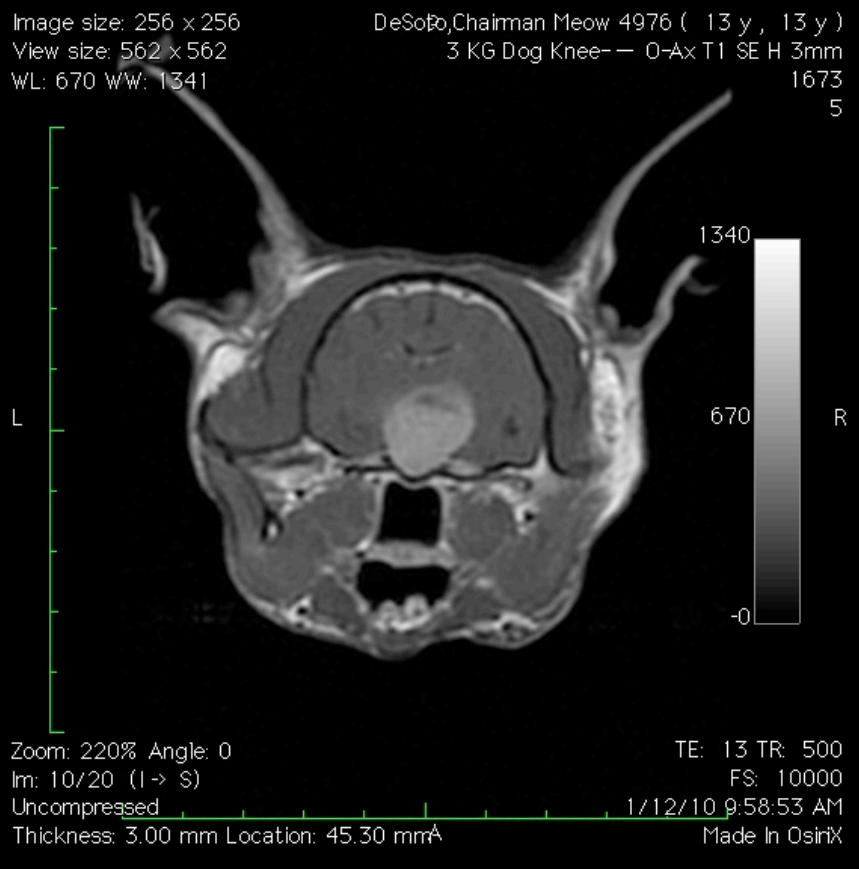


FELINE HYPERADRENOCORTICISM

Therapy for Feline PDH

Surgical Therapy

- Medical therapy prior to surgery
- Bilateral adrenalectomy
  - 3/9 died within 2 months
  - Median survival 5 months
    - Range 1 - 12 + months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FELINE HYPOADRENOCORTICISM

Felt to be rare in the cat

May go unsuspected

Incidence of isolated glucocorticoid deficiency ?

Middle-aged cats

Median: 4 yrs

Range : 1.5 to 14 years

Male = female

Mix breed cats

FELINE HYPOADRENOCORTICISM

Historical Findings

Lethargy

Anorexia

Weight loss

Vomiting

Episodic signs; waxing and waning

Response to fluids; glucocorticoids

FELINE HYPOADRENOCORTICISM

Physical Examination Findings

Depression

Weakness

Mild to severe dehydration

Hypothermia

50 % presented in shock

Duration of signs

Median: 14 days

Range: 5 – 10 days

FELINE HYPOADRENOCORTICISM

Laboratory Abnormalities

Similar to dogs

Hyponatremia

Na/K ratio less than 24

Hyperkalemia

Azotemia

BUN: 31 - 80

Creatinine: 1.6 - 6.0

PO4: 6.1 - 9.1

Hypercalcemia in 1 cat

FELINE HYPOADRENOCORTICISM

Diagnosis

ACTH Stimulation Test

Cortrosyn

5 ug/kg IV

Pre and 60 minute post

FELINE HYPOADRENOCORTICISM

Mineralocorticoid Replacement Therapy

Fludrocortisone acetate (Florinef)

0.1 to 0.2 mg BID

Desoxycorticosterone pivalate (DOCP)

2.2 units/kg IM or SQ

FELINE HYPOADRENOCORTICISM

Glucocorticoid Replacement Therapy

Prednisone

1.25 – 2.5 mg/day

Methyprednisolone acetate

10 mg once a month

Feline Hyperaldosteronism

Incidence ?

Increased awareness

Geriatric disease

Multiple endocrine neoplasia (MEN)

<u>Clinical Signs</u>

Weakness
Lethargy
Cervical ventroflexion
Anorexia

Feline Hyperaldosteronism

About 40 cases of presumed or confirmed feline primary hyperaldosteronism have been reported. Affected cats were presented at a median age of 13 years (mean12.4 years; range5–20 years; n=34). In the remaining cases the age was not specified).

There has been no apparent sex predilection and the breeds have included domestic shorthair, domestic longhair, British shorthair, and Siamese, Burmese, Burmilla, Tonkinese and Persian.

Feline Hyperaldosteronism

Physical Examination

Usually non-specific
Muscle weakness
Look for concurrent
    illness
    Heart disease

    Hyperthyroidism

Laboratory Findings

Hypokalemia
    Can be severe
Sodium usually normal
Increased CPK
Hypertension

Feline Hyperaldosteronism

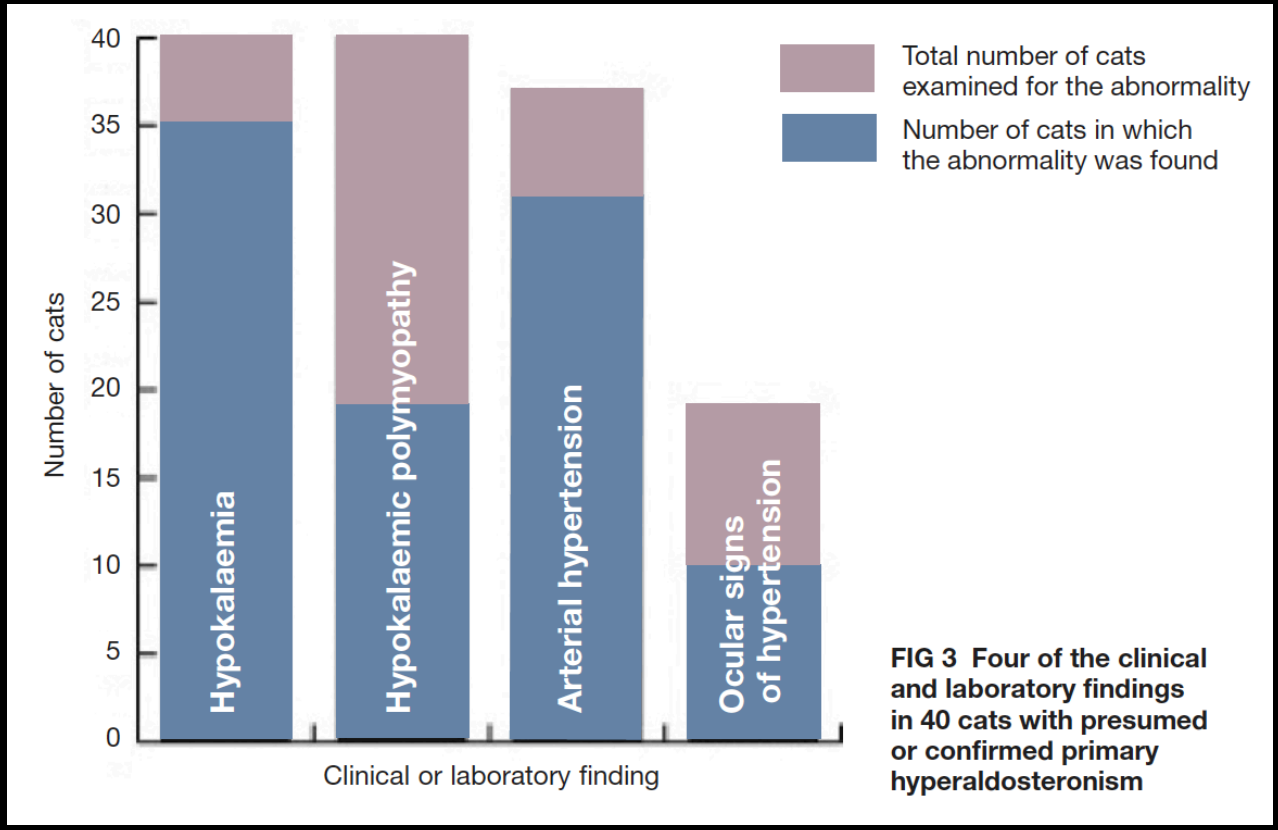
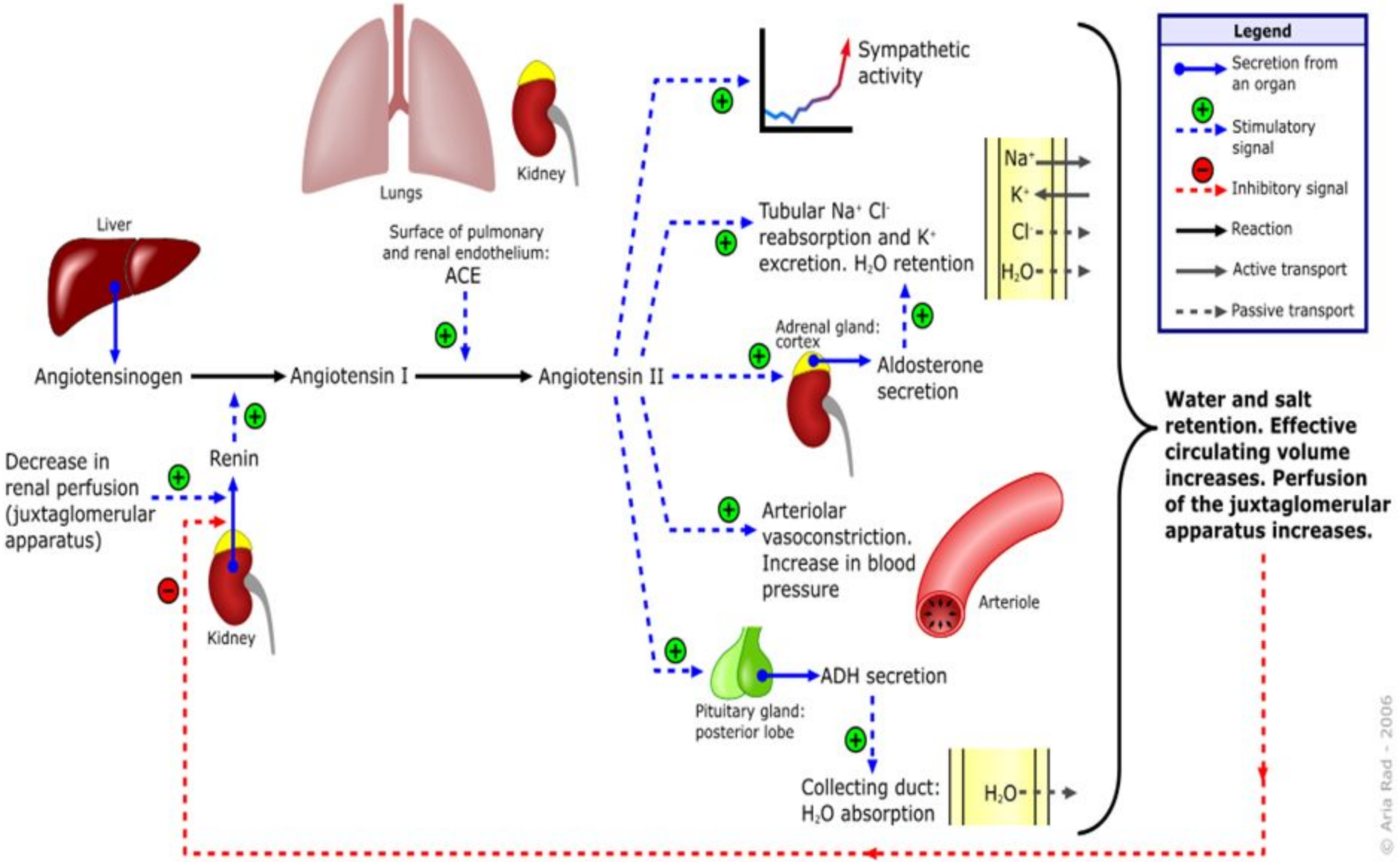


FIG 3 Four of the clinical and laboratory findings in 40 cats with presumed or confirmed primary hyperaldosteronism

Journal of Feline Medicine and Surgery (2011) **13**, 641–650

Renin-Angiotensin-Aldosterone System(RAAS) : systemic effect of Ang II



Feline Hyperaldosteronism

Primary Hyperaldosteronism:
"Conn's syndrome"

Underlying Cause:
- Adenoma
- Carcinoma
- Bilateral adrenal hyperplasia (idiopathic)

High aldosterone, low to normal renin

Subtype of Primary Aldosteronism	Genetic Variant	Encoded Protein	Brief Description
FH Type I	*CYP11B1/CYP11B2* hybrid gene	*CYP11B2*	Ectopic expression in ZF; regulated by ACTH
FH Type II	*CLCN2* mutations	CIC-2	Chloride voltage-gated channel 2
FH Type III	*KCNJ5* mutations	GIRK4	Potassium Voltage-Gated Channel Subfamily J Member 5
FH Type IV	*CACNA*1H mutations	Cav3.2	Calcium Voltage-Gated Channel Subunit α1H

Gene	Encoded Protein and Description	Reference Tissue	Ref.
Upregulated Genes			
CYP11B2	Aldosterone synthase- steroid hydroxylase cytochrome P450 enzyme with 11β-hydroxylase, 18-hydroxylase and 18-oxidase activities	AAC; NLA	[34,39–41]
Calcium Signaling			
VSNL1	Visinin-like 1, calcium sensor protein of visinin/recoverin subfamily	NLA	[59]
CALN1	Calneuron 1, calcium-binding protein with high similarity to calmodulin family	NLA	[41,67]
CALM2	Calmodulin 2, calcium-binding protein of calmodulin family.	Adjacent ZG	[42]
PCP4	Purkinje cell protein 4, regulates calmodulin activity by modulating calcium binding by calmodulin	NFA	[68]
Nuclear receptor Transcription Factors			
NR4A1	Nuclear receptor subfamily 4 group A member 1; steroid-thyroid hormone-retinoid receptor superfamily.	WT-*KCNJ5*-APAs	[56]
NR4A2	Nuclear receptor subfamily 4 group A member 2; steroid-thyroid hormone-retinoid receptor superfamily.	WT-*KCNJ5*-APAs	[56]
NR5A1	Nuclear receptor subfamily 5 group A member 1 (SF1); transcriptional activator of sex determination.	AAC	[39]
NR0B1	Nuclear receptor subfamily 0 group B member 1 (DAX1); functions in proper formation of adult adrenal gland formation.	AAC	[39]
G-protein-coupled Receptors			
LHCGR	Luteinizing hormone/choriogonadotropin receptor	NLA	[60]
GNRHR	Gonadotropin releasing hormone receptor	NLA	[60]
HTR4	5-hydroxytryptamine receptor 4	NLA; NFA	[60,64]
PTGER1	Prostaglandin E receptor 1	NFA	[64]
MC2R	Melanocortin 2 receptor	NLA	[60]
AGTR1	Angiotensin II receptor type I	NLA	[60]
Others			
NEFM	Medium neurofilament protein- biomarker of neuronal damage	*KCNJ5*-mut APAs; ZF-like APAs	[62,63]
TDGF1	Teratocarcinoma-derived growth factor 1- signaling protein that functions in development and tumor growth	NLA	[41]
NPNT	Nephronectin, a secreted matrix protein	NLA	[72]
Downregulated Genes			
GSTA1	Glutathione S-transferase alpha 1- member of a family of enzymes that protect cells from reactive oxygen species	WT-*KCNJ5*-APAs; NLA	[69]
SFPR2	Secreted frizzled related protein 2- agonist of Wnt signaling	NLA	[72]

AAC: adjacent adrenal cortex; APAs: aldosterone-producing adenomas; *KCNJ5*-mut APAs: APAs with *KCNJ5* mutations; NFA: non-functioning adrenocortical adenomas; NLA: normal adrenals; WT-*KCNJ5* APAs: APAs with wild type *KCNJ5* gene; ZF: *zona fasciculata*; ZG: *zona glomerulosa*.

Feline Hyperaldosteronism

Secondary Hyperaldosteronism:

Characterized by:

- High aldosterone, normal to high renin

Caused by:

- Congestive heart failure
- Renal failure
- GI disease
- Hepatic disorders

Feline Hyperaldosteronism

Leads to:

1) Increased potassium excretion in urine
2) Increased sodium reabsorption
3) Increased renal tubular bicarbonate transport/loss of hydrogen ions in urine

Clinical Signs:

Profound muscle weakness

Blindness (retinal detachment secondary to hypertension)

Feline Hyperaldosteronism

Diagnosis:

Plasma aldosterone levels (Michigan State)
6x normal

Plasma renin activity
Low to normal

Diagnostic imaging (AUS, CT)

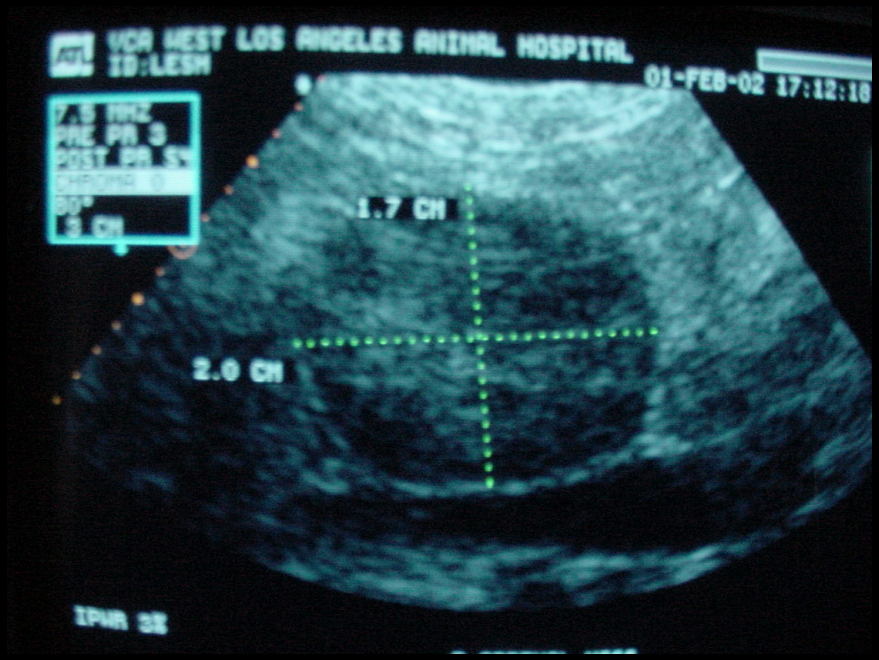
Evaluation of the Oral Fludrocortisone Suppression Test for Diagnosing Primary Hyperaldosteronism in Cats. J Vet Intern Med 2013; 27:1493–1499

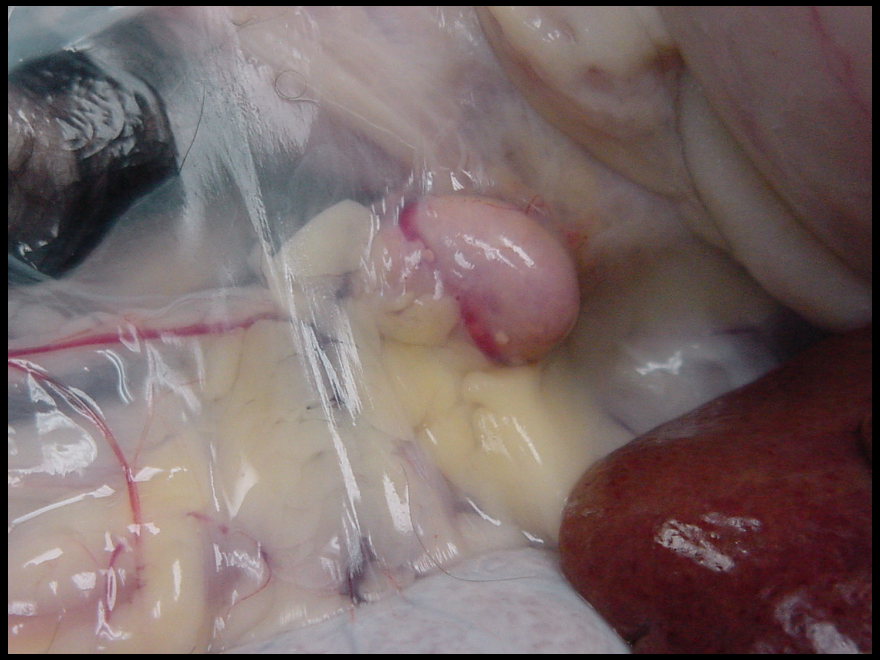
The urinary aldosterone-to-creatinine ratio (UACR) was determined in morning urine before, during, and after 4 days of oral fludrocortisone administration in a dose of 0.05 mg/kg q12h. Arterial blood pressure and plasma potassium concentration were measured before and after fludrocortisone administration.

Results: A basal UACR above 46.5, the upper limit of the reference range, was found in 3 cats with PHA. All PHA cats had basal UACRs >7.5. In all non-PHA cats with a basal UACR >7.5 fludrocortisone administration induced >50% suppression. In contrast, fludrocortisone administration resulted in <50% suppression in 6 of the 9 PHA cats. arterial hypertension.

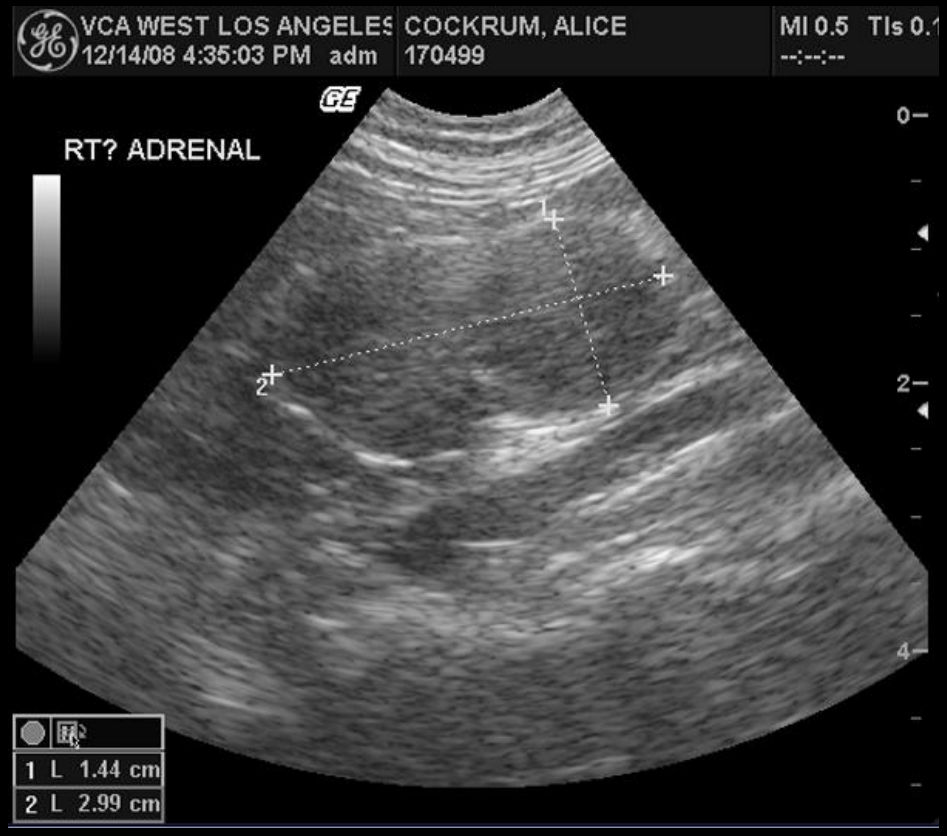
Conclusions and Clinical Importance: Measuring the UACR before and after 4 days of administering fludrocortisone is a practical method of confirming most cases of PHA in cats, and of substantiating the absence of PHA in cats having an ARR within the reference range.

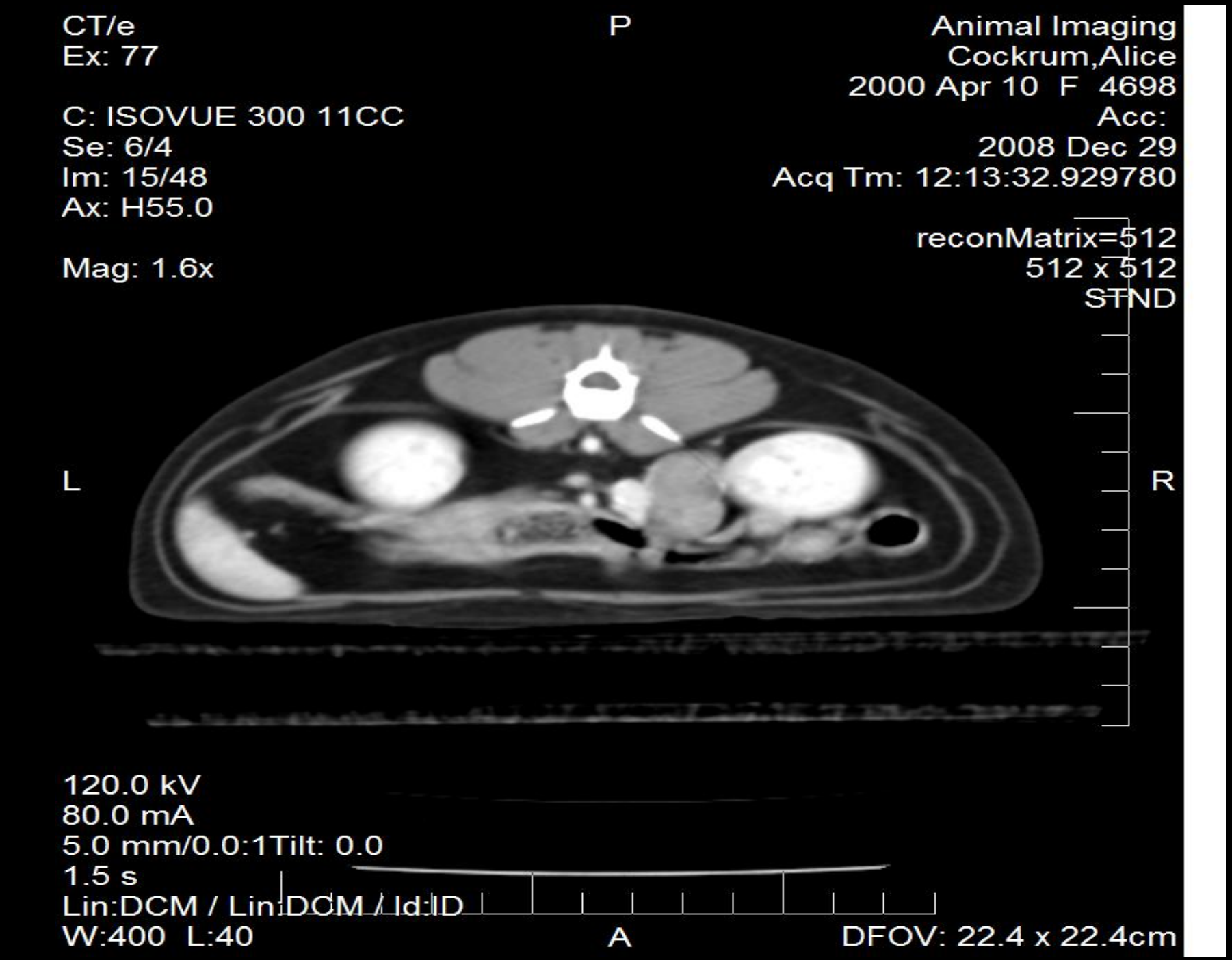
Feline Hyperaldosteronism





Feline Hyperaldosteronism

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Feline Hyperaldosteronism

Treatment

Unilateral adenoma or adenocarcinoma without evidence of metastasis → adrenalectomy

Medical management

- Spironolactone 2-4 mg/kg/day po
- Potassium supplementation
- +/- Amlodipine for hypertension

Feline Hyperaldosteronism

Primary (non-tumorous) hyperaldosteronism

- Progressive renal disease
- Normal abdominal US vs mild adrenomegaly
- Hypertension
- Hypokalemia
- Elevated aldosterone levels
- Suppressed renin levels

Feline Hyperaldosteronism

Non-tumorous hyperaldosteronism (hyperplasia)

Renin-angiotensin-aldosterone system implicated in progressive renal sclerosis

Aldosterone promotes thrombosis and fibrosis

Systemic arterial hypertension and fibroproliferative destruction of kidney

Feline Hyperaldosteronism

Hypokalemic paroxysmal flaccid paresis, retinal detachment with hemorrhages.

Normal BUN and creatinine but later increased

8 cats azotemic at first examination

Adrenal hyperplasia based on histopathology of 3 of the cats. Histopathology of cats at necropsy – interstitial fibrosis, glomerular sclerosis

Incomplete renin suppression

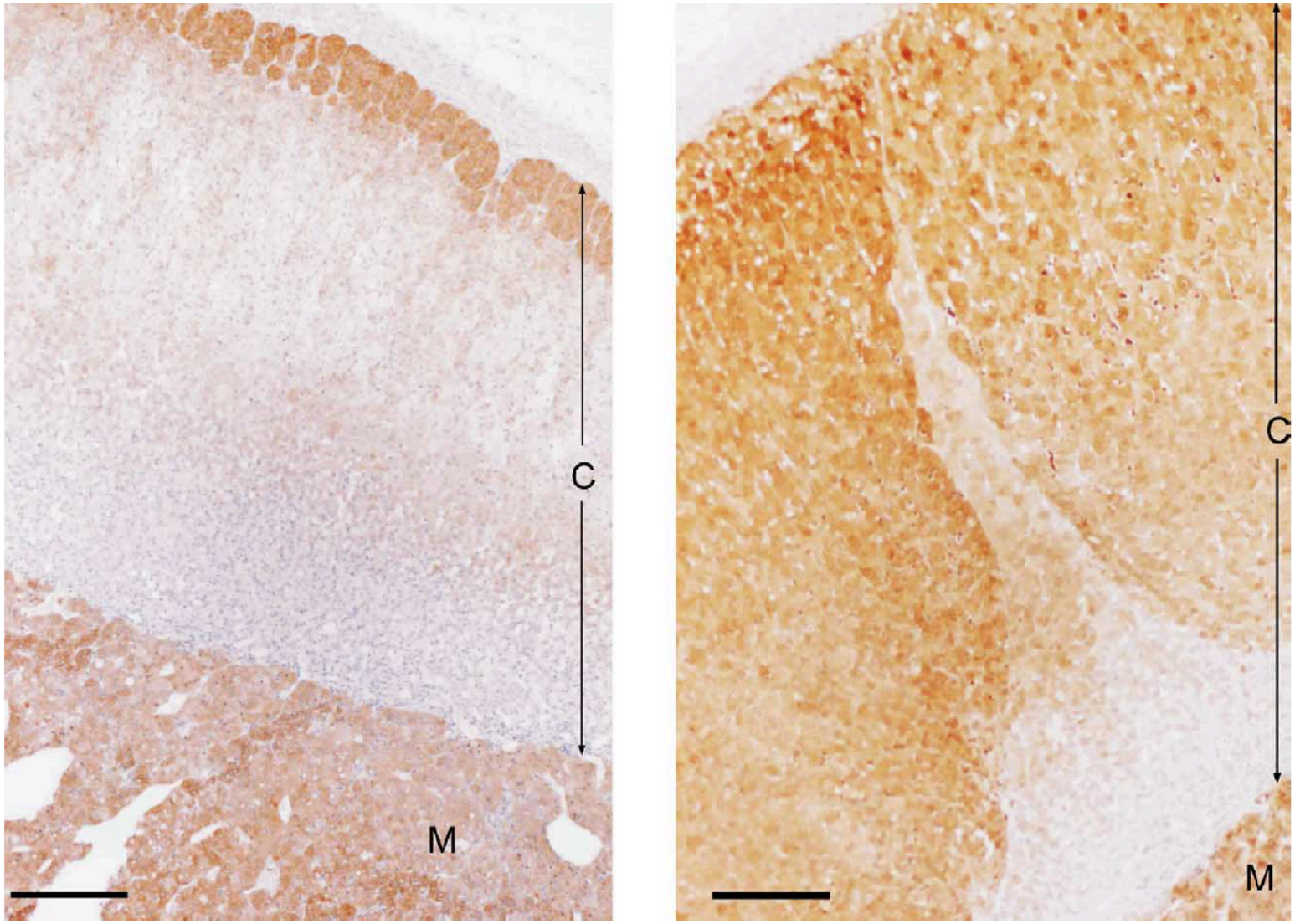
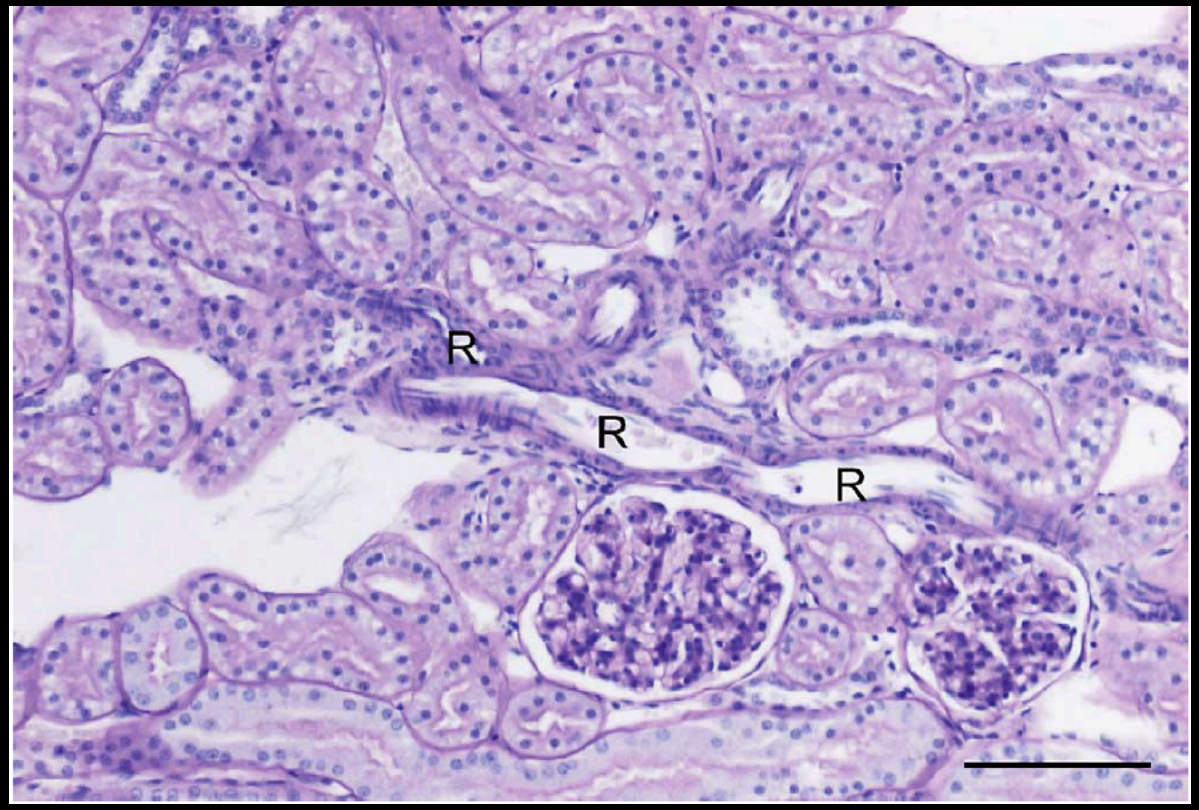


Fig. 4. Two adrenal glands stained with neuron-specific enolase (NSE, bar = 200 μm). In the healthy control cat (left), the staining of the cortex (C) is confined to the zona glomerulosa with some vague staining of the outer parts of the zona fasciculata. In the cat 2 with primary hyperaldosteronism (right), the cortex mainly consists of multiple hyperplastic nodules, staining positively for NSE. In both sections, there is similar staining of the adrenal medulla (M). Bar = 200 μm.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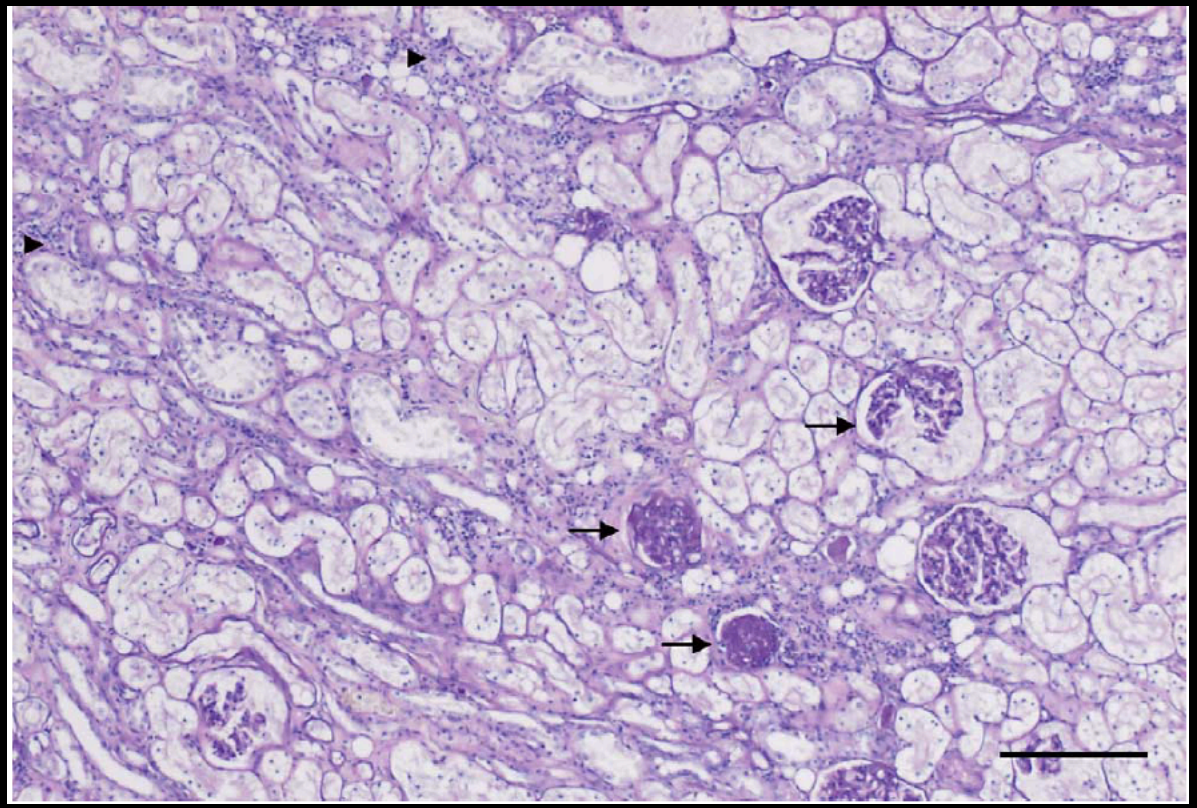

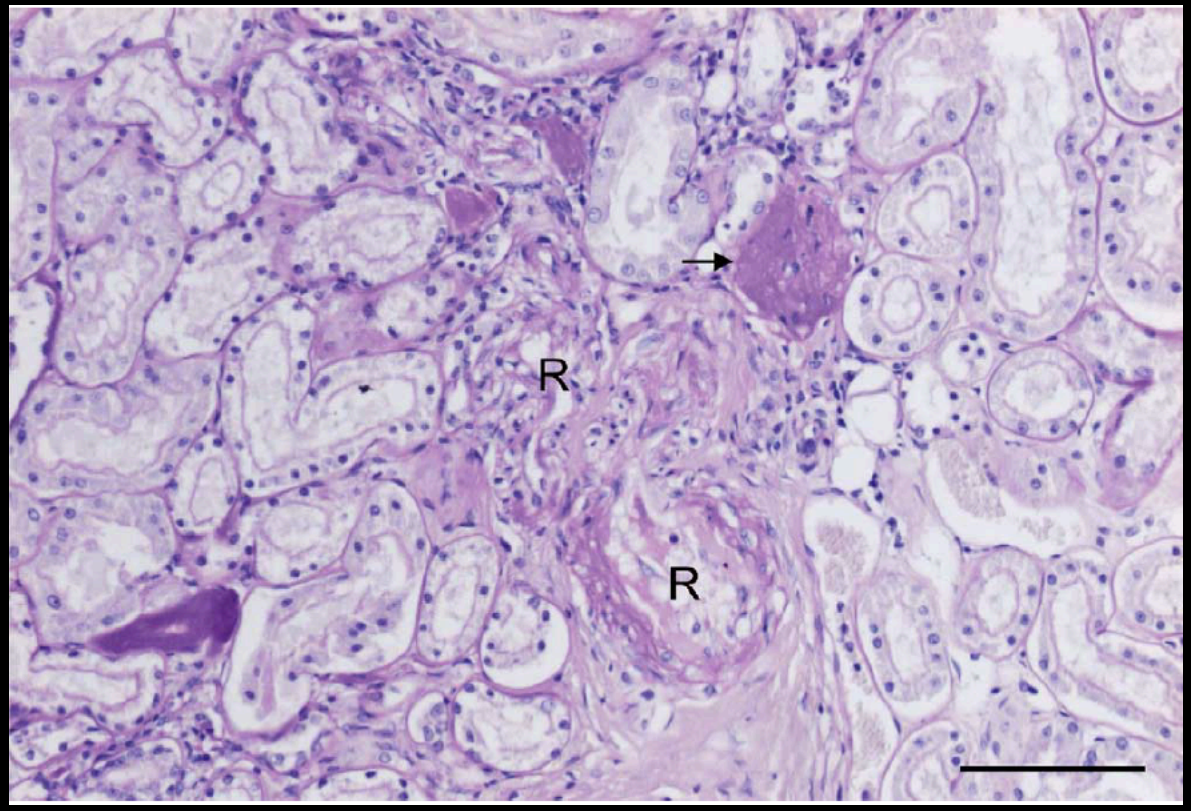
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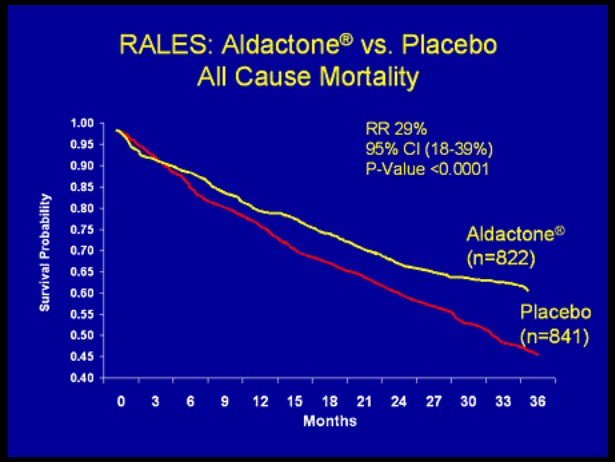
Feline Hyperaldosteronism

Incidence likely much more common than reported

Screen older cats with hypokalemia and/or hypertension

Studies on spironolactone in cats with hyperaldosteronism to prevent ongoing renal injury


RALES: Aldactone® vs. Placebo
All Cause Mortality
RR 29%
95% CI (18-39%)
P-Value <0.0001
Aldactone®
(n=822)
Placebo
(n=841)
Survival Probability
1.00
0.95
0.90
0.85
0.80
0.75
0.70
0.65
0.60
0.55
0.50
0.45
0.40
0 3 6 9 12 15 18 21 24 27 30 33 36
Months

FELINE PRIMARY HYPERALDOSTERONISM

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PRIMARY ALDOSTERONISM, A NEW CLINICAL ENTITY * †

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ALDOSTERONE, the newly discovered normal adrenal secretory product,[1-6] has attracted the attention of a great many clinical investigators because of its apparent rôle in the pathogenesis of a number of clinical disorders. This extremely potent sodium-retaining corticoid has been found to be present in excessive amounts in the urine of edematous nephrotics,[7,8] cardiacs with congestive failure,[9,10] patients with decompensated hepatic cirrhosis [11-13] and women with eclampsia.[14-16] All of these conditions manifest marked edema, but it is obvious that the *primary* difficulty in each condition is *not* due to increased activity of a sodium-retaining steroid. It seems reasonable to assume that in the course of the development of each of these conditions a metabolic event occurs which is common to them and which triggers the production of excessive quantities of aldosterone. We would therefore classify such conditions as being associated with *secondary aldosteronism*.

Primary aldosteronism, by which we mean that the disease originates in the adrenal gland, is *not* associated with edema, and in its pure state manifests itself in the form of an interesting complex of symptoms and a fascinating disturbance of electrolyte metabolism.

The data to be presented have been obtained in the course of an extensive metabolic balance study upon a *single patient*. The investigation extends from April, 1954, to April, 1955, and includes 227 days of rigid metabolic control. It appears to establish the existence of a new clinical syndrome, which we have named "primary aldosteronism." [17,18] The data afford a reasonable explanation for the abnormality of electrolyte metabolism which

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