Unusual Doesn't Mean Uncommon: Skin Diseases You Don't Want to Miss

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Calcinosis Cutis

Calcinosis cutis describes the deposition of calcium salts into dermal tissue (usually calcium phosphate or calcium carbonate). Four types are recognized in humans: Iatrogenic, Idiopathic, Dystrophic, and Metastatic. There is overlap between categories and these labels are not particularly helpful in veterinary medicine. The most common cause of calcinosis cutis in veterinary species is hyperglucocorticoidism. Typically, this is either secondary to hyperadrenocorticism (endogenous or exogenous) or steroid administration. Lesions typically develop on the dorsal neck and then spread caudally down the topline. Localized calcinosis cutis can occur secondary to chronic application of topical steroids. This is often apparent on the caudal ventral abdomen secondary to steroid sprays. Less commonly, calcinosis cutis can develop secondary to percutaneous absorption of calcium. Such exposure to calcium can occur when a pet comes in contact with certain floor cleaners, fertilizers, and ice melt products.

Calcinosis cutis can occur in any breed but it is more common in English Bulldogs. It is also more common in patients receiving Depo-Medrol injections. The clinical appearance of calcinosis cutis changes over the progression of the syndrome. Early lesions are chalky white to pink with indistinct margins. More advanced lesions are white, firm, and usually surrounded by intense inflammation. Pruritus is usually present and may be severe. Ulceration is common and secondary infection usually follows.

Diagnosis is easily confirmed with biopsy as the changes are unique and often dramatic. Collect biopsy samples from areas not affected by self-trauma and ulceration. Biopsy reveals diffuse or multifocal calcification of dermal collagen. Epidermal thickening and dermal edema are typically present as well. Calcinosis cutis is one dermatologic condition that can be seen on radiographs. It should be noted that serum calcium levels are not elevated in this syndrome.

Treatment involves eliminating exposure to environmental calcium and discontinuing steroid administration. If neither of these are a factor then cortisol testing is recommended, as hyperadrenocorticism is very likely. If the patient does have hyperadrenocorticism, then that condition needs to be managed in order to eliminate the calcinosis cutis. Patients without hyperadrenocorticism or exposure to external calcium or steroid containing products may have other severe systemic disease such as renal disease. Alternatively, some cases will develop secondary to repetitive micro-trauma (lesions typically on the pressure points of the limbs).

No treatment directly removes the calcium (aside from surgical excision). DMSO gel can be used to dissolve the calcium deposits. However, DMSO should be applied twice daily and may require weeks to months of treatment. Most owners cannot tolerate the smell of DMSO in their house for that length of time. Without DMSO, the calcium deposits will dissolve in two to twelve months. Patients with a history of calcinosis cutis should not receive steroid therapy in the future.

Hepatocutaneous Syndrome

Hepatocutaneous syndrome has also been called superficial necrolytic dermatitis (SND), metabolic epidermal necrosis (MEN), N\necrolytic migratory erythema (NME), and diabetic dermatopathy. I recommend against using the term diabetic dermatopathy because it is confusing and not descriptive. In addition, not every dog with hepatocutaneous syndrome has diabetes.

The pathogenesis of hepatocutaneous syndrome involves death of keratinocytes in the upper layer of the epidermis due to presumed amino acid starvation. Most affected dogs have a distinctive chronic hepatopathy; but, serum chemistry evaluation may not reveal any abnormalities. Potential causes of the hepatopathy include phenobarbital, primidone, mycotoxin, and gastroenteritis. In humans, this syndrome is almost always associated with glucagonoma. However, Glucagonoma is rare in dogs and accounted for only 8% of cases in one study.

Hepatocutaneous syndrome is generally a disease of older dogs. Only four cases have been reported in cats. Skin lesions are typically the first sign as opposed to more common systemic signs of liver disease. Crusts and erosions occur in areas of trauma/wear. Thus, the paw pads are usually severely affected. The elbows, hocks, and muzzle are frequently involved as well. Many affected patients are often reluctant to walk due to painful erosions and fissures on the paw pads.

Diagnosis requires biopsy of skin lesions with intact crusts. Histopathologically the changes are often described as a “French Flag”. Abdominal ultrasound can also be very helpful. A classic “honeycomb” pattern to liver is present in most cases of hepatocutaneous syndrome. However, inexperienced ultrasonagraphers may misinterpret the liver changes. In addition, the degree of change found on ultrasound does not necessarily correlate to severity of skin disease. CBC, serum chemistry, and urinalysis are also recommended. Nonregenerative anemia is common due to chronic disease. As stated before, liver values may or may not be elevated. Hyperglycemia is common and may require insulin therapy. Glucagon levels are elevated in patients with glucagonoma. However, glucagonoma is rare in dogs and cats and glucagon measurement is not readily available.

Management of hepatocutaneous syndrome is difficult because this disease is a marker of severe internal disease. Consider referring these patients. Affected animals may need both a dermatologist and an internist.

For glucagonoma-related disease it is recommended to remove the glucagonoma surgically. Unfortunately, glucagonomas have usually metastasized to the liver and abdominal lymph nodes by the time dermatologic lesions manifest. Cats with glucagonoma may also develop metastasis to the lungs and intestines. Even if metastasis has not occurred, affected patients are typically geriatric and my not be good surgical candidates. Octreotide, a synthetic somatostatin analogue, may be helpful for glucagonoma related disease. Octreotide binds to somatostatin receptors 2 and 5 to inhibit the release of glucagon. Octreotide will not affect the actual tumor but can yield quick and dramatic improvement in skin lesions. Octreotide is given two to four times daily indefinitely until the neoplasm progresses to the point of euthanasia or natural death. Theoretically, Octreotride would also be helpful for hepatic neuroendocrine tumors causing elevated glucagon levels and thus hepatocutaneous syndrome. However, hepatic neuroendocrine tumors are extremely rare with only one case reported in the dog and one in the cat.

A more common therapy is intravenous Aminosyn. Aminosyn can be useful regardless of the underlying cause (glucogonoma or hepatic disease). Aminosyn is the most effective therapy for hepatopathy related disease (which is the most common form). However, Aminosyn does not fix the underlying liver problem. Aminosyn provides nutrition to the starving keratinocytes. Aminosyn injections are typically given once to twice weekly initially and then spread out with injections given

every 4-8 weeks long term. Aminosyn can yield a clinical response for up to twenty-two months. Unfortunately, Aminosyn is expensive and the injections must be given over several hours which requires hospitalization. A typical Aminosyn dose is 500ml/dog or 25mg/kg over 6-8 hours.

Supportive nutritional therapy is always recommended for hepatocutaneous syndrome. Nutritional therapy involves increased protein intake via supplementation with egg yolks and cottage cheese, increased fatty acid intake, and zinc supplementation (zinc methionine 2mg/kg/day). The typical life expectancy with supportive therapy alone is 2 to 5 months.

Steroid therapy can provide temporary improvement of clinical signs. However, patients eventually become resistant to steroid effects, and steroid administration predisposes to diabetes mellitus (remember that many patients are hyperglycemic at presentation). Topical steroid sprays or ointments may be very useful for focal lesions and carry less risk of inducing diabetes.

Monitoring for and addressing secondary infection becomes a constant battle in hepatocutaneous syndrome. Bacterial infection is common due to damage to the epidermal barrier. *Malassezia* dermatitis may develop as well. Bacterial culture and oral antibiotics may be necessary. Many of these patients do not eat well and it may be difficult for the owner to administer an oral antibiotic. Consequently, antiseptic sprays and wipes are particularly helpful.

Cutaneous Lymphoma

Cutaneous lymphoma is an uncommon malignant neoplasia of the dog and cat. Two types of cutaneous lymphoma are recognized: epitheliotrophic and non-epitheliotrophic. Epitheliotrophic lymphomas are classified T cell lymphomas and include mycosis fungoides, Sezary syndrome, and pategoid reticulosis. Non-epitheliotrophic lymphomas are typically large cell lymphomas and can be either B or T cell in origin. Older animals are usually affected but this disease can occur at any age.

These neoplasms are important even though they are rare because they imitate many other diseases. Non-epitheliotrophic lymphoma typically manifests as single or multiple nodules. Exfoliative erythroderma may occur separately or in addition to nodular disease. Patients with exfoliative erythroderma can easily be misdiagnosed as allergy, scabies, or seborrhea. If the mucus membranes and/or muzzle are affected by non-epitheliotrophic lymphoma it can appear visually indistinct from lupus erythematosus, pemphigus vulgaris, and bullous pemphigoid.

The most common epitheliotrophic lymphoma is mycosis fungoides. This condition displays multiple clinical manifestations. Erythroderma is typically present (same as non-epitheliotrophic). Once again, this erythroderma may appear visually indistinct from allergy, scabies, and seborrhea. Focal lesions progress from patches to plaques to tumors. The final stage involves wide-spread dissemination of tumors with lymph node involvement. Multiple types of lesions can be present at the same time and the speed of progression is not predictable or consistent. Additionally, initial lesions can be very subtle. For example, a client may notice the development of dry flaky seborrhea. During examination, you might find a couple small patches of alopecia without inflammation and a nodule which the owner cannot remember.

Diagnosis is relatively straightforward via biopsy. The point of this lecture is merely to encourage you to biopsy older animals or animals with sudden onset of disease more quickly. Cytology is always recommended as well. Occasionally you will find an unusually large population of lymphocytes on cytology when what you expected was neutrophils and cocci.

Therapy depends on the location and the extent of the disease. Consultation with an oncologist should always be recommended. Survival time varies greatly based on aggressiveness of the neoplasia and when the disease is diagnosed. In my clinical experience, most patients survive 2-3 months after diagnosis but this can range from a few weeks up to 18 months. For clients un-interested in oncology referral or classical "chemotherapy", I recommend steroids as monotherapy. Steroid monotherapy can provide 1-3 months of quality time by reducing the intensity of lesions and subsequent discomfort.

Pemphigus foliaceus

Pemphigus foliaceus is one of the most common auto-immune skin diseases seen in dogs and cats. This disease is characterized by pustules and honey colored crusts. This condition is typically idiopathic but it can develop secondary to drug exposure. Pemphigus foliaceus is often seen in patients previously diagnosed with allergic dermatitis; however, no link between the two has been proven.

In pemphigus foliaceus the immune system is attacking a particular protein in the complex structure (called a desmosome) that links keratinocytes together. Destroying the bonds between keratinocytes is termed acantholysis and results in acantholytic cells. Acantholytic cells are typically plump and round because they are no longer connected to their neighbors. They stain darkly and have a clearly visible nucleus. Different forms of pemphigus exist and one of the primary differences between them is in what layer of the skin this acantholysis occurs. For pemphigus foliaceus the damage occurs in the two uppermost layers (the stratum corneum and the stratum granulosum). More serious forms of pemphigus affect deeper layers of the skin and cause significantly more damage. As acantholysis occurs, vesicles and sterile pustules are formed. These are fragile and easily damaged because they are located in the uppermost layers of the epidermis. Depending on the intensity of the immune response, pustules can develop and rupture in under an hour or over the course of days. For comparison, pyoderma pustules develop more slowly and are more resilient (more difficult to break). In addition, pyoderma pustules are typically centered around a hair follicle. Both pemphigus pustules and pyoderma pustules will contain neutrophils but intact pemphigus pustules will not contain bacteria.

As already mentioned, the classic lesions of pemphigus foliaceus are pustules and crusts. These lesions can occur anywhere on the body but are commonly found on the face and trunk. Pustules can develop inside the aural opening resulting in serum leakage and crust debris falling into the ear canals. The result is typically a wicked otitis externa. In many cases the nasal planum is also abnormal. The planum typically becomes dry, thick, and crusted. Ulcerations of the nasal planum can occur secondary to crust being traumatically removed. However, pemphigus foliaceus does not cause ulceration of the oral cavity or mucus membranes. The paw pads may be affected as well. Discreet pustules may be seen on the pads but more often the pads are thickened, dry, and crusted. Some dogs will be reluctant to walk but that is uncommon with pemphigus (much more common with hepatocutaneous syndrome).

Diagnosis is via biopsy. Intact pustules are preferred because they offer the clearest picture of the disease process. However, crusts are also very useful biopsy specimens. When collecting biopsies for potential pemphigus foliaceus it is critical not to scrub the skin. In most cases it is advised to avoid shaving the animal's fur as well. Even the slightest disturbance to the skin can damage the fragile pustules seen with this condition. In the event that no pustules are present, the proof of pemphigus might be in the crust on top of the skin rather than in the skin sample itself. Consequently, always include crust debris in the formalin jar and request the crust be processed, when you biopsy for pemphigus.

Treatment, which is really to say management, is almost always successful but required life-long. Some cases of drug induced pemphigus foliaceus will remain in "remission" even when immune suppressive therapy is discontinued. However, it is often difficult to prove which cases are drug induced which makes predicting which patients will be able to stop therapy nearly impossible. Initial therapy requires steroid administration. Oral daily prednisolone/prednisone dosages of 2mg/kg to 6mg/kg are often required. Steroid therapy often yields dramatic improvement in two to four weeks when dosed adequately. Some patients will respond better to other steroids such as dexamethasone or triamcinolone. Recheck examinations every two to four weeks are critical to assess response to therapy and tailor drug therapy. Secondary bacterial infection is common in pemphigus and your clients will not be able to discern the difference between a pyoderma pustule (which needs antibiotics) and pemphigus pustule (which would cause you to evaluate your immune suppressive plan). In general, the goal is to slowly taper steroid therapy once clinical "remission" has been achieved. Over the course of three to four months some dogs will achieve good clinical response and can be maintained with every other day steroid therapy. However, the majority of patients will experience significant steroid side effects (such as weight gain, polyuria, polydipsia, polyphagia, behavioral abnormalities). Because of steroid side effects and the fact that most patients require life-long immune suppressive therapy it is typically necessary to add another medication as a steroid sparing agent. First line drugs for this purpose are cyclosporine and azathioprine. Second line drugs include mycophenolate and leflunomide. In most cases, I will start a steroid and a steroid sparing drug at the beginning of treatment. All of the above listed steroid sparing drugs have a delay of four to eight weeks until they become clinically effective. By starting both types of drugs at the same time, I am able to reduce steroid therapy sooner.