

Weekend with the Specialists

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Newport Beach, California

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TiffanyBlocker,DVM, DACVO

Eye Care For Animals, Tustin CA

Complicated Corneal Conditions

Introduction:

A sound knowledge of anatomy and function of the eye and its adnexa is important in understanding complex issues involving structures of the eye. The cornea is an avascular but metabolically active organ which functions to transmit light into the eye for further visual processing. The ability to maintain a clear cornea is dependent on not only proper corneal metabolism but on surrounding structures to function and protect this delicate but highly important structure.

Eyelid structure and function affects corneal health. Eyelids spread tear film and stabilize it by their many meibomian glands which produce the outer oily layer of the triple layer precorneal tear film. In addition proper eyelid function allows adequate spreading of the tear film over the ocular surface, provides protection from exposure, and reflexive action to protect the ocular surface from injury. Improper eyelid function can lead to insufficient spreading of the tear film resulting in tear film evaporation and corneal injury. Examples of disorders leading to evaporative tear film disorders include lagophthalmos, ectropion, facial nerve paralysis, etc.

Tear film and its constituents are essential in protecting the ocular surface. This triple layer consisting of an inner mucin layer derived from conjunctival goblet cells and corneal epithelial cell glycocalyx; the middle aqueous layer derived from lacrimal and third eyelid glands; and the oily layer layer as mentioned above from meibomian glands. This triple layer tear film not only flushes away debris, provides moisture, but is the major player in ocular surface immune defense. Without it the ocular surface becomes opaque, is prone to injury and invasion from environmental and local pathogens.

The cornea is comprised of three main layers but with other important constituents. This delicate structure still functions in a highly metabolic fashion but at the same time retaining relative dehydrated status in order to remain a clear refractive organ for light assembly into the eye. The outer epithelial layer is intimately associated with the tear film; the middle stromal layer with specially arranged collagen fibrils and very few keratocyte cells, and the inner endothelium (the

critical single layer of highly metabolically active cells mostly responsible for maintaining corneal deturgence). Injury or disease affecting any of these layers can result in permanent scarring and decreased vision. Diseases left ongoing without treatment will likely lead to permanent blindness.

The clinical relevance is that accurate identification of a problem involving the cornea is essential and will ultimately guide and direct treatment of the problem. The quicker the corneal injury can be fixed or the corneal disease or associated condition managed the better the outcome for corneal clarity and function. Keep in mind many of the discussed corneal conditions need long term therapy in order to maintain corneal health.

Corneal edema is characterized by swelling, thickening, and a blue haze to the cornea. This is incited by either damaged epithelium or endothelium. The damage may be temporary or permanent. Loss of the protective epithelium due to an ulcer or injury will result in imbibition of the tears into the stroma resulting in edema. In contrast, endothelial injury due to intraocular inflammation, elevated IOP, or primary endotheliopathy will also result in corneal edema because the pumping mechanism has been disrupted. This can be temporary as in elevated IOP or uveitis or can be permanent if the above are left untreated or with continued degeneration of the endothelial cells.

Neovascularization of the cornea is always abnormal. There is always a cause. The pattern and depth of neovascularization can signify where and what the inciting cause is. A patient with dorsal corneal neovascularization without an ulcer may be rubbing, may have eyelid disease or may have aberrant cilia (ectopic cilia, distichia, trichiasis). Deep vessels signify deep disease. Stromal ulcerative keratitis or uveitis are examples. Remember new vessels advance from the limbus and do so at a slow rate of approximately 1 mm per day. Once the underlying cause has been removed vessels regress often leaving ghost vessels which are easily revascularized with reinitiation of disease.

Corneal fibrosis is the end result of prior disease or injury. Degree of fibrosis will vary with degree of injury, longevity of disease. Although fibrosis is a natural consequence of corneal injury it reduces corneal clarity and ultimately vision and therefore careful tailoring of medications or selection of surgeries are essential to try and reduce the amount of fibrosis in our patients visual field. Judicious use of topical steroidal anti-inflammatories can reduce the formation and degree of fibrosis. In general cats corneas seem to recover from disease with less scar tissue than dogs.

Corneal pigmentation is common in ophthalmology patients and brachycephalic dog breeds make up the majority of patients seen for this condition. Other conditions associated with corneal melanosis and pigmentation include chronic superficial keratitis and keratoconjunctivitis sicca. The truth is not all patients who present with corneal pigmentation have KCS. So what causes pigmentation? In essence, anything leading to chronic irritation can result in corneal pigmentation. Pigment cells congregate at the limbus and surrounding conjunctiva and those breeds with heavier pigment in these areas seem to pigment more readily. Brachycephalic conformation plays a big part in formation of corneal pigment. These features include nasal trichiasis, medial canthal trichiasis, entropion, prominent globes, shallow orbits, lagophthalmos, decreased corneal sensitivity. The above features lead to evaporative tear film disorder and reduced overall protection of the corneal surface due to exposure resulting in chronically irritated corneal surface and laying down of not only pigment but neovascularization and fibrosis in severe cases. Therapy is best initiated before pigment progresses and is aimed at improving globe coverage with surgeries such as permanent canthoplasties, nasal fold resection, improving tear film and protecting the ocular surface with lubricants. Keratectomies and irradiation can be helpful in reducing the pigment but is often replaced with scar tissue and the long term benefit is only temporary.

Corneal ulcers are easily diagnosed with proper equipment, thorough evaluation of the ENTIRE corneal surface and fluorescein dye. However, the cause of the ulcer may not be as easily discerned. This may lead to recurrence of an ulcer, refractory ulcer, or worsening of the ulcer such that perforation of the cornea occurs. Tailoring your history and examination technique can provide insight into the cause of the ulcer. Location of the ulcer, degree of surrounding corneal edema, fibrosis (if any), neovascularization can give clues as to the cause of the ulcer as well as the longevity of the ulcer. Critical evaluation of the surrounding adnexa for foreign bodies, aberrant cilia, as well as thorough diagnostics including STT1 and IOP can assist in finding the cause of the ulcer. Superficial ulcers should heal in 7 days. Assuming the patient is wearing a protective e-collar and the client is being diligent with medications, an ulcer that has not healed in 7 days is considered non-healing. Re-examination for causes for the ulcer that may have been overlooked before is crucial. Not all patients with non-healing ulcers have SCCED. This is a middle-aged to older dog condition (aka Boxer ulcer) affecting the cornea and creating spontaneous ulcers that are always superficial with a characteristic lipping of the epithelium. Surgical keratotomy is almost always curative in cases that do not respond to simple cotton tipped debridement. These ulcers can recur and both eyes are predisposed. SCCED should not

be a high differential in a young dog with a non-healing ulcer. Other causes should be considered.

Complicated ulcers include stromal ulcers that are worsening, not healing, melting ulcers, and deep ulcers. Corneal abscesses though less common can become complicated quickly if proper treatment isn't initiated. Cytology and culture can help determine organism if septic. Therapy for these ulcers should not be taken lightly and these patients need to be seen frequently. Deep ulcers are best managed surgically in most cases and referral to an ophthalmologist should be strongly considered. Bacteria are the largest culprits of septic stromal ulcers and therapy should be broad-spectrum covering both gram positive and gram negative organisms keeping in mind that not all drugs penetrate well through the cornea. In particular abscesses without ulcer need treatment with antibiotics that penetrate through an intact epithelium. Organisms resistant to commonly used antibacterials are becoming increasingly common. Fungal keratitis is not as common and will often be overlooked without cytology. I see a few cases each year. Any sign of collagenolysis REQUIRES anticollagenolytic therapy. Sterile collection of autogenous serum, doxycycline, acetylcysteine, are some commonly available therapies used in the treatment of melting ulcers for their anti-collagenolytic properties. Our facility uses banked plasma mainly. Although acetylcysteine is widely available I rarely use it due to frequent complaints of severe ocular irritation upon application. Medical management needs to be aggressive and frequent in septic ulcers. Every one hour treatment round the clock and rechecking the next day. Don't forget the Elizabethan collar. Don't forget to treat the associated uveitis and pain. I usually use oral medications for these respectively. Surgical intervention is warranted in deep ulcers, worsening melting ulcers, descemetocelles, and perforations.

Immune-mediated corneal diseases include chronic superficial keratitis, punctate keratitis. These conditions are almost always bilateral and local immune-suppressants are recommended. Long term therapy is often necessary and recrudescence is expected if therapy is suspended. Other immune-mediated ocular or systemic conditions may be concurrent (ie. Immune-mediated KCS). Some patients require treatment with systemic immunosuppressants although in my experience this is rare.

Sometimes corneal changes are the first thing noticed by the owner and this precipitates an appointment with you the veterinarian. There are numerous conditions that cause secondary corneal pathology. It will be your challenge to determine whether the corneal changes are primary or secondary to some other condition or disease. Good examination technique, simple

diagnostics (STT, FS, IOP) and sound judgement will help facilitate appropriate treatment for the patient. We will take a look at various patients with corneal pathology and determine whether it is primary or secondary and go over therapies and prognosis.

Disease and conditions affecting the cornea are numerous and have not enough time to go over the entire list. There are excellent references that deserve a place on your bookshelf as well as resources available by phone and internet contact for the more challenging cases. Early referral to an ophthalmologist can improve outcome in these challenging cases and serve as continued education for you for future cases.

Sarah J. Miller, DVM, Diplomate ACVIM (Cardiology)

Degenerative Valvular Disease – What’s New?

Chronic degenerative valvular disease is the most common cardiovascular disease in small animals, and is also known as endocardiosis or myxomatous valve degeneration.

It is seen more commonly in older small breed dogs, and males appear to be predisposed and develop more severe disease.

Anatomy:

Mitral valve (dog) – large anterior leaflet, smaller posterior leaflet and small commissural cusps between the two leaflets. Both leaflets are semicircular and are attached to the mitral valve annulus (fibrous ring) and to the papillary muscles (through chordae tendineae).

Tricuspid valve – two primary leaflets and multiple commissural cusps. The mural leaflet is significantly larger than the septal leaflet.

Aortic valve – three semi-lunar cusps.

Pathology:

- Mitral valve lesions are the most common, but the tricuspid valve and rarely the aortic valve can also be affected.

- Gross inspection reveals thickened and redundant valve leaflets. The free margins of the leaflets are the most commonly affected areas, which have nodules and are opaque.

Mitral valve prolapse – a portion of the body of the leaflet protrudes into the left atrium.

Structures involved: leaflets and chordae tendineae

Lesions:

- Redundancy of the leaflets
- Lengthening of the chordae tendineae
- Thickened and/or fenestrated leaflets

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Histopathology:

The atrioventricular valves have four layers:

- Atrialis (endocardial)
- Spongiosa (collagen, fibroblasts, elastic fibers and mucopolysaccharides)
- Fibrosa (collagen bundles)

- Ventricularis (endocardial)

In myxomatous AV degeneration the spongiosa increases in size and the fibrosa degenerates. A significant increase in extracellular matrix is observed and fibroblasts proliferate forming nodules.

Etiology:

- Likely hereditary
- Evidence suggests that degenerative valvular disease is inherited as a polygenic threshold trait in Cavalier King Charles Spaniels.

Pathophysiology:

- Valvular regurgitation → increased atrial volume → atrial dilatation
- Eccentric hypertrophy → annular dilation → worsening regurgitation
- Increased atrial pressure → CHF
- Severe regurgitation → decreased forward flow
- Decreased forward flow → Renin-angiotensin-aldosterone system (RAAS) stimulation

- Pulmonary hypertension can develop secondary to chronic pulmonary venous hypertension.
- Myocardial failure usually occurs in the latter stages of the disease and is more commonly identified in large breed dogs.
- Atrial tears/rupture can cause cardiac tamponade secondary to acute hemopericardium.

History/clinical signs:

- coughing
- labored breathing
- syncope
- distended abdomen

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Physical exam:

- mucous membrane color and CRT
- jugular veins
- thoracic auscultation
- peripheral pulses

Common PE findings:

- Heart murmur
- Increased intensity of the first heart sound
- Systolic click
- Third heart sound
- Arrhythmias
- Tachypnea/tachycardia
- Crackles and wheezes
- Distended jugular veins
- Brisk femoral pulses

Diagnostic tests:

Thoracic radiographs

Electrocardiogram

Echocardiogram

Blood pressure

Therapy:

Asymptomatic disease:

- ACE inhibitors?
- β -blockers?

Heart failure:

- Diuretics
- Vasodilators
- Positive inotropes

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What's new?

Etiology:

Genomic expression patterns and possible genetic biomarkers for canine degenerative mitral valve disease.

Diagnosis:

Laboratory Tests

- B-type natriuretic factor/peptide (BNP)?
- Atrial natriuretic factor peptide (ANP)?
- Cardiac troponin-I (TnI)?

Treatment:

Recent clinical trials concerning the use of ACE inhibitors, β -blockers and pimobendan in asymptomatic disease and heart failure will be reviewed.

QUEST – Pimobendan vs benazepril trial in patients with congestive heart failure secondary to degenerative mitral valve disease.

VETPROOF (follow up) – Enalapril trial in asymptomatic patients with degenerative mitral valve disease.

Benazepril study - University of Alford – Benazepril trial in asymptomatic patients with degenerative mitral valve disease.

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THYROID NODULES, BUMPS, & LUMPS: WHEN IS MEDICAL THERAPY A USEFUL OPTION?

Michael R. Broome DVM, DABVP

THYROID NODULES IN HUMAN PATIENTS

In humans, thyroid nodules are common, occurring in over half of individuals over 50 years of age. Over 95% of these thyroid nodules are benign, small to moderate in size, and are not associated with clinical or biochemical signs of hyperthyroidism. Some of these patients that present with a single thyroid nodule are later found to have many benign enlarged nodules within the thyroid (ie, multinodular goiter), some of which will develop signs of hyperthyroidism (toxic nodular goiter; Plumber's disease). Although the underlying cause of most human thyroid nodules is not known, a low-iodine diet, Hashimoto's thyroiditis, or prior radiation treatment can contribute to nodule development.

The most common medical treatment used in management of thyroid nodules in human patients is thyroid suppressive therapy, in which L-thyroxine is used to suppress pituitary TSH secretion and slow the growth of the thyroid nodule. In all human patients found to have a thyroid nodule, a major concern is the possibility of thyroid cancer, in which more aggressive therapy is required. The finding that thyroid replacement results in shrinkage of the nodule makes thyroid cancer less likely. Unfortunately, there is not clear evidence that treatment with L-thyroxine consistently shrinks thyroid nodules or even that shrinking small, benign nodules is necessary in most patients.

THYROID NODULE/MASSES IN DOGS AND CATS

In most dogs and cats that present with a thyroid nodule or cervical mass, the pathogenesis and treatment are quite different from that of the human patient with a thyroid nodule (see Table 1). As discussed below, administration of T4 to suppress the goiter or nodule, as sometimes used in humans, is successfully used in some conditions (eg, some forms of congenital hypothyroidism). Most of the time, however, other treatments must be used, as dictated by the final diagnosis.

The most common situation for veterinarians to find a thyroid nodule would be in the middle to older cat. Some of these nodules are thyroid in origin; others are nonthyroidal in origin

(eg, parathyroid or lymphatic nodules). Some are functional, some are non-functional or in the process of evolving toward overt hyperthyroidism (See Table 1). Indeed, the presence of an incidental mass in the cervical/thyroid area can sometimes be an enigma in companion animal practice. Surgical biopsy may not be justified if lesions are non-functional, which is often the case early in the clinical course when T4 determinations are in the reference interval.

Hyperthyroidism in Cats

Since hyperthyroidism was first reported 31 years ago, the prevalence of thyroidal nodules and the associated hyperthyroid state has been detected at an increasing frequency, with a prevalence now estimated to be as high as 2% of cats in general practice. Histopathology of affected thyroids usually reveals thyroid hyperplasia or benign thyroid adenoma; however, in a small percentage of cats (especially those with long-standing hyperthyroidism management with antithyroid drugs), thyroid adenocarcinoma is diagnosed. The time course of the progression of normal feline thyrocytes to hyperfunctioning adenomatous hyperplasia/adenoma and then to thyroid carcinoma is not known.

The presence of a palpable thyroid nodule is one of the cornerstones in securing a diagnosis of hyperthyroidism, but a functional hyperthyroid state must be confirmed on the basis of other characteristic clinical features, (ie, weight loss in the face of a good appetite). The diagnosis of hyperthyroidism can usually be confirmed by measurement of a single serum T4 concentration. In some cats with early hyperthyroidism or which have concurrent nonthyroidal disease, the T4 concentration may intermittently fluctuate into the normal range. If the T4 is high-normal or borderline, diagnostic options include repeating the T4 level or measuring a free T4 concentration (by equilibrium dialysis or equivalent assay). Thyroid imaging (scanning) with pertechnetate (^{99m}Tc) is also a very useful diagnostic aids in the evaluation of hyperthyroidism in cats because it delineates functioning thyroid tissue. With pertechnetate thyroid scanning, a one-to-one ratio usually exists between the size and intensity of the salivary glands and the two thyroid lobes. In contrast, most cats with hyperthyroidism will have obvious enlargement of one or both thyroid lobes, together with an increased uptake of pertechnetate into the abnormal thyroid tissue, as compared to the salivary glands. Calculation of the percentage thyroidal ^{99m}Tc uptake can also be determined for additional diagnostic value. Another major usefulness of thyroid imaging, however, is in determining the extent of thyroid gland involvement and in detecting possible metastasis.

The treatment of choice for an individual hyperthyroid cat depends on several factors, including the age of the cat, presence of other major medical problems, availability of a skilled surgeon or I-131 facility, and owner's opinion and financial options. Of the 3 forms of treatment available, only surgery and radioactive iodine remove and destroy the adenomatous thyroid

tissue, respectively, and thereby "cure" the hyperthyroid state. Use of an antithyroid drug (e.g., methimazole or carbimazole) will block thyroid hormone synthesis; however, since antithyroid drugs do not destroy adenomatous thyroid tissue, the nodule is not destroyed and will continue to grow in size. In some cats, benign thyroid adenoma or adenomatous hyperplasia appears to transform into thyroid carcinoma, especially after long-term treatment with antithyroid drugs.

Euthyroid Goiter in Cats

Experienced veterinarians can palpate ventral cervical nodules(s) in many middle-aged to older cats. It is not uncommon in 2010 to palpate a cervical nodule in a cat with no clinical or laboratory signs of hyperthyroidism. Possible differential diagnoses include early hyperthyroidism, thyroid cyst or cystadenoma, or non-functional thyroid adenoma or carcinoma. Nonfunctional thyroid carcinoma does occur but is rare in the cat. If an obvious cervical nodule is palpated in a cat with a normal T4 concentration, a fine needle aspirate should be considered to determine the tissue of origin. Thyroid imaging is again a very useful diagnostic aid in these cats and is considered by most to be the most sensitive means of diagnosis of early preclinical hyperthyroidism. In most of these cats, medical therapy is not indicated until clinical or biochemical hyperthyroidism develops.

Thyroid Cysts in Cats

Reports of cystic thyroid masses in cats are not uncommon, usually developing in cats with overt hyperthyroidism. Some of these masses may rapidly increase in size and rarely, signs related to local compression of adjacent structures (e.g., trachea) may develop in some cats. Diagnosis is based on palpation of the fluctuant mass, documentation of the cystic lesion with ultrasound, and aspirating the cystic fluid (which is typically serosanguinous). One can also determine T4 levels in the fluid to help confirm that the cystic lesion is of thyroid origin. Thyroid imaging can also be very helpful in determining if the cystic mass is of thyroid origin.

Treatment with either surgical excision or radioiodine has proven most successful in these cats. Long-term medical treatment of these cases is not recommended since the cystic lesions may increase greatly in size over time.

Congenital Hypothyroidism in Cats and Dogs

In dogs and cats, there are 2 major causes for congenital primary hypothyroidism: 1) thyroid dysmorphogenesis (defect in the biosynthesis of thyroid hormones); and 2) thyroid hypo- or aplasia. With thyroid dysmorphogenesis, the loss of T4's negative feedback effect on the pituitary leads to increased secretion of TSH, with resultant stimulation and hyperplasia of

the thyroid gland. This can lead to an enlarged thyroid gland (goiter). In contrast, the thyroid would be small in animals with thyroid hypo- or aplasia.

Thyroid hormones are essential for normal post-natal development of the skeletal and nervous systems. Therefore, congenital hypothyroidism is characterized by disproportionate dwarfism and neurologic abnormalities. Obviously many signs observed in adult-onset hypothyroidism can also be present in affected puppies and kittens. On physical examination, hypothermia, bradycardia and palpable goiter may be present in those animals with thyroid dysmorphogenesis.

In young dogs and cats with suspected congenital hypothyroidism, thyroid scintigraphy can be a useful diagnostic aid since the thyroid image differs depending on the cause. With thyroid dysmorphogenesis (hypo- or aplasia), no thyroid uptake is seen, whereas the thyroid lobes have a normal to increased size with normal to increase uptake in dogs and cats with thyroid dysmorphogenesis.

Treatment for congenital hypothyroidism consists of L-T4 supplementation; with therapy, the goiter will decrease in size as the circulating TSH concentration falls into the reference range. For congenital hypothyroidism, prognosis is rather guarded and will largely depend on the underlying etiology of the hypothyroidism and age at diagnosis.

Thyroiditis in Dogs

Autoimmune or lymphocytic thyroiditis is the main pathologic process causing hypothyroidism as an adult-onset condition in dogs. It is well known that at least 50% of primary hypothyroidism in dogs result from immune-mediated thyroiditis. Rarely, early in the course of the inflammatory process, palpable enlargement of the thyroid gland is possible in some of these dogs. As thyroiditis progresses, parenchyma is destroyed and replaced by fibrous connective tissue and the goiter resolves. Diagnosis of hypothyroidism and thyroiditis is based upon measurement of serum T4, cTSH, and thyroglobulin autoantibodies. Some of these dogs with thyroiditis will develop autoantibodies to T4, T3, or both. These autoantibodies produce spurious results when serum or plasma T4 or T3 are measured by radioimmunoassay, often resulting in an elevated apparent concentration of the thyroid hormones in affected dogs. Not uncommonly, these values will be markedly increased, causing the veterinarian to consider the possibility that the dog has hyperthyroidism due to thyroid neoplasia. The differentiation between hyperthyroidism and clinical hypothyroidism (due to thyroiditis) can usually be made on a clinical basis, as well as by measuring free T4 concentrations (which typically are low in this situation). If hypothyroidism is present in these dogs with lymphocytic thyroiditis, treatment with L-T4 supplementation is indicated.

Thyroid Tumors in Dogs

In dogs, thyroid tumors are common, representing approximately 1 to 4% of all canine neoplasms. As opposed to the relatively small, non-invasive thyroid tumors (i.e., adenomatous hyperplasia) associated with hyperthyroidism in cats, most clinically detected thyroid tumors in dogs are large, invasive carcinomas that are not hyperfunctional (i.e., do not produce hyperthyroidism). Most thyroid carcinomas in dogs arise from follicular cells, although up to a third of thyroid tumors may arise from parafollicular (C-cells), resulting in medullar C-cell carcinomas. Thyroid follicular carcinomas can be further subclassified as follicular, compact, compact-follicular (mixed), papillary, or undifferentiated, depending on the pattern of growth. Most canine thyroid tumors are mixed compact-follicular, whereas pure follicular or compact tumors or undifferentiated tumors are less common. Papillary carcinoma, a common tumor type in human patients, is very rare in dogs. Unfortunately, histological differentiation of these thyroid tumor types is generally of little help clinically when deciding on the best treatment for these carcinomas. In dogs with thyroid carcinoma, both local invasion of tumor into adjacent and distant metastasis are common. Approximately 50% of dogs with thyroid carcinoma have metastasis at time of diagnosis. During the natural course of disease, 65-90% of dogs with untreated disease will develop metastasis.

Many dogs with thyroid tumors are presented because the owner has noticed an enlargement of the neck. In >75% of dogs diagnosed in 1 survey, either the cervical swelling was the only reason for seeking veterinary care or the thyroid mass was detected by the veterinarian during an examination for another problem. Unlike the relatively small, freely movable thyroid tumors of the cat, most thyroid tumors in dogs are very large, easily palpable, and are well-embedded (fixed) into the surrounding soft tissues of the neck.

Thyroid imaging (scanning) is useful in the evaluation of dogs with thyroid masses because the procedure delineates functioning thyroid tissue. ^{99m}-pertechnetate (^{99m}-Tc) thyroid scans do not provide direct information regarding thyroid function, but such imaging procedures do aid in demonstrating the location of abnormal thyroid tissue. Thyroid imaging can also be performed to help determine the extent of thyroid invasion or metastasis. Failure to identify distant metastatic sites with thyroid imaging, however, cannot prove that distant metastasis does not exist.

Treatment of thyroid neoplasia in dogs is dictated by the size of the primary tumor, extent of local tissue invasion, presence of detectable metastasis, presence of hyper- or hypothyroidism, and available options. Because most clinically detected thyroid tumors in the dog are malignant, treatment is rarely curative. Nevertheless, one should generally advise some form of treatment because palliative relief and increased lifespan can usually be achieved in most dogs with thyroid carcinoma. Surgery, chemotherapy, cobalt irradiation, and use of

radioactive iodine therapy, alone or in combination, may be indicated depending on the individual dog. Medical control of the hyperthyroid state can be achieved by the daily administration of an antithyroid drug such as methimazole or carbimazole (5 to 15 mg/dog, twice, daily), but such medical treatment will not do anything to prevent tumor growth or metastasis.

TABLE 1. DIFFERENTIAL DIAGNOSIS FOR CERVICAL NODULES/MASS IN DOGS AND CATS

Category	Subcategory	Typical Clinical Syndrome	Species Affected
Neoplastic Disorders of Thyroid	Euthyroid goiter	None	Cat
	Thyroid cysts/cystadenoma	Euthyroid or hyperthyroidism	Cat
	Thyroid adenomatous hyperplasia	Hyperthyroidism	Cat
	Thyroid adenoma	Hyperthyroidism	Cat
	Thyroid malignancy/carcinoma	Usually hyperthyroidism	Cat
	Thyroid carcinoma	Usually nonfunctional	Dog
	Thyroid medullary carcinoma	Usually nonfunctional	Dog, Cat
Immune-Medicated Disorders of Thyroid	Thyroiditis (Hashimoto's)	Hypothyroidism	Dog, Cat?
	Hashimoto's hyperthyroidism	Transient hyperthyroidism	Dog
Congenital Disorders of Thyroid	Congenital hypothyroidism	Hypothyroidism	Cat, Dog
	Juvenile hypothyroidism	Hypothyroidism	Cat, Dog
Endocrinopathies with Thyroid/Parathyroid Nodule	Acromegaly	Growth hormone excess; secondary thyroid enlargement	Cat, Dog

	Primary hyperparathyroidism	Hypercalcemia; parathyroid nodule palates like thyroid	Cat, Dog
Congenital Cysts in Cervical Region	Ultimobranchial cyst	None	Dog, Cat
	Thyroglossal cyst	None	Dog, Cat
	Branchial cyst	None	Dog, Cat
	Dermoid cyst	None	Dog, Cat
		None	Dog, Cat
Nonthyroidal Neoplastic Disorders	Lipoma/Liposarcoma	None	Dog, Cat
	Lymphosarcoma	None	Dog, Cat
	Inflammatory conditions (e.g., abscess, granuloma)	None	Dog, Cat
	Salivary mucoceles	None	Dog, Cat
Non-thyroid Neoplastic Disorders	Regional soft tissue sarcomas, lymphoma, metastatic oral tumors	None	Dog, Cat

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Keywords

thyroid, hyperthyroidism, adenoma, adenomatous hyperplasia, thyroid carcinoma, multinodular goiter, toxic nodular goiter

Diabetes Mellitus, acute presentation and complications.

By Dr. Ravi Seshadri, DVM, DABVPP, DACVECC

Hyperosmolar Hyperglycemic Syndrome (or State) {HHS}

Hyperosmolar hyperglycemic state (HHS) is one of two serious metabolic derangements that occurs in patients with diabetes mellitus and can be a life-threatening emergency. The condition is characterized by hyperglycemia, hyperosmolarity, and dehydration without significant ketoacidosis. It is less common than the other acute complication of diabetes, diabetic ketoacidosis (DKA), and differs in the magnitude of dehydration, ketosis, and acidosis. HHS usually presents in older patients, dogs and cats equally distributed, and carries a higher mortality rate than DKA.

Most patients present with severe dehydration and focal or global neurologic deficits. In as many as one third of cases, the clinical features of HHS and DKA overlap and are observed simultaneously (overlap cases). Based on the consensus statement published by the American Diabetic Association, diagnostic features of HHS may include the following:

- Plasma glucose level of 600 mg/dL or greater
- Effective serum osmolality of 320 mOsm/kg or greater
- Profound dehydration
- Serum pH greater than 7.30
- Bicarbonate concentration greater than 15 mEq/L
- Marginal ketonuria and absent-to-low ketonemia
- Some alteration in consciousness

HHS was previously termed hyperosmolar hyperglycemic nonketotic syndrome, or Hyperosmolar non ketotic syndrome (HONK).

Pathophysiology

Hyperosmolar hyperglycemic state (HHS) most commonly occurs in patients with type 2 diabetes mellitus who have some concomitant illness that leads to reduced fluid intake. Infection

is the most common cause, but many other conditions can cause altered mentation, dehydration, or both. The concomitant illness may not be identifiable.

In patients with a preexisting lack of or resistance to insulin, a physiologic stress such as an acute illness can cause further net reduction in circulating insulin.

The basic underlying mechanism of HHS is a reduction in the effective circulating insulin with a concomitant elevation of counter-regulatory hormones, such as glucagon, catecholamines, cortisol, and growth hormone. Decreased renal clearance and decreased peripheral utilization of glucose lead to hyperglycemia.

Hyperglycemia and hyperosmolarity result in an osmotic diuresis and an osmotic shift of fluid to the intravascular space, resulting in further intracellular dehydration. This diuresis also leads to loss of electrolytes, such as sodium and potassium.

Unlike patients with DKA, patients with HHS do not develop significant ketoacidosis, but the reason for this is not known. Contributing factors likely include the availability of insulin in amounts sufficient to inhibit ketogenesis but not sufficient to prevent hyperglycemia.

Additionally, hyperosmolarity itself may decrease lipolysis, limiting the amount of free fatty acids available for ketogenesis. Also, lower levels of counter-regulatory hormones have been found in patients with HHS compared with those with DKA.

Mortality/Morbidity

The mortality rate is high (10-20%) and usually due to a comorbid illness. The mortality rate of HHS increases with increasing age and with higher levels of serum osmolality. HHS is more likely in older patients especially those with significant obesity. DKA on the other hand is more commonly seen in middle aged patients and most of these patients are in a catabolic state. The catabolic state leads to marked weight loss. Patients with HHS have significant osmolar shifts and are predisposed to cerebral edema or other myelin injury.

- Most patients with hyperosmolar hyperglycemic state (HHS) have a known history of diabetes.
- In 30-40% of cases, HHS is the patient's initial presentation of diabetes.
- HHS usually develops over a course of days to weeks unlike DKA, which develops more rapidly.
- Often, a preceding illness results in several days of increasing dehydration.
- Adequate oral hydration may be impaired by concurrent acute illness (eg, vomiting) or chronic comorbidity (eg, dementia, immobility).

- Patients may have polydipsia, polyuria, weight loss, weakness.
- Patients do not typically exhibit abdominal pain, a complaint that is often noted in patients with DKA.
- A wide variety of focal and global neurologic changes may be present, including the following:
 - ♦ Drowsiness and lethargy
 - ♦ Delirium
 - ♦ Coma
 - ♦ Focal or generalized seizures
 - ♦ Visual changes or disturbances
 - ♦ Hemiparesis
 - ♦ Sensory deficits

Physical

Examine the patient for evidence of hyperosmolar hyperglycemic state (HHS), focusing on hydration status, mentation, and signs of possible underlying causes, such as a source of infection.

- Vital signs
 - STAT glucose should be checked immediately and is usually greater than 600 mg/dL.
 - Tachycardia is an early indicator of dehydration; hypotension is a later sign suggestive of profound dehydration due to volume loss secondary to osmotic diuresis.
 - Tachypnea may occur due to respiratory compensation for metabolic acidosis in overlap cases.
 - Assess core temperature rectally.

- Abnormally high or low temperatures suggest sepsis as an underlying cause.
 - Lack of fever does not rule out infection.
 - Hypothermia is a poor prognostic factor.
- Hypoxemia can be a concurrent problem affecting mentation.
- General appearance and hygiene may provide clues to the state of hydration, presence of chronic illness, and reduced level of mentation.
 - Examination may reveal altered hydration status (eg, sunken eyes, dry mouth).
 - Cranial neuropathies, visual field losses, and nystagmus may be appreciated, which are symptoms of HHS. They are usually reversible with therapy.

Causes

- In general, any illness that predisposes to dehydration may lead to hyperosmolar hyperglycemic state (HHS). A wide variety of major illnesses may trigger HHS by limiting patient mobility and free access to water.
- A preceding or intercurrent infection is common, but the underlying cause may be difficult to ascertain. Pneumonia and urinary tract infections (UTIs) are the most common underlying causes of HHS.
- Stress response to any acute illness tends to increase hormones that favor elevated glucose levels. Cortisol, catecholamines, glucagon, and many other hormones have effects that tend to counter those of insulin.
- Patients with underlying renal dysfunction and/or congestive heart failure are at greater risk.
- Drugs that raise serum glucose levels, inhibit insulin, or cause dehydration may cause HHS. Examples include the following:
 - Diuretics
 - Steroids
 - Total parenteral nutrition and fluids that contain dextrose

Poor compliance with insulin therapy or diet can result in HHS.

Diabetic Ketoacidosis (DKA)

Diabetic ketoacidosis (DKA) is an acute, major, life-threatening complication of diabetes. DKA mainly occurs in patients with type 1 diabetes, but it is not uncommon in some patients with type 2 diabetes. DKA is defined clinically as an acute state of severe uncontrolled diabetes that requires emergency treatment with insulin and intravenous fluids. Biochemically, DKA is defined as an increase in the serum concentration of ketones greater than 5 mEq/L, a blood glucose level of greater than 250 mg/dL (although it is usually much higher), blood pH of less than 7.2, and a bicarbonate level of 18 mEq/L or less.

Pathophysiology

Diabetic ketoacidosis (DKA) is a complex disordered metabolic state characterized by hyperglycemia, acidosis, and ketonuria. DKA usually occurs as a consequence of absolute or relative insulin deficiency that is accompanied by an increase in counter-regulatory hormones (ie, glucagon, cortisol, growth hormone, epinephrine). This type of hormonal imbalance enhances hepatic gluconeogenesis, glycogenolysis, and lipolysis.

Hepatic gluconeogenesis, glycogenolysis secondary to insulin deficiency, and counter-regulatory hormone excess result in severe hyperglycemia, while lipolysis increases serum free fatty acids. Hepatic metabolism of free fatty acids as an alternative energy source (ie, ketogenesis) results in accumulation of acidic intermediate and end metabolites (ie, ketones, ketoacids). Ketones include acetone, beta hydroxybutyrate, and acetoacetate.

Progressive rise of blood concentration of these acidic organic substances initially leads to a state of ketonemia. Natural body buffers can buffer ketonemia in its early stages. When the accumulated ketones exceed the body's capacity of extracting them, they overflow into urine (ie, ketonuria). If the situation is not treated promptly, more accumulation of organic acids leads to frank clinical metabolic acidosis (ie, ketoacidosis), with a drop in pH and bicarbonate serum levels. Respiratory compensation of this acidotic condition results in rapid shallow breathing (Kussmaul respirations).

Ketones, in particular beta hydroxybutyrate, induce nausea and vomiting that consequently aggravate fluid and electrolyte loss already existing in DKA. Acetone produces the characteristic fruity breath odor of ketotic patients.

Hyperglycemia usually exceeds the renal threshold of glucose absorption and results in significant glycosuria. Consequently, water loss in the urine is increased due to osmotic diuresis induced by glycosuria. This incidence of increased water loss results in severe dehydration, thirst, tissue hypoperfusion, and, possibly, lactic acidosis.

Typical free water loss in DKA is nearly 100 mL/kg of body weight. The initial half of this amount is derived from intracellular fluid and precedes signs of dehydration, while the other half is from extracellular fluid and is responsible for signs of dehydration.

Hyperglycemia, osmotic diuresis, serum hyperosmolarity, and metabolic acidosis result in severe electrolyte disturbances. The most characteristic disturbance is total body potassium loss. This loss is not mirrored in serum potassium levels, which may be low, within the reference range, or even high. Potassium loss is caused by a shift of potassium from the intracellular to the extracellular space in an exchange with hydrogen ions that accumulate extracellularly in acidosis. A large part of the shifted extracellular potassium is lost in urine because of osmotic diuresis. Patients with initial hypokalemia are considered to have severe and serious total body potassium depletion. High serum osmolarity also drives water from intracellular to extracellular space, causing dilutional hyponatremia. Sodium also is lost in the urine during the osmotic diuresis.

Typical overall electrolyte loss includes potassium, sodium, and chloride. Additional electrolyte losses include magnesium and phosphorous. The combined effects of serum hyperosmolarity, dehydration, and acidosis result in increased osmolarity in brain cells that clinically manifests as an alteration in the level of consciousness.

Mortality/Morbidity

When diabetic ketoacidosis (DKA) is treated properly, it rarely causes any residual effects. The mortality rate of DKA (or HHS) is sometimes dictated by Owner financial commitment. Best results are always observed in patients treated in ICUs during the first 1-2 days of hospitalization.

- Cerebral edema remains the most common cause of mortality. Cerebral edema frequently results from rapid intracellular fluid shifts. Other causes of mortality include severe hypokalemia, hypophosphatemic anemia and comorbid states (eg, pneumonia, renal dysfunction / pyelonephritis)

History

- Insidious increased thirst (ie, polydipsia) and urination (ie, polyuria) are the most common early symptoms of diabetic ketoacidosis (DKA).
- Nausea and vomiting usually occur and may be associated with diffuse abdominal pain.
- Generalized weakness and lethargy is noted.

- Altered consciousness in the form of mild disorientation or confusion is a possible symptom. Although frank coma is uncommon, it may occasionally occur when the condition is neglected or if dehydration or acidosis is severe.
- Symptoms of possible associated intercurrent infection may include fever, dysuria, coughing, malaise, and arthralgia, among others.
- Frequently DKA occurs because patients develop GI signs and then Owners decrease insulin therapy due to anorexia.
- History of rapid weight loss is a symptom in patients who are newly diagnosed with type 1 diabetes.

Physical

- Signs of dehydration - Weak and rapid pulse, dry tongue and skin, hypotension, and increased capillary refill time
- Patient odor - Characteristic acetone odor
- Signs of acidosis - Shallow rapid breathing or air hunger (Kussmaul or sighing respiration), abdominal tenderness, and disturbance of consciousness
 - Although these signs are not usual in all cases of diabetic ketoacidosis (DKA), their presence signifies a severe form of DKA.
 - Emphasizing that no direct correlation exists between the degree of acidosis, hyperglycemia, and the disturbances in the level of consciousness is important.
- Signs of intercurrent illness - urinary tract infection (UTI), pneumonia, and pancreatitis, among others
 - Noticing that the body temperature may be within the reference range or low, even in the presence of intercurrent infection, is particularly important.
 - Search for signs of infection is mandatory in all cases.

Treatment :

All critically ill diabetic patients need to be adequately volume resuscitated prior to definitive therapy. The volume resuscitation is usually based on crystalloid replacement fluid. Sodium levels should be carefully monitored to make sure that sudden changes in sodium do not create cerebral injury. It is imperative in patients with cardiac dysfunction that volume resuscitation does not lead to pulmonary edema or pleural effusion. Cats are especially prone to volume overload due to a higher incidence of occult cardiac disease.

Once appropriate interstitial rehydration has occurred insulin therapy can be considered. Always place a central line for venous sampling access and to facilitate fluid therapy. Humulin R (regular insulin) CRI is the authors choice for treatment. Numerous algorithms are available in the literature for managing a CRI of insulin and serial blood glucose monitoring. The CRI permits dial up or dial down of effective insulin rates. Simultaneously supplemental glucose as substrate can be administered if the patient is still ketotic. Until ketosis is resolved and the patient is eating and drinking well we do not transition to longer acting insulin. Humulin N is still ideal as a twice a day insulin in dogs and Glargine is the long acting insulin of choice in cats. In both cases tight glycemic control is not attempted at the first hospitalization. Based on serial glucoses a conservative dosage of insulin is selected and the patient is discharged.

During the hospitalization phase it is important to evaluate the patient for concurrent diseases. Presence of Cushings disease, pancreatitis, lymphoma, or other illness with potential long term implications can significantly affect the way in which these patients are managed. If the patient has chronic IBD or GI signs, regulation can become more difficult since these patients do not eat in a regular manner. Any comorbidities identified have to be treated either immediately or planned for in the long term management.

Electrolytes and acid base status have to be checked frequently through the hospitalization. Administration of insulin leads to significant transcellular shifts of potassium and phosphorous. Presence of hypomagnesemia can make it very difficult to normalize serum sodium levels. During therapy a drop of phosphorous to below 2 mEq/L can lead to catastrophic anemia secondary to erythrocyte fragility. Refeeding syndrome can contribute to hypophosphatemia and phosphorous supplementation is extremely important.

Long term care: Owner education and compliance is very important in good overall control of diabetes. Inadequate control leads to Owners frustration and euthanasia may results. Almost all dogs with diabetes develop cataracts at some point in time and may need surgical care if retinal function is appropriate. Use of home glucose monitoring protocols whether with interstitial blood glucose monitors or by teaching Owners techniques of ear pricks helps in better glycemic regulation. Alternatively blood glucose curves in hospital or periodic assessment of fructosamine

can give veterinarians a good overview of adequacy of therapy. Veterinary specific insulins have had erratic availability as well as some quality control issues and should only be used with frequent monitoring.

Nibs and Mabs: New Approaches to fighting cancer

Mona Rosenberg, DVM, DACVIM - Veterinary Cancer Group

Acknowledgements: Pfizer and Dr. Cheryl London

What are kinases?

Kinases are proteins that have the ability to phosphorylate other proteins

Activation initially involves phosphorylation of tyrosine or serine/threonine; requires ATP

This phosphorylation permits binding of other cytoplasmic molecules to the receptor, leading to further phosphorylation and downstream signaling

Kinases can be on the cell surface, in the cytoplasm, and in the nucleus

Kinase Signaling

Stimulation of kinases initiates an ordered sequence of biochemical reactions within a cell, resulting in: Gene activation/inhibition, Proliferation, Survival, Migration

Receptor Tyrosine Kinases and Angiogenesis

Kinases and Cancer

Kinases are often dysregulated in cancer

Mechanisms of dysregulation include: overexpression, mutation, chromosomal, translocation, autocrine loop of activation

These contribute to growth factor independent signaling that contributes to uncontrolled cell growth, survival, and motility

RTKs are often implicated in this dysregulation: they stimulate the growth of tumor cells and are important mediators of tumor- stromal cell and tumor-endothelial cell interactions involved in angiogenesis

RTK Dysregulation Is Associated With Many Human Cancers (table insert)

KIT Dysfunction Plays a Role in the Proliferation of Canine and Possibly Feline MCT

KIT is critical for the development and growth of canine mast cells

Expressed on mast cells and activated by stem cell factor (SCF)

Prevalence of KIT mutations is approximately 25% in grade 2/3 canine MCTs

Internal tandem duplications (ITDs) in exons 11 and 12 (juxtamembrane domain) lead to constitutive phosphorylation of KIT in the absence of SCF binding
KIT ITD mutations are associated with an increased rate of recurrent disease and mortality in dogs with MCT
Exon 8 and 9 mutations have been identified and are constitutively activating

Strategies to Inhibit Tyrosine Kinases

Most TKIs work by blocking the ability of the kinase to bind ATP (i.e., competitive inhibitor), as this is necessary for donating the phosphate group that phosphorylates the TK as well as downstream targets; inhibitors are often called small molecule inhibitors
RTKs can also be inhibited through the use of monoclonal antibodies that bind the extracellular domain of the target; this does not necessarily alter the phosphorylation status of the RTK, but may lead to receptor endocytosis and downregulation or immune mediated tumor cell destruction (complement/ADCC)

Small Molecule Inhibitors

Small molecules designed to target a specific protein, often at ATP binding pocket
Block the function of that protein and disrupt cellular processes/signaling
Usually given orally, sometimes intravenously and work at low micromolar or nanomolar concentrations
Effectiveness often dependent on the reliance of tumor cells on that pathway
Toxicities result from blocking pathways in normal cells
Inhibitors can be very specific or may have multiple off-target effects

Therapeutic Efficacy

Dependent on extent/duration of target inhibition
Tumor cells need to rely on the particular pathway being targeted
Unlike chemotherapeutics, activity may not be completely tied to maximum tolerated dose (MTD)

- effective target inhibition may occur below the MTD

Unlike chemotherapeutics that often irreversibly damage DNA, target inhibition is often reversible

- pathway inhibition usually relieved following metabolism of therapeutic

Resistance usually driven by mutation in target binding site that prevents inhibitor from binding, or development of alternative signaling pathways

Small-Molecule Inhibitors Have Proven Effective in Treating Human Cancers (table insert)

Small-Molecule Inhibitors and Human Cancers (table insert)

Tyrosine Kinase Inhibitors in Veterinary Medicine

Limited use in veterinary medical oncology - lack of well-defined targets for specific cancers, little data regarding safety and toxicity of many agents, some therapeutics cannot be used (i.e., humanized monoclonal antibodies), often cost prohibitive

Canine/feline cancers for which targets have been identified - mast cell tumors, osteosarcoma, GIST, sarcomas

Small molecule inhibitors that have been evaluated in dogs/cats - Gleevec, Kinavet, Palladia

Gleevec (imatinib mesylate)

Oral small molecule inhibitor

Inhibits binding of ATP

Active against Bcr-Abl, Kit, and PDGFR

Originally designed to inhibit the bcr-abl fusion protein found in human patients with CML

- approximately 90% remission rate

Inhibits Kit signaling - over 50% remission rate for human gastrointestinal stromal tumors which possess activating mutations in Kit similar to those mutations in canine MCTs

Gleevec Use in Dogs and Cats

Few publications; hepatotoxicity can be limiting and has been reported anecdotally

Isotani et al, 2008: response to therapy in 10/21 dogs treated with Gleevec; response rate was 100% in

dogs with MCTs possessing a Kit ITD (n=5, 1 CR, 4 PR)

Marconato et al, 2008: response to therapy in 3 dogs with systemic mast cell disease treated with Gleevec.

Isotani et al, 2008: response to therapy in a cat with systemic mastocytosis and exon 8 Kit mutation

Dosing is somewhat empirical (4-10 mg/kg) and often based on available tablet sizes (100 mg/400 mg)

Isotani et al, 2008: Response to therapy in a cat with systemic mastocytosis and exon 8 Kit mutation

Kinavet (Masitinib mesylate)

Small molecule RTK inhibitor: 2-aminothiazole, AB Science

Competitive inhibitor of ATP binding; prevent phosphorylation on tyrosine of Kit and others

Effective against : Kit, PDGFR, (FGFR3?)

IC 50 for Kit inhibition: 0.005-0.030 mM

Kinavet: Clinical Field Study

Recurrent or non-resectable Grade II or III MCTs

May have never received treatment

No evidence of lymph node or systemic disease

Baseline target lesion of at least 1 cm

Design - Dogs were randomized to receive either masitinib or placebo in a 4:1 ratio, evaluation at weeks 1, 2, 4, 6, and 2 mth, 3 mth, 4 mth, 5 mth, and 6 mth following study entry, response assessment at 4 mths, confirm at 6 mths, no placebo escape, dogs allowed to continue on drug after study completion

if doing well

Kinavet: Summary of Responses

Masitinib increased overall time to progression (TTP) compared with placebo from 75 to 118 days (n=202, P = 0.038).

This effect was more pronounced when masitinib was used as first-line therapy: increase in the median TTP from 75 to 253 days (P = 0.001)

TTP was also increased for dogs receiving masitinib whether the tumors expressed mutant (83d vs not reached: P = 0.009) or wild-type Kit (66d vs 253d: P = 0.008).

There was no statistically significant difference in ORR between placebo (14.7%) and masitinib (15.6%)

Kinavet: Summary of Responses

“Rate of best response” was very high in both placebo and masitinib treated dogs

Placebo: CR=21% CR+PR=36%

Masitinib: CR=26% CR+PR=55%

The spontaneous (placebo) CR rate reported in this study is extremely high, and has not been reported in other MCT studies

Palladia (toceranib phosphate)

Small molecule RTK inhibitors developed by SUGEN, Inc.: SU5416, SU6668, SU11248, SU11654 (*Palladia*), indolinone cores

Competitive inhibitor of ATP binding; prevents phosphorylation on tyrosine of associated RTK
Effective against members of the “split kinase” family including: VEGF-R, PDGF-R, Flt-3, Kit
Both direct anti-tumor and direct anti-angiogenic activity

Palladia Phase I Study

57 dogs entered into study

Established maximum tolerated dose: 3.25 mg/kg EOD

Investigated pharmacokinetics in dogs with cancer and established appropriate dosing regimen

6 complete responses, 10 partial responses, 15 dogs with stable disease for >10 wks

16 of 57 with response to therapy: 28%

mast cell tumors

sarcomas, carcinomas, myeloma, melanoma

31 of 57 considered to have evidence of biological activity: 54%

Grade II MCT with Kit Mutation (photos shown)

Clinical Summary: Mast Cell Tumors

Kit Mutation Positive

4 CR, 5 PR, 1 SD

Biological activity 10/11=91%

Kit Mutation Negative

1 CR, 1 PR, 1 SD

Biological activity 3/11=27%

- Dogs with ITDs were more likely to respond to Palladia therapy: $p=0.003$
- Dogs with no evidence of lymph node involvement were more likely to respond to Palladia therapy: $p=0.03$

Katie: Metastatic Mammary Carcinoma (photo shown)

Fawn: Multiple Myeloma (graph insert)

Palladia: Clinical Field Study

Recurrent Grade II or III MCTs: lymph node metastasis eligible, no evidence of systemic disease, baseline target lesion of at least 2cm, response assessment at 6 weeks, option for escape to active drug if on placebo

Design: dogs were randomized to receive either Palladia or placebo in a 4:3 ratio, weekly evaluation for the first 6 weeks, response assessment at weeks 3 and 6, if progressive disease at week 3 or 6, unblind and eligible for active drug if on placebo, blinded phase ends at 6 weeks, with continuation in open-label phase; rechecks every 3-6 weeks in open-label phase

Study Design (chart shown)

Palladia: Summary of Objective Response (graph shown)

Palladia: Summary of Biologic Response

- Among dogs receiving Palladia during the blinded phase, the objective response rate for dogs with KIT ITD mutation was 60.0% and 31.3% for dogs without the mutation ($P=0.0099$)
- During the blinded plus the open label phase, the objective response rate in dogs with KIT ITD mutation was 69% compared to 36.8% in dogs that did not possess the mutation

Treatment of Mast Cell Tumors

Reported single agent response rates in the setting of gross disease:

- Vinblastine (n=100):	12-27%
- Lomustine (n=19):	42%
- Palladia (n=145):	42.8%

Reported multi-agent response rates in the setting of gross disease:

- Vinblastine/Prednisone (n=15):	47%
- Vinblastine/Cytosar/Prednisone (n=11)	63%
- Vincristine/Cytosar/Hydroxyurea/Pred (n=17)	59%

Given the significant activity of Palladia as a single agent, it is possible that, similar to the case with other chemotherapeutics, Palladia will have even greater activity when administered in combination with prednisone

My Thoughts on the Clinical Utility of Gleevec and Kinavet

Both drugs inhibit Kit and PDGFR

Biologic activity would be expected in tumor types where Kit and PDGFR may be dysregulated

Canine and feline mast cell tumors

Tumors with negative prognostic indicators, high grade tumors, recurrent tumors, non-resectable/multiple tumors, kit mutation positive tumors

Canine GISTs

Kit positive

My Thoughts on the Clinical Utility of Palladia

Biologic activity would be expected in tumor types where Kit, PDGFR, VEGFR may be dysregulated or where an anti-angiogenic effect was desired

MCT with gross disease

Vinblastine/Pred-based therapy, followed by Palladia/pred

Grade 3 tumors, Grade 2 tumors requiring medical treatment (i.e., negative prognostic indicators..LN+, rapid growth, recurrence, etc), multiple MCTs/large non-resectable tumors,

KIT mutation positive tumors

MCT with microscopic disease

Vinblastine/pred-based therapy, followed by Palladia/Pred if Grade 3 tumor or if Grade 2 tumor with negative prognostic indicators

My Thoughts on the Clinical Utility of Palladia: Other Tumors

1. Gastrointestinal Stromal Tumors

Similar to GIST in people, dog GISTs often carry Kit mutations like those found in MCTs, human GIST respond well to Kit inhibitors

2. Soft Tissue Sarcomas

Responses noted in Phase I study, mechanism unclear (PDGFR/anti-angiogenic), currently no effective chemotherapy for metastatic soft tissue sarcomas

3. Mammary Carcinomas

Responses noted in Phase I study, mechanism unclear (PDGFR or Kit/anti-angiogenic), currently no effective chemotherapy for metastatic mammary tumors

4. Multiple Myeloma

Response noted in Phase I study, mechanism unclear (VEGFR, Kit/anti-angiogenic), currently no available effective therapy for relapsed MM

Side Effects of Kinase Inhibitors

All kinase inhibitors have toxicities

The spectrum of toxicities is often dictated by the array of receptor/target inhibition

- In general, the more receptors inhibited, the more toxicities observed

Toxicities observed are often similar to those that occur with other systemic therapies such as chemotherapy

In most instances, toxicities can be prevented or readily managed with appropriate supportive care or dose modulation/schedule modulation

Life-threatening toxicities are rare, although early recognition of potential problems is critical

Side Effects of Kinase Inhibitors

Spectrum and severity of toxicities are likely influenced by several factors including:

- stage of disease: dogs with more advanced disease generally have a lower performance score that could potentially influence toxicities; this has been shown to be the case in humans treated with multi-targeted therapies

- type of cancer: dogs with macroscopic MCTs are known to have high circulating levels of histamine that can predispose to GI ulceration and other GI toxicities; these could be compounded by Palladia therapy

- pre-existing conditions: liver disease, renal disease, cardiac disease can all influence performance scores, and these may also impact drug metabolism/elimination thereby compounding toxicities

- concomitant meds: certain drugs may exacerbate GI toxicity or impair drug metabolism

Side Effects of Kinase Inhibitors

Anorexia, lethargy, diarrhea, GI bleeding, vomiting

Agent specific toxicities: neutropenia (Palladia), muscle cramping (Palladia), hypoalbuminemia (Kinavet), protein losing nephropathy (Kinavet), hepatotoxicity (Gleevec)

Prevention/Management of Side Effects

Administer with food/a meal

H2 blockers or proton pump inhibitors may help prevent GI irritation/ulceration, particularly in MCT patients (famotidine, omeprazole, sucralfate, misoprostol)

Anti nausea agents may help with anorexia (metoclopramide, ondansetron, Cerenia)

Medications that treat or prevent diarrhea (Peptobismol, loperamide (Imodium), metronidazole)

If clinical signs do not readily resolve, consider treatment break with alteration of dose and/or schedule

Summary of Adverse Drug Events (AEs) 10/1/09 – 2/28/10

81 AEs Reported

77 Adverse responses with 14 mortalities: majority (62/77) reported in mast cell tumor (MCT) patients, 15/77 reported in other tumor types

3 Lack of efficacy

1 Human exposure

Clinical Signs Reported in Non-Mortality Cases

10/1/09 – 2/28/10

Emesis (40%), Diarrhea/hemorrhagic diarrhea (38%), gastroenteritis/abdominal pain (36%), lameness/joint pain/local pain/musculoskeletal disorder (25%), lethargy (22%), anorexia (18%), alopecia (11%), GI tract hemorrhage (11%), skin lesions/delayed wound healing/dermatitis/abscess (9%), pigmentation disorder (9%), muscle tremor (7%), pancreatitis (7%), ataxia (4%), hepatomegaly (4%), convulsion, cataract, tachycardia, doughy abdomen (2%)

AEs occurring in >10% of PALLADIA-treated dogs during blinded phase of clinical trial

Diarrhea (46.0%), anorexia (includes decreased appetite) (39.1%), lethargy (35.6%), vomiting (32.2%), lameness (17.2%), weight loss (14.9%), musculoskeletal disorder (11.5%), blood in stool/GI bleed/hemorrhagic diarrhea (12.6%)

Laboratory Abnormalities Reported in Non-Mortality Cases, 10/1/09 – 2/28/10

Neutropenia/leukopenia (29%), Anemia (11%), Thrombocytopenia (7%), Hepatopathy (4%), Elevated BUN (4%), Neutrophilia (2%)

Laboratory AEs occurring in >10% of PALLADIA-treated dogs during blinded phase of clinical trial

Neutropenia (46.0%), Thrombocytopenia (24.1%), ALT (24.1%), Albumin (12.6%)

Mortality Adverse Event Reports (n=14), 10/1/09 – 2/28/10

79% (11/14) were in poor prior condition

MCT disease had been diagnosed for an average of 4.6 months (range = 1 week to 12 months) prior to initiation of PALLADIA treatment

Average treatment duration was 11 doses, EOD (range = 5 to 51 doses)

11/14 cases (79%) reported using a dose reduction and/or drug holiday to manage the adverse reactions

8/14 cases were most likely euthanized or died due to progression of disease

6/14 cases were more difficult to determine if the direct chemotherapeutic side effects or the complications associated with MCT necrosis and subsequent histamine release was the cause of the poor outcomes

Non-Mortality Adverse Event Reports (n=63), 10/1/09 – 2/28/10

Majority (52/63) had MCT; 11/63 non-MCT, Average dose was 3 mg/kg, Average length of treatment before a reaction was observed was 4 weeks (range 1 dose to 22 weeks), 30% described PALLADIA dose reductions, treatment breaks and/or dose schedule modifications that were instituted to manage AEs, Palladia was discontinued in 20/63 (32%) of these cases due to AEs (75% of those 20 cases did not report any attempts at dose reductions or drug holidays), Majority were monitored closely by veterinarians weekly or q 2 weeks (Illustrates that early detection and medical intervention are critical), Most frequently used concomitant medications: GI protectants, Prednisolone on alternating days with PALLADIA, Maropitant, Metronidazole

Palladia in non-MCT patients

Phase I study indicated potential biologic activity in tumor types beyond MCT: Metastatic carcinomas and sarcoma (STS, OSA), Melanoma, Myeloma

Several dogs experienced SD for extended periods (6 months) and a few underwent partial responses to therapy

Multi-targeted RTKs similar to Palladia (Sutent/Sorafenib) have shown activity in several different tumor types in people.

Palladia in non-MCT patients: Phase I study (table shown)

Palladia in non-MCT patients

Tumor Types: Anal gland adenocarcinoma n = 16, Thyroid carcinoma n = 9, Squamous cell carcinoma

n = 5, Osteosarcoma n = 4, Hemangiopericytoma n = 2, GIST n = 2, Hemangiosarcoma n = 2, Primary lung adenocarcinoma n = 2, Histiocytic disease, melanoma, nasal adenocarcinoma, TCC, gastric CA, neuroendocrine CA, nephroblastoma, renal cell CA, vaginal CA

Palladia in non-MCT patients

Time on Palladia: Median: 18 weeks (126 days, mean 18.1 weeks), Range: 4-56 weeks

Overall response to therapy: SD n = 29, PR n = 16, MR n = 3, CR n = 3

Palladia in non-MCT patients: Anal gland ACA

Response to therapy: SD: n = 10, PR: n = 5, MR: n = 1

Anal Sac Adenocarcinoma (radiographs shown)

Palladia 3.25 mg/kg EOD, then 2.7 mg/kg EOD; on therapy for 5+ months

Anal Sac Adenocarcinoma (radiographs shown)

Palladia 2.72 mg/kg MWF for 3+ months

Goal of Targeted Therapy

To identify abnormal protein/pathway common to certain cancers and to develop therapies that specifically target this pathway

Approaches include: monoclonal antibodies, small molecules, anti-angiogenic agents, anti-sense approaches, gene therapy, tumor vaccines

Targeted Therapy: The Human Experience

Several successes in the human arena, most have involved the use of monoclonal antibodies or small molecule inhibitors, in some instances, the targeted therapies have become part of standard of care, although this process often takes years. Herceptin for breast cancer, Rituximab for B cell LSA, Gleevec for CML/GIST

Targeted Therapy: The Human Experience

The effectiveness of targeted therapies is generally dependant on the reliance of tumor cells on the protein/pathway affected by the therapy - aberrant expression of a receptor/pathway does not mean the tumor cell is necessarily relying on that receptor/pathway for growth/survival

Inhibitors can be very specific, as in the case of monoclonal antibodies, or have multiple targets as

occurs with several small molecule inhibitors

Toxicities result from effects of target inhibition on normal cell types

Small Molecule Inhibitors

Most small molecule inhibitors work by blocking the ability of their target to engage in functional activity.

For several targets this entails preventing the binding of ATP, as this is critical for donating phosphate groups necessary for the initiation/maintenance of signaling.

In some instances, small molecule inhibitors act to prevent protein-protein interactions that are necessary for signaling

Usually given orally, sometimes intravenously and work at low micromolar or nanomolar concentrations

Therapeutic Efficacy

Dependent on extent/duration of target inhibition

Tumor cells need to rely on the particular pathway being targeted

Unlike chemotherapeutics, activity may not be completely tied to maximum tolerated dose (MTD)

- effective target inhibition may occur below the MTD

Unlike chemotherapeutics that often irreversibly damage DNA, target inhibition is usually reversible

- pathway inhibition usually relieved following metabolism of therapeutic

Resistance typically driven by mutation in target binding site that prevents inhibitor from binding, or development of alternative signaling pathways

Resistance to targeted therapeutics

Resistance to targeted therapeutics is a common occurrence, especially when used in the gross disease setting, and when the inhibitor is used as a monotherapy

Resistance may occur through multiple mechanisms - development of mutations in the target that limit or preclude drug binding, gene duplication overwhelming the inhibitor, development of additional dysregulation/mutation/pathways that circumvent the inhibitor

Evidence suggests that in many cases, resistance is present in small numbers of tumor cells at the initiation of treatment

This supports the notion that use of targeted therapies in the microscopic disease setting is likely to provide more durable tumor control

Targeted therapies in veterinary medicine

Limited use in veterinary medical oncology - lack of well-defined targets for specific cancers, little data regarding safety and toxicity of many agents, some therapeutics cannot be used (i.e., humanized monoclonal antibodies), often cost prohibitive

Canine/feline cancers for which targets have been identified - mast cell tumors, osteosarcoma, GIST, sarcomas

Small molecule inhibitors that have been evaluated in dogs/cats - Gleevec, Kinavet, Palladia

Target profiles of imatinib, masitinib, toceranib (graph shown)

Response to Gleevec (photos shown)

Current status of Kit inhibitors and MCTs

The development path for Kit inhibitors in veterinary medicine mirrored that in human medicine
-Analysis of target specificity, proof of target modulation in vitro required, demonstration of activity in mouse models, from identification of an inhibitor to approval takes years, It is clear that Kit inhibitors have biologic activity against MCTs although challenges exist with respect to the exact role these inhibitors should play in treating mast cell disease, should treatment be based on the presence of Kit mutation?, how should Kit inhibitors be combined with standard therapies?, what should be the duration of treatment?, macroscopic vs microscopic disease setting?

Role of multi-targeted inhibitors beyond MCTs

Palladia inhibits VEGFR in addition to PDGFR and thus may be useful in the anti-angiogenic setting used in metronomic protocols

Evidence now suggests that VEGF/VEGFR inhibitors when combined with low dose cytotoxics have broad activity in the metronomic setting

Recent human clinical trials have shown biologic activity of metronomic protocols combining Avastin (mAb directed against VEGF) with cytotoxics (cytoxan plus capecitabine or methotrexate)

-63% of patients in one study with metastatic breast cancer had PR (31.8%)/SD (31.8%) >24 wks

-68% of patients in one study with metastatic breast cancer had CR (2%), PR (46%), or SD (41%)

Preliminary data suggests that Palladia can be safely administered with cytoxan and certain NSAIDs; biologic activity noted in Anal Sac ADC, Thyroid CA, SCC, OSA

Challenges of metronomic anti-angiogenic therapy

While both cytotoxic agents and anti-angiogenic agents appear to be critical for effective metronomic therapy, there is little data regarding the class of cytotoxic that is most appropriate.

Dosing regimens for cytotoxics in metronomic protocols are generally empirically derived and not based on clear modulation of circulating endothelial precursors

Efficacy in the microscopic disease setting is generally unknown and for the most part untested

There are currently no established biomarkers to monitor the potential efficacy of metronomic protocols that incorporate VEGF/VEGFR inhibition - Plasma VEGF, Circulating endothelial precursors, Soluble VEGFR

Targeted therapies: Future directions

Several new targets are under investigation in the human clinical arena

Many of these are now being explored in veterinary medicine – mTOR, STAT3, HSP90, HDACi, Her2/Neu, CD20

Targeted therapies: HDAC inhibitors

Global DNA hypermethylation and histone hypoacetylation resulting in suppression of gene expression is a hallmark for many cancers

HDACi treatment results in hyperacetylation of H3 and H4, which induces re-expression of previously silenced genes in cancer cells, such as P21 and TRAIL

Other non-histone targets, such as HSP90, STAT3 and tubulin are also acetylated following HDACi treatment, altering their function.

These changes presumably restore the ability of cells to undergo cell cycle arrest and apoptosis

SAHA in the treatment of MCTs (photos shown)

Summary

The number of targeted agents in active human clinical trials has increased dramatically over the past 5 years

Despite this, few agents have demonstrated substantial single-agent activity

Significant challenges remain regarding how best to use these agents, particularly with respect to identifying those individuals most likely to respond to therapy

In the human arena, targeted therapies have only recently been used in the microscopic disease setting. Studies are ongoing regarding how best to combine these agents with standard of care (i.e., RT and chemo)

New Clinical Trial

- Partially funded!, Splenic hemangiosarcoma, 5 doses of doxorubicin, Toceranib “maintenance”

Pododermatitis

Joel D. Griffies, DVM

Diplomate American College of Veterinary Dermatology



Animal Dermatology Clinic

Tustin . San Diego . Marina del Rey . Pasadena, CA

Marietta, GA . Louisville, KY . Indianapolis, IN

Introduction

Pododermatitis - inflammation of the paws - may affect the nail fold (paronychia), interdigital spaces, foot pads, claws and/or remainder of the skin of the paws. When presented with a case of pododermatitis, familiarity with the list of potential differential diagnoses for various presentations may prove beneficial to limit the most likely etiology. Listed below are differentials to consider based on species, presence or absence of symmetry and single or multiple digits or feet affected:

Canine Asymmetric Pododermatitis: Trauma, Irritant, Foreign body, Infection (Bacterial : *Staph. intermedius*, *Nocardia*, *Actinomyces*, *Pseudomonas*, *Proteus*; Fungal: dermatophytes, *Malassezia*, blastomycosis, cryptococcosis, eumycotic mycetoma, candida), Parasitic-demodex , Neoplasia , Miscellaneous: acral lick dermatitis (multitude of causes), calcinosis circumscripta, arteriovenous fistula, osteomyelitis

Canine Symmetric Pododermatitis: Irritant contact, Allergies - atopy, food, contact, Infection (bacterial - *Staph. Intermedius*; Fungal-*Malassezia*), Parasitic: (demodex, pelodera, hookworms, leishmaniasis), Autoimmune (Pemphigus foliaceus, P. vulgaris, bullous pemphigoid, SLE). Immune Mediated (sterile granuloma/pyogranuloma, cold agglutinins, vasculitis, Dermatomyositis, drug eruption, EM-TEN), Metabolic (Superficial necrolytic dermatitis, calcinosis circumscripta), Nutritional (Zinc responsive dermatosis), Immune suppression (congenital or acquired)(bacterial, dermatophytes, candidiasis, demodicosis), Psychogenic/neurogenic (Acral mutilation of GSH pointers), Congenital (Familial vasculopathy of GSD, Vasculitis of Jack Russell Terriers, idiopathic footpad hyperkeratosis, Familial hyperkeratosis in Irish terriers, Kerry blue terriers and dogues de Bordeau, acrodermatitis of bull terriers, tyrosinemia), Miscellaneous (Dermatofibrosis, neoplasia, distemper).

Feline Pododermatitis: Immune mediated (Pemphigus foliaceus, plasma cell pododermatitis, drug eruption, EM-TEN), Allergic (Atopy, food sensitivity), Eosinophilic granuloma (may or may not be allergy related)

Diseases Restricted to One or Two Claws: Trauma, Bacterial Infection, Dermatophytosis/fungal infection, Neoplasia

Canine Symmetric Onychomadesis (Nail Sloughing:) Autoimmune/Immune Mediated (Pemphigus/pemphigoid, SLE, "Lupoid" onychodystrophy, Vasculitis, Cold agglutinin disease, drug eruption), Superficial necrolytic dermatitis, Hypothyroidism?, Neoplasia, Food sensitivity, Bacterial infection, Idiopathic

Canine Onychodystrophy (Deformed/Friable Nails: Lupoid onychodystrophy, Primary seborrhea (e.g., cocker spaniel), Senile change, Idiopathic, Acrodermatitis in bull terriers

Feline Paronychia: Pemphigus foliaceus, Bacterial, Dermatophytosis, Malassezia

Feline Nail Disease: Onychorrhexis (trauma; post inflammatory; dermatophytosis),
Onychomadesis (cold agglutinin disease, drug eruption, vasculitis), Neoplasia (Pulmonary
Bronchial Adenocarcinoma)

Pododermatitis - Specific Diseases

Demodicosis

Demodicosis is a mandatory differential diagnosis for any canine pododermatitis, whether symmetrical or involving only one paw. Demodex infections may be restricted to only the paws in some cases. Diagnosis is made by hair plucking or scraping. In patients with very chronic paw changes with excessive scarring, biopsies may be necessary to rule out this diagnosis. Some breeds, (Chinese Shar pei) may also require a biopsy for demodex diagnosis. Patients with only one paw or all feet involved should typically be classified as generalized demodicosis and worked up and treated as such. Pododemodicosis cases are often difficult to treat topically with localized or spot therapy (i.e., Goodwinol), and most require systemic therapy (e.g., 0.3-0.6 mg/kg oral ivermectin or moxidectin daily or every other day in non herding breeds or milbemycin oxime, 1-2 mg/kg daily) More recently a topical amitraz/metaflumizone product (Promeris[®]) has been used successfully in the treatment of demodicosis. Typical protocol includes topical application every 2 weeks until 2 negative skin scrapes then once monthly. Regardless of the type of therapy treatment should be for 2 months beyond remission and may be needed for life. For adult onset demodicosis one should always look for underlying immunocompromising diseases ie, cushings, diabetes, neoplasia, etc, as a predisposition to the development of this problem.

Allergic Dermatitis

Both atopy and food sensitivity in the dog commonly cause pododermatitis usually in association with pruritus. Salivary staining is common. The dermatitis produced is often diffuse in the interdigital and ventral interpad spaces and may also involve the flexor surface of the front paws and extensor surface of the rear paws just proximal to the carpal and tarsal pads. Claw fold involvement (paronychia) may predominate in some. This dermatitis is commonly complicated by secondary bacterial and/or *Malassezia* dermatitis (especially interdigital spaces, claw folds). These secondary infections should be identified and treated. Milder *Malassezia* cases may be treated with an antifungal/antibacterial topical shampoo or wipe (Containing miconazole, ketoconazole, climbazole and chlorhexidine). Many cases will require systemic therapy with oral antifungals (ketoconazole, fluconazole itraconazole) followed by maintenance oral and/or topical therapy.

Recurrent Bacterial Interdigital Pododermatitis

Bacterial pododermatitis in the canine is usually associated with *Staphylococcus intermedius*. Lesions are usually more focal, crusted, papular or pustular and may produce draining tracts. Lesions are often incorrectly referred to as "interdigital cysts." Differential diagnoses include other bacterial and fungal infections, foreign bodies and sterile nodular granuloma/granulomas. Short-coated breeds (e.g., Doberman, Mastiff, English Bulldog) appear to be prone to idiopathic (no systemic disease documented) recurrent bacterial infections in this area. In the English Bulldog conformational defects are also a major predisposing factor. In the author's practice, common therapies for such cases most commonly include higher doses of antibiotics such as cephalexin or fluorquinolones until at least 2 weeks beyond remission. Some cases need culture and susceptibility testing to identify appropriate antimicrobial choices. Resolution may

be facilitated by the use of topical mupirocin (Bactoderm, Pfizer) q 12h and germicidal shampoos (especially chlorhexidine or benzoyl peroxide containing). Pentoxifylline (20 -30 mg/kg q 8-12h) may also be of benefit to enhance perfusion, reduce fibrosis and reduce inflammation in chronic, fibrotic lesions. Some routinely use metronidazole (10 mg/kg q 12h) as an adjunctive therapy to help reduce inflammation. Very recurrent problems are treated with long term, lower dose daily cephalexin or pulse cephalexin therapy (3 days per week) or with bacterins (Staphage Lysate, Delmont Laboratories).

Vasculitis

Vasculitis often involves the extremities and not uncommonly the footpads in both dogs and cats. Lesions are often focal, erosive to ulcerated or have well-delineated, pale or "punched out" lesions and interestingly may often appear in the more central portions of the pad (pressure points). Patients may or may not have other skin lesions (e.g., purpura, erosions/ulcerations, dermatitis, edema) or claw dystrophies. The diagnosis is supported by skin biopsy, of deep samples from the margins of lesions. Although many cases of vasculitis are idiopathic, emphasis must be placed on looking for other underlying causes (e.g., local bacterial infection, systemic diseases such as Rickettsia or systemic lupus erythematosus). Treatment for idiopathic vasculitis often includes pentoxifylline (15-20 mg/kg q 8h) as a first choice with cyclosporine (Atopica) or immunosuppressive dosages of glucocorticoids (e.g., 2.2-4.4 mg/kg q 24h or prednisone/prednisolone to start) in more severe cases. Other therapies that may be beneficial include glucocorticoids combined with azathioprine, tetracycline and niacinamide, (or doxycycline and niacinamide), dapsone and sulfasalazine Tacrolimus topically (ProTopic®) may also be useful for localized lesions.

Pemphigus Complex

Inflammation/crusting at the pad/skin junction is common on the paws of dogs with pemphigus foliaceus and pemphigus vulgaris (Rosenkrantz WS, 2004). There is usually interdigital involvement and paronychia is not uncommon. In some patients, hyperkeratosis, crusting, inflammation and erosion will involve the pads of all four feet. In cases of Pemphigus foliaceus, these lesions can occasionally be , the only areas involved at initial presentation. Pain is variable, but may be the primary reason for presentation. Some dogs will be reluctant or unable to walk because of the discomfort. Severe lesions may also have pustule formation, often seen as a greenish/yellowish discoloration of the pad. Significant epithelial loss of the pads may be encountered. Purulent material, if present, should have a cytologic examination performed. The presence of large numbers of neutrophils and/or eosinophils and acantholytic keratinocytes would be highly suggestive of pemphigus foliaceus or pemphigus vulgaris. Bacteria are usually not present in the cytology of unruptured pustules, but may contaminate ruptured lesions. In cats, with pemphigus foliaceus, the paws (especially clawfolds) are the most common area for the initial development of skin lesions (Preziosi, Goldschmidt, Greek, 2003). In one study (Greek, 1993) initial affected sites in the cat were clawfolds (78%), paws (43%), face (39%), ears (30%). Pad changes include swelling, hyperkeratosis, scaling, crusting, hardening and fissuring. Pain is variable, and may be severe. Pain may be disproportionately severe for the degree of pad change present. Diagnosis is supported by cytology (look for greenish/yellowish discoloration at pad/skin junction) and confirmed by biopsy.

Therapy: Treat secondary bacterial and *Malassezia* infections and utilize classic immunosuppressive/anti-inflammatory drugs such as glucocorticoids, azathioprine, +/- tetracycline/niacinamide, cyclosporine. Cyclosporine can be very effective in cases of feline pemphigus but typically not as a sole therapy in the dog.

Superficial Necrolytic Dermatitis (Hepatocutaneous Syndrome, Metabolic Dermatoses, Metabolic Epidermal Necro(ly)sis)

SND is an uncommon dermatosis seen in dogs and recently has been described in the cat. In dogs, SND has been associated most commonly with idiopathic hepatocellular collapse, cirrhosis, glucagon producing pancreatic adenocarcinoma, hyperglucagonemia and glucagon secreting liver metastases (primary tumor not found, hepatopathy secondary to phenobarbital/dilantin administration, hepatopathy possibly associated with primidone or phenobarbital and hepatopathy secondary to ingestion of mycotoxins (Campbell, Matousek, Lightensteiger, 2000) (March, Hillier, Weisbrode,). In the author's practice a few cases associated with inflammatory liver disease (chronic active hepatitis, etc.) have also been seen. The disease is generally seen in middle aged to older dogs. and may wax and wane. Concurrent diabetes mellitus is relatively common (especially later in the course of the disease). Pad and/or pad/skin junction lesions are common early associations with this disease and often consist of inflammation, crusting and hyperkeratosis progress to fissuring. All pads are usually involved. The interdigital spaces and nail folds are also typically inflamed and crusty. With progressive involvement and fissuring, the paws often become very painful and lameness and reluctance to walk may present significant problems. Other areas of skin involvement are often seen (muzzle, periocular, perioral, perianal, perivulvar, scrotal, pressure points over elbows and hocks). In severe cases, the claws may be dystrophic and may slough. Secondary infections of paw lesions are common and may contribute significantly to pain, lameness or pruritus. These include bacteria (usually *Staphylococcus*), *Malassezia*, and occasionally candida or dermatophytes.

Diagnosis is by skin biopsy (characteristic parakeratosis, superficial epidermal vacuolation, epidermal hyperplasia). Once the diagnosis is made the author also prefers to evaluate the liver via abdominal ultrasound and in most cases ultrasound guided liver biopsy.

Treatment for SND primarily revolves around the finding that these patients have significant deficiencies in amino acids. Potential options may include the following: 1. Diet high in good quality protein (e.g., supplement with Hill's a/d). Enteral or parenteral feeding may be necessary 2. Management of diabetes mellitus if present. Response to insulin may be erratic. 4. Symptomatic treatment for secondary infections. 5. Amino acid supplementation: Egg yolk supplementation (3-6 yolks per day) has been noted to be of some benefit, perhaps because of the amino acid profile provided. Others have used protein supplements favored by body builders, Intravenous amino acid therapy has been noted to benefit people with hepatopathy related SND. A number of clinicians have also seen significant benefit from canine cases treated with products such as FreAmine III or Aminosyn 10% Crystalline Amino Acid Solution (Abbott Laboratories). Protocols include 500 ml per dog (or 25 ml/kg) administered slowly over about 8-12 hours in a large central vein (jugular vein). Consideration should be given to measuring blood ammonia prior to this infusion in that it is possible to contribute the hepatic encephalopathy with this therapy. The patient is re-examined in 7-10 days. If significant improvement is noted, no further infusions are given. Prolonged remissions have been noted after only one infusion. If minimal to no response is noted, the infusions are repeated every 7-10 days for 4 treatments. If an individual does not improve in this time, it is unlikely that they will respond. The infusion is repeated with each exacerbation of the skin lesions. Some patients go several months between infusions but others who require monthly infusions to maintain remission. As the disease progresses, the need for infusions will likely increase. However, there are anecdotal reports of indefinite remissions following the first treatment. 6. Essential fatty acid

supplementation - we have, at present been supplementing primarily with omega 3 fatty acids at twice the bottle dosage of a high potency omega 3 fatty acid supplement (3 V caps - DVM pharmaceuticals). 7. Zinc supplementation is also instituted in all individuals. We have used 2mg/kg/day of zinc methionine. 8. Niacinamide therapy may also be considered - 250-500 mg/dog q 8 – 12h. 9. For focal inflammatory lesions (e.g., pododermatitis), when infection problems have been as well as possible controlled, consider the use of topical glucocorticoids - e.g., generic triamcinolone acetonide BID initially. Gradually reduce this frequency and, if possible, switch to hydrocortisone for long term, maintenance therapy. 10. Systemic steroids (e.g., prednisone starting at 1 mg/kg/day) have been noted to benefit some individuals. Effects are usually transient (will eventually become refractory to these dosages of therapy) and there is concern for exacerbating diabetes mellitus. 11. Ketoconazole as been used with some benefit in this disease (5-10mg/kg q 12h perhaps because of its effects on secondary Malassezia infections or perhaps for its antiinflammatory and antipruritic effects

Idiopathic Digital Hyperkeratosis (Also see Localized Keratinization Defects)

Hyperkeratosis of the footpads, with or without involvement of the planum nasale is seen as an idiopathic disorder, usually in older dogs. However, it may occur in any aged individual. Certain breeds, such as the cocker spaniel, may be predisposed. Hyperkeratotic "feathers" or "fronds" are most commonly noted at the margins of the pads. In some instances, the hyperkeratotic tissues may be very hard, resulting in fissures. This likely causes the pain sometimes associated with this disease. If depigmentation, inflammation, erosion or ulceration is present in association with these lesions, consideration should be given to differentiating this disorder from SLE, pemphigus complex, SND and cutaneous lymphoma. The diagnosis is generally based on history and physical examination, and, if necessary, skin biopsy. Histologically, idiopathic pad

hyperkeratosis is characterized by epidermal hyperplasia and marked orthokeratotic to parakeratotic hyperkeratosis. Therapy is considered only if the hyperkeratosis is problematic. Excess keratin may be removed with scissors or a blade. When the keratin is not hard/dry, keratolytics may be applied (e.g., KeraSolv gel, DVM Pharmaceuticals - 6.6% salicylic acid, 5% sodium lactate, 5% urea in propylene glycol or Retin A (tretinoin, Ortho). When the keratin is hard, rehydrating the pad by soaking the paw for 5-10 minutes, then applying an occlusive agent (petrolatum or 50:50 propylene glycol in water) may be of benefit. This is done daily initially. Debris is removed by shampooing every 3-7 days. Owners must be warned of the potential "mess factor" associated with these topical therapies. Consideration should also be given to looking for and/or treating secondary bacterial infections. Another topical product tried by the author combines an occlusive agent along with germicidal effects (Bag Balm by Dairy Assoc. CO, Inc. Lyndville VT 05851. This contains 8 hydroxy-quinoline sulfate 0.3% (germicidal) in a petrolatum and lanolin base. The product is applied once or twice daily initially, and then the frequency is gradually reduced to maintenance. Oral Vitamin A therapy may also be of benefit. Dosage is 8,000-20,000 units q 12 h. The author generally starts with 8,000 to 10,000 units q 12 h. Retinoid therapy (e.g., isotretinoin at 1 mg/kg/day or acitretin 0.5 mg/kg/day) may have some efficacy but the high cost and need for continued therapy are prohibitive.

Zinc Responsive Dermatitis

The footpads of dogs with zinc responsive dermatosis may become hyperkeratotic (as noted in the Malamute, Siberian Husky, and occasionally in other breeds such as the Doberman pinscher and Great Dane) (White S, et al 2001). This condition can also be seen in dogs that are on diets that are deficient in zinc. This was a problem in California years ago associated with certain generic dry dog foods. Zinc responsive dermatosis pad lesions are usually

relatively mild, compared to other skin lesions. Pad hyperkeratosis is most commonly noted in conjunction with skin lesions involving other areas of the body. Diagnosis is by skin biopsy (widespread parakeratotic hyperkeratosis) and response to zinc supplementation (2 mg/kg/day zinc methionine, 5 mg/kg/day zinc gluconate or 10 mg/kg/day zinc sulfate). The potential multifactorial nature (nutritional?) of this problem is supported by the fact that some individuals respond better when they are treated with essential fatty acids, or low every other day dosages of glucocorticoids (improved absorption?) or hypoallergenic or restrictive diets. Very refractory cases have been treated with IV zinc sulfate (10-15 mg/kg zinc sulfate; diluted 1:1 with saline and given very slowly IV. Panting or possible anaphylaxis, seizures have been anecdotally reported. Perivascular leakage will produce severe local necrosis, if leakage occurs, recommend intralesional steroid and topical DMSO. IV therapy is repeated once weekly for 4-6 weeks, then every 1-6 months for maintenance. Note: this dose is for zinc sulfate (the salt) and not elemental zinc. 50 mg/ml of zinc sulfate contains 0.2 mg/ml elemental zinc.

Feline Eosinophilic Granuloma Complex

Eosinophilic plaques and eosinophilic granulomas may occasionally be noted to affect the pad or pad/skin junction of cats. Although underlying hypersensitivity disorders must be explored (e.g., atopy, food and insect sensitivity), many of the cases appear to be idiopathic. Diagnosis is by skin biopsy. Response to glucocorticoid therapy has generally been good (methylprednisolone - 1.1-2.2 mg/kg q 24h initially, then tapered to q 48-72h). Some cases may require alternative glucocorticoids, (i.e. triamcinolone) or other immunosuppressive therapies such as chlorambucil, gold salts or cyclosporine. Spontaneous resolution may be noted.

Feline Plasma Cell Pododermatitis

The underlying cause of this problem is not known, but likely relates to an immunologic disorder

(Guaguere E, Hubert B, Delabre C, 1992). In some cases, seasonal changes suggest an allergic basis. Some cases may be associated with underlying viral disease (i.e. FIV, FeLV). The earliest change seen is usually the development of a white, scaly, cross hatch pattern and scaling of the pads. Occasionally, the pads may progress to erosions or ulcerations and often appear swollen or “inflated”. There may be significant hemorrhage. These changes vary from being asymptomatic to involving significant pain and lameness. Systemic signs are also variable (pyrexia, lethargy, anorexia, peripheral lymphadenopathy). General laboratory screening usually reveals a hyperglobulinemia. Pad biopsies show a perivascular accumulation of plasma cells, with lesser numbers of lymphocytes and neutrophils. Leukocytoclastic vasculitis has been described. It has been suggested that the early lesions may involve significant infiltration with eosinophils. Some cases will spontaneously resolve with no therapy. In one study glucocorticoids cleared 4/6 cases (Pereira, PD and Faustino, AMR 2003). Therapeutic options include doxycycline (5 mg/kg q 12h; for antiinflammatory effect) (Bettenay SV, Mueller RS, Dow K, Friend S, 2003), glucocorticoids (prednisolone at 4.4 mg/kg q 24h), methylprednisolone acetate, oral triamcinolone acetonide beginning at 2-4 mg/cat q 24h, glucocorticoids and golds salts or glucocorticoids and chlorambucil or surgical excision. Cyclosporine has also produced favorable results at 5 mg/kg q 24h. Some treated patients may be able to eventually weaned off all medications, while others require ongoing therapy at lower dose or less frequent administration.

Paraneoplastic Alopecia and Internal Malignancies in the Cat

Cats with pancreatic adenocarcinoma or bile duct carcinomas may present with a symmetric alopecia involving the ventrum and extremities (Turek, 2003). Hairs are usually readily epilated. The footpads or footpad/skin junctions may be dry and scaly/crusty and occasionally fissured

and painful. Diagnosis is by skin biopsy from haired areas of the body (severe follicular and adnexal atrophy with follicular miniaturization and mild perivascular inflammation). Footpad biopsies may not be as rewarding and primarily show chronic inflammatory and secondary infections. It is also recommended to do workups to document visceral neoplasia. The prognosis is grave.

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Current Advances in Cruciate Ligament Tear Repair

Peter Sebestyen, DVM, Dipl. ACVS

Veterinary Surgical Specialists of Orange County

Tustin CA, USA

Cranial cruciate ligament tear is a common cause of chronic pelvic limb lameness in dogs. The economic impact of this condition was estimated to be over 1.3 billion dollars in 2005 (Wilke 2005). The cranial cruciate ligament prevents cranial translation of the tibia during weight bearing. Failure of the ligament results in subsequent instability, lameness and progressive degenerative joint disease. Although acute traumatic tear may occasionally be seen, more commonly it occurs gradually as a fatigue failure of the ligament, often under conditions of normal loading. Genetic basis of the cruciate ligament tear has always been assumed due to breed predisposition and it was recently confirmed in the Newfoundland breed (Wilke 2006 and 2009).

Many surgical procedures have been reported to treat patients with cranial cruciate ligament tear. The surgical techniques aim to stabilize the cranial cruciate deficient stifle with either extra-capsular or intra-articular implants. In the early eighties a dynamic stabilization method was introduced. Dynamic stabilization was achieved with leveling the tibial plateau by performing osteotomy. The tibial plateau leveling osteotomy neutralizes the cranial tibial translation during weight bearing (Slocum 1987). By the millennium the TPLO became the gold standard of cruciate repair especially in large breed dogs. In 2005 a prospective clinical trial was published describing the effect of TPLO, lateral suture and intra-articular fascia late graft techniques on limb function upon recovery (Conzemius 2005). Force plate analysis showed no significant differences at six months postoperatively and the authors concluded that the surgical technique had no influence on the outcome. The publication came as a shocking surprise to the world of veterinary surgery since the TPLO was considered a superior technique by most surgeons at that time. There could be a number potential explanation for controversy between clinical experiences and scientific evidence. Patients with cranial cruciate ligament tear may be at different stages of the disease at the time of diagnosis. This spectrum includes dogs with an

acute tear, significant instability and minimal secondary changes at the beginning of the spectrum and also patients with severe degenerative changes, meniscal pathology and minimal or no instability at the end of the range. Patients at different level of this disease spectrum may respond differently to the same uniform treatment. Dogs with acute tear, severe cranial drawer and lack of DJD would gain the most from stabilizing procedures. However, patients with chronic disease, more advanced DJD and meniscal pathology may benefit little from stabilization. Intra-articular treatments, meniscal management and physical therapy may be more important treatment modality for this subset of patients. Having recognized these differences further research is aiming to develop an algorithm for treating patients with cruciate disease at different stages stressing either stabilization or intra-articular treatments.

Joint stability emphasis: Relatively small percentage of dogs present with acute cruciate ligament tear without secondary changes. They are the best candidates for extra-articular stabilizing methods as the primary dysfunction is caused by instability alone. Many modifications have been recently made to the original lateral suture method. The recently introduced Tightrope CCL repair uses stronger suture material in more isometric fixation points to preserve range of motion and prevent failure from cyclic loading. The technique advocates more stable fixation utilizing bone tunnels as opposed to the conventional fabella-to-tibial tuberosity suture. The tightrope suture may be applied non-invasively via small stab incisions minimizing postoperative morbidity. Despite of these improvements, the tightrope suture is expected to loosen with time and if periarticular fibrosis fails to develop in the meantime, instability will recur. The tightrope and other lateral suture stabilizing methods are best suited to treat joints with severe instability and minimal or no secondary changes. They make less therapeutic sense for treating partial tears with minimal or no instability. Patients on the middle of the disease spectrum with minimal or no joint instability, and moderate to severe secondary changes are better candidates for geometry altering treatment methods.

Slocum developed dynamic stabilization technique from the basis of the tibial compression test. The basis of his hypothesis was that the magnitude of cranial tibial thrust (CrTT) is proportionate to the tibial plateau angle (TPA). If the TPA is leveled to 0-5 degree with the functional axis of the tibia (or the direction of the main compressive forces), the CrTT becomes zero. (Slocum 1983). The tibial plateau leveling osteotomy (TPLO) was developed and its positive biomechanical effect was confirmed by in vitro studies.

Tepic proposed the theory of tibial tuberosity advancement (TTA) based a biomechanical model of the human knee (Tepic 2002). In this model the total joint force is parallel to the patella tendon and not to the functional axis of the tibia. At a patella tendon-tibial plateau angle (PTA) of 90 degrees or less, the total joint force will not generate cranially directed vector force and the joint is stable even without cranial cruciate ligament. Based on

this, advancement of the tibial tuberosity was proposed to create a PTA equal or less than 90 at normal standing angle of the stifle eliminating the cranially directed forces (Tepic 2002).

Although these techniques have been developed based on different theories, both procedures accomplish similar benefit. TTA has several biomechanical advantages; however, the clinical significance of this is unknown. TTA is a simpler procedure with less steep learning curve and less room for technical errors. TPLO is more versatile and can be applied to a wider spectrum of cases than TTA.

Intra-articular treatment emphasis: There have been significant changes in the way we perform intra-articular treatment today for a cranial cruciate deficient stifle. Intra-articular treatment includes debridement of the remains of the failed ligament and management of meniscal pathology. We can carry out these via conventional arthrotomy or arthroscopy. Arthroscopy has become the standard of care treating shoulder and elbow joint disease in canines. Arthroscopy offers quicker recovery, better visualization due to illumination and magnification. Stifle arthroscopy provided less short-term postoperative morbidity in comparison to conventional parapatellar arthrotomy (Hoelzler 2004). The routine parapatellar stifle arthrotomy was associated with more progressive DJD when it was compared to minimally invasive arthrotomy (Lineberger 2005). In addition to being minimally invasive, arthroscopy offers increased sensitivity at recognizing meniscal pathology. In vitro study concluded that arthroscopy with probing had 8 times higher sensitivity to detect meniscal pathology than conventional parapatellar arthrotomy (Pozzi 2008).

Traditionally the remains of the completely or partially torn cruciate ligament were to be removed. Debridement of the broken ligament fibers is thought to lessen the inflammation; however, there is no scientific proof for this. In case of a complete tear, debridement of the remaining cruciate ligament makes therapeutic sense and it is unlikely to cause any harm even if it does not necessarily produce any obvious benefit. In case of a partial tear where the joint stability is still maintained, excising the remaining ligament will result in severe instability so actually makes matters worse. The incomplete tear with maintained joint stability is referred to as functional partial tear and it should not be debrided. As opposed to a non-functional partial tear where the physically intact parts of the ligament are not capable of maintaining joint stability. Non-functional cruciate ligament tear should be debrided similar to the complete tear. The most compelling testimony regarding the effectiveness of TPLO has come from “second look” arthroscopy in patients with functional partial tears. In these patients the cruciate ligament was not debrided, the meniscus was left intact and at second look, the cruciate ligament and the menisci appeared normal and functional (Beale 2006).

Meniscal tear has been described as a late complication following TPLO and TTA in 6-14 % of the cases necessitating re-operation. These late meniscal injuries are either missed at

the initial surgery (latent tear) or may subsequently develop following the stabilization (postliminary tear). Slocum recommended releasing the intact meniscus during TPLO procedure to reduce rate of postliminary meniscal injury. The basis of this recommendation was the clinical observation of the relatively frequent late meniscal injuries after TPLO. Although the cause of the postliminary meniscal tear is not understood, it has been suggested that the residual stifle joint instability is responsible for the damage. Recent study evaluated the effect of the meniscal release on the rate of subsequent meniscal injury following TPLO (Thieman 2006). The study concluded that in joints undergoing open arthrotomy without meniscal release there is a 3.8 times higher chance for subsequent meniscal tear. Interestingly, the group of patients treated with stifle arthroscopy without meniscal release performed as well as the open arthrotomy with meniscal release. The authors concluded that the so called subsequent or postliminary tears are likely latent meniscal tears that were missed at the time of the initial procedure. These minor meniscal tears later progress to a clinically significant, more severe meniscal injury manifesting as "postliminary" tears. As we have a higher chance to detect these minor meniscal injuries with arthroscopy, the incident of late meniscal injury will be less. The authors also concluded that meniscal release should be performed whenever complete and thorough exploration of the medial meniscus cannot be, or is not, performed.

While meniscal repair is possible in selected cases, the majority of meniscal damage will be treated by removal of the damaged part or partial meniscectomy. The medial meniscus is an important stabilizer of the stifle and contributes to normal load transmission of the joint. Disruption of this meniscal function will lead to joint instability and increased loading stress on the cartilage and subsequently results in osteoarthritis. Therefore preservation of much healthy meniscal tissue as possible should be the primary goal of any meniscal surgery.

Summary: Our patients with cruciate ligament disease may present with a wide range of severity in joint laxity and secondary changes. As chronicity increases, joint instability decreases and the benefits of stabilizing techniques diminish. Patients with stable partial tears represent a special subpopulation and are likely to respond better to a geometry altering method rather than to a static extra-articular stabilization. Non-invasive intra-articular management via stifle arthroscopy is proven to lessen postoperative morbidity, increase sensitivity to detect meniscal pathology and induces less osteoarthritic changes than conventional arthrotomy.

What am I supposed to do with that epulis?

Eric Van Nice, Fellow, Academy of Veterinary Dentistry,

Diplomate, American Veterinary Dental College

Advanced Veterinary Specialty Group, Tustin CA

Veterinarians frequently encounter gingival masses in their patients in the course of routine examinations and dental cleanings. Then we wonder what is the best course of action. Should we trim the gingival mass back to normal contours? Should we extract the tooth? Should we curette the alveolus? Should we extract the teeth on either side of the mass? Are we supposed to get 3 mm margins? 1 cm margins? 2 cm margins? How about radiation therapy? Maybe we should get an oncology consult and see if chemotherapy will help. Maybe we should have obtained blood work and chest x-rays and lymph node aspirates before we started cutting.

What am I *really* supposed to do with that epulis?!

Here's the problem: epulis just means gum lump, nothing more. It is not a diagnosis, it is a gross visual description. And there are a wide variety of conditions that may result in gum lumps. So their biologic behavior varies as well. One treatment does not fit all.

That is why diagnosis must come before treatment. It is tempting to attempt definitive treatment in one procedure and be done with it. But this approach may result in over- or under-treatment. What if you extracted a tooth and curetted the alveolus and then found out it was a malignancy that not only needed 1 cm margins but now you have disseminated the cancer? Or how would you feel if you took a 1 or 2 cm margin segmental mandibulectomy and it turned out your patient only needed an extraction or two? And what would your client say about that?

So we need two steps. You need to discuss with your client all appropriate treatment options and the prognosis for each before deciding how much to cut. Again, *diagnosis first, treatment second*.

Step 1 is obtaining dental x-rays and a biopsy to determine the expected biologic behavior of the disease. Dental x-rays help characterize the lesion as more or less aggressive, and help determine how far it extends into bone and around adjacent teeth.

Here are some guidelines to help interpret dental x-rays of these lesions:

Non-aggressive

Well-defined bony lysis
Distinct margins
Narrow zone of transition
Thinning expanding cortex
Smooth layers of periosteal new bone
Displacement of adjacent teeth

Aggressive

Poorly defined bony lysis
Ragged margins
Wide zone of transition
Cortical lysis
“Sunburst” lytic and productive periosteum
Leaves adjacent teeth in position

Cytology may be helpful in some cases but does not give the pathologist as much information as biopsy. Try to get a wedge or a punch sample right down to include bone. This is usually a very brief general anesthesia with a local or regional block. We often send home some pain control meds until the next step.

Step 2 is surgical removal of the lesion. This is scheduled after you get the biopsy report back and have a good discussion with the client about treatment options and prognosis for each. How much you remove is determined by the histologic diagnosis. This may be definitive or palliative, and further staging such as CT/MRI may be helpful. An oncology consult is a great idea, because radiation, chemotherapy or other adjunct treatment may be options as well.

A quick outline of epulide considerations

<u>Epulis diagnosis</u>	<u>Biologic behavior</u>	<u>Surgical treatment</u>
Focal fibrous hyperplasia	More benign	Perio cleaning, gingivectomy
Fibroma, AKA "fibromatous" or "ossifying epulis"	Benign, but recurs with inadequate excision	extraction, 3mm margins
Feline epulis syndrome	"	en bloc w/ 3 mm margins
Giant cell epulis Acanthoma, AKA "acanthomatous epulis", recurs Acanthomatous ameloblastoma, Odontogenic tumors, Odontomas, APOT/CEOT, Fibroameloblastoma etc	Locally invasive, but don't metastasize, with inadequate excision " " " "	en bloc w/ 1 cm margins
Plasmacytoma	Locally invasive, Slow to metastasize	en bloc w/ 1 cm margins, and/or chemotherapy
Feline sarcoid	multifocal, invasive, No metastasis?	?????????????
Malignancies including Squamous cell CA, Fibrosarcoma, Melanoma, Lymphoma, Malignant odontogenic tumors, (carcinomas, sarcomas)	Locally invasive, may metastasize early metastasis	further imaging, staging, en bloc w/ 1 to 2 cm margins, oncology consult

Further reading:

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