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INTRODUCTION
This session will include case discussions focussing on challenging cases in internal medicine. Among other topics, diagnosis and treatment of adrenal tumors will be reviewed.

ADRENAL TUMORS
The adrenal gland consists of two functional units, the cortex and the medulla. The cortex secretes steroid hormones like glucocorticoids, mineralocorticoids and androgens, while the medulla primarily produces catecholamines.

In dogs and cats tumors of both the cortex and the medulla have been described. Adrenal tumors (ATs) can be small or large, unilateral or bilateral, benign or malignant, encapsulated or invasive, functional or non-functional, primary or metastatic. Differentials for ATs are: functional adrenocortical adenoma or carcinoma, pheochromocytoma, metastatic neoplasia or incidentaloma. Importantly, ATs can look similar to macronodular hyperplasia (due to pituitary dependent hyperadrenocorticism), hematomas, granulomas or cysts within the adrenal glands.

Adrenocortical tumors secreting glucocorticoids
Adrenocortical tumors producing glucocorticoids are the most frequent ATs. About 15% of the naturally occurring canine hyperadrenocorticism (HAC) cases are caused by ATs. In most cases the tumor is unilateral, the two glands being affected about equally, but bilateral tumors also occur. In dogs, 50% of the ATs causing HAC are benign and 50% are malignant. Clinical signs represent glucocorticoid excess and include polyuria, polydipsia, polyphagia, abdominal enlargement, hepatomegaly, cutaneous changes (alopecia, cutaneous atrophy, calcinosis cutis, hyperpigmentation), muscle weakness, exercise intolerance, excessive panting, truncal obesity, lethargy, immunosuppression, insulin resistance, and decreased sexual function. There may also be mass-related symptoms and signs caused by metastases. Rare complications of ATs are vascular obstruction by tumor thrombi of the caudal vena cava and hemo(retro)peritoneum secondary to rupture of an adrenal tumor.

The diagnosis of HAC should be based on appropriate clinical signs, followed by supporting laboratory abnormalities (e.g. high serum alkaline phosphatase, high cholesterol, increased urinary protein:creatinine ratio, increased platelet count) and confirmed by specific screening tests (low dose dexamethasone suppression test, urine cortisol:creatinine ratio). To distinguish AT from the pituitary form of HAC, endogenous ACTH can be measured and the adrenals can be visualized by ultrasonography and/or computer tomography. Low and high dose dexamethasone suppression test can be helpful in differentiating between the adrenal or pituitary forms of HAC, but are sometimes misleading. Importantly, if a unilateral AT is the reason for HAC, the contralateral adrenal gland should be decreased in size. If this is not the case, bilateral adrenal neoplasia or a combination of adrenal and pituitary HAC or a combination of AT and pheochromocytoma must be suspected.

Possible treatment options for ATs secreting glucocorticoids involve surgical resection of the tumor or medical therapy. Good surgical candidates are dogs in which no metastases are identified and in which the tumor seems resectable. Successful removal of the affected adrenal will result in complete recovery without the need for lifelong medication. After unilateral adrenalectomy, normal adrenal gland tissue will be atrophic, which makes the supplementation of glucocorticoids and sometimes mineralocorticoids necessary in the peri- and postoperative period. As soon as the tumor is identified during surgery, dexamethasone (0.1 mg/kg) is administered as a CRI over 6 hours. Thereafter, parenteral glucocorticoids should be continued for 48-72 hours until the patient is alert and eating. Oral supplementation with prednisolone can then replace parenteral therapy and is slowly discontinued over 3-6 months. Supplementation with mineralocorticoids is necessary if moderate hyponatremia (< 135 mmol/L) and hyperkalemia (> 6.5 mmol/L) develop after surgery.

Dogs with inoperable tumors, metastatic disease or with disease recurrence should be treated medically. Medical therapy can either be adrenocorticolytic (e.g. mitotane) or adrenocorticostatic (e.g. trilostane). The advantage of using adrenocorticolytic drugs is that possible tumor metastases are
destroyed. However, often high doses of mitotane are necessary to control clinical signs. Trilostane, a competitive inhibitor of steroid synthesis, has recently been shown to be safe and effective as palliative treatment of adrenal HAC, even in the presence of metastases. The aim of trilostane however, is to control the effects of excessive glucocorticoid secretion, the drug does not have an effect on tumor growth or metastases.

**Adrenocortical tumors secreting steroid hormones other than cortisol**

Increased secretion of progesterone or other sex hormones (estradiol, testosterone, androstendione) from ATs has been reported in cats and dogs, but seems rare in both species. In dogs and cats with clinical signs of HAC, presence of an adrenal mass, but inconclusive screening test results, the presence of increased concentrations of other adrenal steroids should be investigated. Additionally, a sex hormone producing tumor should be suspected in neutered animals with sudden onset of behavioural sexual changes (e.g. aggression, urine spaying).

Adrenolecctomy is the treatment of choice and usually results in resolution of clinical signs.

**Adrenocortical tumors secreting aldosterone**

Primary hyperaldosteronism due to an AT is rare in dogs. Both, benign and malignant adrenocortical tumors producing aldosterone have been reported. The described cases presented with episodic weakness, polydipsia, polyuria and an adrenal mass. In all cases hypokalemia, high aldosterone concentrations, and mild hypertension were documented.

Feline hyperaldosteronism may be caused by a unilateral aldosterone-secreting tumor (carcinoma or adenoma) or bilateral hyperplasia. Cats present with clinical signs resulting from systemic hypertension (e.g. intraocular hemorrhage) or with signs of polymyopathy (e.g. ventroflexion, muscle weakness) resulting from hypokalemia. Cats are usually older with a mean age of about 10 years. To definitively diagnose primary hyperaldosteronism, the documentation of an inappropriately increased aldosterone concentration in combination with a low plasma renin activity is necessary.5

Unilateral adrenalectomy is the treatment of choice for confirmed unilateral primary hyperaldosteronism. If surgery is not an option, medical treatment with the mineralocorticoid-receptor antagonist spironolactone (2mg/kg q12h) and oral supplementation with potassium gluconate (0.5mmol/kg q12h) is possible. Persistent arterial hypertension can be treated with the calcium blocker amlodipine (starting dose: 1/8 - 1/4 of a 5mg tablet/cat q24h).5

**Adrenal medullary tumors: Pheochromocytoma**

Pheochromocytomas are functional endocrine tumors that most commonly arise from the adrenal medulla and secrete catecholamines as their major secretory product. Adrenal pheochromocytomas are diagnosed uncommonly in dogs and only rarely in cats and are often incidental findings at necropsy. Pheochromocytoma should be considered a malignant tumor which commonly invades into surrounding vessels and metastasises to liver, lung, regional lymph nodes, spleen, bone and central nervous system. Pheochromocytomas are identified predominantly in older dogs (mean age 11 years). Clinical signs develop as a result of excessive secretion of catecholamines or as a result of the space-occupying nature of the tumor and its metastatic lesions. Signs suggestive of functional activity of the tumor include weakness, lethargy, collapse, vomiting, panting, dyspnea, tachypnea, seizures, tachyarrhythmias, abdominal pain, fever, and cardiac arrest.

A diagnosis of pheochromocytoma requires a high index of suspicion. No consistent abnormalities in the CBC, serum biochemical panel or urinalysis are seen. Identification of an adrenal mass on abdominal ultrasound in a patient with consistent clinical signs and possibly hypertension is highly suspicious. However, normal adrenal glands do not rule out pheochromocytoma and catecholamine secretion by the tumor, and thus systemic hypertension tends to be episodic. In humans, diagnosis of pheochromocytoma is based mainly on biochemical detection of excessive production of the secretory products of the tumor. Widely used tests include measurement of the concentration of catecholamines and their metabolites metanephrine and normetanephrine in 24-hour-urine samples, or metanephrines in plasma. It was recently shown that dogs with pheochromocytomas had significantly higher urinary epinephrine, norepinephrine and normetanephrine to creatinine ratios compared with healthy dogs.6 The normetanephrine:creatinine ratio had the highest discriminating power.6 Whether other diseases (e.g. HAC) cause an increase in the concentration of urine catecholamines and metanephrines is now under investigation.
The most effective treatment for pheochromocytoma is surgical resection. Medical management to reverse the effects of excessive adrenergic stimulation should be attempted prior to surgical resection. Alpha-adrenergic blockade (phenoxybenzamine: starting dose 0.25 mg/kg PO q12 hours) should be started two weeks before surgery to control hypertension and minimize the risk of a hypertensive crisis during surgery. Medical management may also be an option in dogs with recurrence of pheochromocytoma after surgery or in dogs in which tumor resection was incomplete. As above, the starting dose of phenoxybenzamine is 0.25 mg/kg q12h, which is gradually increased until clinical signs are controlled or hypotension occurs.

Incidentaloma

In human medicine, an adrenal incidentaloma is defined as an adrenal mass, generally 1 cm or more in diameter that is discovered serendipitously during a radiologic examination performed for indications other than an evaluation for adrenal disease. Cases in which a symptomatic adrenal-dependent syndrome is “missed” because of an insufficient history or physical examination, are excluded. The majority of adrenal incidentalomas in humans are clinically nonhypersecreting, benign adrenocortical adenomas.

In veterinary medicine, the widespread use of abdominal ultrasonography has resulted in more frequent identification of incidentalomas. In case of an incidentally discovered adrenal mass it is critical to carefully review the history for signs that may support either HAC, pheochromocytoma or hyperaldosteronism. If owners describe typical signs, appropriate diagnostic tests are initiated as outlined above. In cases with no obvious clinical signs and a small (< 2 cm), homogeneous adrenal mass, the adrenal tumor is followed by ultrasonography every 2-4 months. If no clinical signs are obvious, but the adrenal tumor is large (> 2 cm) and inhomogeneous, further diagnostic work-up and adrenalectomy is recommended.

REFERENCES