Skin Disease is not Always Just Skin Deep:
Dermatological Manifestations of Internal Disease

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C.A. Outerbridge DVM, MVSc, DACVIM, DACVD
Professor of Clinical Dermatology
School of Veterinary Medicine, University of California Davis.
Davis, California

Overview and Objectives

The skin's functions in providing innate protection and maintaining homeostasis along with the systemic factors that can influence its integrity make it a critical sentinel for systemic disease. Some cutaneous changes are immediate visual clues to evaluate for specific diseases.
Evaluation for disturbances in hemostasis or vascular integrity is clearly indicated when petechiations and/or ecchymoses are identified on the skin or mucosal surfaces of patients. The color change seen in an animal with icteric mucous membranes is a clear indicator to evaluate for causes of jaundice in that patient. Changes in the appearance of the skin may be markers of pathology occurring in another organ system or they may represent a disease process that is multi-systemic, such as seen with some infectious diseases or in systemic lupus erythematosus.

Both the appearance and integrity of the skin are influenced by several systemic factors that can be influenced by internal disease. These factors include the nutritional status, hormonal levels and interactions, perfusion and vascular integrity and the overall health and systemic organ function of the individual animal. Consequently, changes in the skin can be a critical sentinel for internal disease. The skin is also readily accessible for diagnostic sampling and can in some cases provide the necessary information for making the diagnosis of systemic disease. Recognizing those skin changes that are clinical markers for underlying systemic disease can expedite the diagnosis and timely management of those diseases. Underlying hormonal, neoplastic, infectious, metabolic, vascular and autoimmune diseases can present with cutaneous clues.

Cutaneous Changes Associated with Hormonal Disturbances

Endocrine diseases provide excellent examples of the connection between disease and the skin. Hypothyroidism, hyperadrenocorticism (HAC), and sex hormone imbalances from testicular neoplasia, ovarian tumors or adrenal tumors can alter the skin's appearance and function. Disturbance in growth hormone and sex hormones other than estrogen will not be discussed.

Thyroid Hormones

Thyroid hormones are very important to the skin and promote the initiation of the anagen phase of the hair follicle cycle[1, 2]. Hypothyroidism results in disturbances in cornification, an increase in the number of hair follicles in telogen and accumulation of glycosaminoglycan in the dermis[2, 3]. Clinically, this results in alopecia, a dull, dry hair coat, variable hyperpigmentation, scaling, and myxedematous changes. The normal barrier function of the epidermis is likely impaired in hypothyroid animals and in animal models, impaired neutrophil and lymphocyte function has been reported. Consequently, recurrent pyoderma and otitis externa can occur in hypothyroid animals[3]. Dogs presenting with a history of recurrent or refractory otitis externa or recurrent pyoderma should have hypothyroidism

considered as a risk factor for these secondary skin infections. However, many dogs are misdiagnosed or in some cases the diagnosis is missed as it can be difficult to make due to nonthyroidal influences on thyroid function testing. Understanding thyroid physiology, thyroid function testing and all nonthyroidal influences (NTI) on thyroid function testing are critically important as a low baseline T4 on a serum biochemistry panel is insufficient evidence alone. Endocrine function testing is beyond the scope of these lectures.

Spontaneous hypothyroidism in cats is rare. One reported case had similar clinical signs to dogs with a dull dry, hair coat that was lighter in color than normal and the cat had a puffy face[4] but experimentally thyroidectomized cats did not; they reportedly groomed less, developed matting and seborrhea but only focal alopecia on pinnae and pressure points[3]. A recent study identified seven cats with spontaneous hypothyroidism with six having bilateral goiter and four had hair coat changes[5]. Hyperthyroid cats can develop matting, seborrhea, increased shedding and over-grooming[3]. With chronicity, alopecia may develop with hypotonic, thin skin[3].

Cortisol Disturbances:

Excessive glucocorticoids cause cornification abnormalities, inhibit fibroblast proliferation and collagen production and cause pilosebaceous gland atrophy. Clinically, excessive cortisol (endogenous or exogenous) also results in disturbances in cornification, dermal thinning and delayed wound healing in most species[6].

Canine Cutaneous Changes due to Hypercortisolemia

Dogs with HAC or iatrogenic hypercortisolism can develop bilaterally symmetrical alopecia, thin hypotonic skin (with or without striae), increased susceptibility to bruising, easily visible dermal vasculature, phlebectasias (ventrum and medial thighs), comedones, milia, calcinosis cutis and increased susceptibility to recurrent pyoderma and adult onset demodicosis.

Calcinosis Cutis is a broad term and includes all forms of dystrophic or metastatic calcification of the skin. It is most often used for the dystrophic calcification seen in dogs, secondary to hyperadrenocorticism or iatrogenic hyperglucocorticoidism. The chinchilla is the only other species to develop calcinosis cutis with hyperadrenocorticism[7]. In dogs, erythematous papules coalesce into firm, gritty plaques that may ulcerate and develop hemorrhagic crusts. Lesions develop in areas prone to chronic flexure movement and the dorsal cervical, axillary or inguinal areas are common lesional sites. Dystrophic calcification can also involve mucosal membranes and the tongue. Metastatic calcification producing nodular calcium deposits in the skin, especially footpads, has been reported in dogs and cats with chronic renal failure. The author has documented calcinosis cutis lesions in the inguinal region of a dog supplemented chronically with calcitriol post-parathyroidectomy. The mineral present in calcinosis cutis has been shown by infrared spectrometry to be apatite crystals [7]. A recent study showed predisposed breeds to include Labrador retrievers, Rottweilers, boxers and Staffordshire terriers[7]. Lesions of calcinosis cutis typically resolve over time if the underlying metabolic disturbance can be removed. In some cases, osseous metaplasia can occur. The resulting osteoma cutis lesions will not regress.

Feline Cutaneous Changes due to Hypercortisolemia

Naturally occurring hyperadrenocorticism is rare in the cat and skin lesions have been seen in about half of the reported cases these include alopecia, thin skin, increased susceptibility to bruising, scaling, comedones and fragile skin[8].

Acquired skin fragility in cats is most often associated with hyperadrenocorticism (more often in cats with adrenal tumors), iatrogenic hyperglucocorticoidism, or excessive levels of progestational compounds from either adrenal tumors or the iatrogenic effect of administered progestational compounds. Affected cats have extremely thin, fragile skin that easily bruises and can be torn with simple manipulations, often during restraint or handling. There are also rare reports of feline skin fragility being associated with diseases causing severe cachexia, such as cats with hepatic lipidosis, feline infectious peritonitis, and hepatic neoplasia[9].

Estrogen: Hyperestrogenism

Increased estrogen can arise from cystic ovaries, granulosa cell tumors, testicular tumors (Sertoli cell tumors most commonly (see paraneoplastic syndromes below) or iatrogenically from estrogen supplementation for urinary incontinence or chronic exposure to human topical estrogen products. Estrogen inhibits anagen initiation resulting clinically in alopecia. Hyperpigmentation is often present and can be diffuse or macular. Alopecia often begins in the perineal, caudal thigh, inguinal and flank regions. Identification and correction of the underlying cause of hyperestrogenism may require abdominal ultrasound evaluating for ovarian tissue remnants or ovarian pathology or presence of cryptorchid testes. Ultrasound of the testicles for presence of a tumor can also be utilized if a mass is not palpable. If pathology is identified ovariohysterectomy or castration is indicated. In the already spayed female or neutered male possible exposure to exogenous sources of estrogen (diethylstilbestrol) for urinary incontinence or exposure to human use of estrogen topical therapy for hormone replacement therapy (HRT) needs to be evaluated.

Cutaneous Paraneoplastic Syndromes

A paraneoplastic syndrome is defined as either a disease or clinical signs that develop distant from the site of a tumor, is caused by the presence of the tumor or its metastasis but is not resulting from the local presence of neoplastic cells. Paraneoplastic syndromes are mediated by hormones, cytokines or growth factors released by tumors or by an immune response targeted against the tumor. Paraneoplastic skin diseases are seen most often in middle aged to elderly individuals and represent a group of skin disorders that if recognized alert the clinician to underlying systemic neoplastic disease.

Testicular Tumors (Hyperestrogenism)

In male dogs with testicular tumors (with presumed hyperestrogenism) a visually distinctive lesion of linear preputial hyperpigmentation and/or erythema is often seen. This lesion has been seen by the author in dogs with histologically confirmed seminomas or Leydig (interstitial cell) testicular tumors. Hyperestrogenism can also cause feminization in the male dog and in severe cases bone marrow suppression and aplastic anemia. Alopecia and hyperpigmentation with hyperestrogenism also occur. Intact animals should be neutered. Already neutered animals should be evaluated for possible exogenous sources of estrogen.

Feline Paraneoplastic Alopecia

This rare, yet uniquely characteristic skin disease occurs in association with pancreatic adenocarcinoma. Affected cats develop precipitous, ventrally pronounced alopecia in which the skin appears very shiny and smooth but is not fragile. Some cats may also have dry, exfoliative, and shiny footpads often with concentric circular rings of scale. On necropsy exocrine pancreatic adenocarcinoma with hepatic metastases is the most common tumor found but bile duct carcinoma has been reported in two cases[10]. The disease affects older cats, and the chief clinical complaint is often the acute and dramatic alopecia that affects the ventral trunk, medial aspects of the limbs and the ventral cervical region but can generalize. Remaining hair will epilate easily. Secondary *Malassezia* infections are common and may contribute to why some affected cats groom excessively. Histopathology of a skin biopsy reveals epidermal hyperplasia with marked follicular and adnexal atrophy. Any cat with a tentative diagnosis of paraneoplastic alopecia should undergo an abdominal ultrasound to evaluate for the presence of a pancreatic or hepatic mass. Temporary resolution of the cutaneous disease was reported in a cat after the primary pancreatic tumor was removed; the lesions recurred with the development of metastatic disease[11].

Feline Thymoma-Associated Exfoliative Dermatitis

A rare, exfoliative dermatitis has been described in middle aged to older cats with thymomas[6] . The exact pathogenesis is not known but is thought to be an immunologic etiology potentially T cell mediated. Histologically it is similar to an erythema multiforme or graft versus host type of reaction. Skin lesions tend to begin on the head and pinnae but can quickly generalize to involve the entire cat. Generalized erythema and marked scaling are present. Secondary infections with bacteria and Malassezia may develop. Respiratory signs secondary to the cranial mediastinal mass may be present at the time of presentation but in most cases skin changes precede any other systemic signs. Histopathology of representative skin lesions reveals a cell poor, hydropic interface with apoptosis of basal cell keratinocytes. If detected and diagnosed, removal of the thymic tumor will lead to resolution of the dermatologic clinical signs[10,12,13.] A recent report describes a group of cats that had clinical and histologic features of this exfoliative dermatitis but had no concurrent thymoma, the cats were managed with immunosuppressive medications[14].

Renal Cystadenomas and Nodular Dermatofibrosis (RCND)

RNCD or nodular dermatofibrosis was considered a paraneoplastic skin disease and it is now recognized to be a genetic disease in the German Shepherd breed. It is a syndrome characterized by the development of a generalized nodular dermatofibrosis with associated renal cystadenocarcinomas or cystadenomas has been described in dogs, most often in German shepherds and their crosses.[15] There does not appear to be a sex predilection and the syndrome is diagnosed in middle-aged dogs, typically between 6-8 years of age. In the German shepherd dog, the development of this syndrome is suggested to have an autosomal dominant mode of inheritance.[16] There are genetic tests to detect the causative mutation in the gene (FLCN) that is located on Chromosome 5 and codes for folliculin. Folliculin is thought to act as a tumor suppressor and help control the growth and division of cells. In affected intact female dogs, uterine leiomyomas can develop. The pathogenesis linking nodular cutaneous lesions and renal and uterine tumors remains obscure. Nodules are found most often on distal extremities and can ulcerate or result in lameness. As the disease progresses numerous nodules may develop involving the trunk and head as well. Nodules range in size from several millimeters to

centimeters in diameter and are typically firm on palpation with variable amounts of pigmentation and hair present on the epithelial surface. Histopathologic evaluation of the cutaneous nodules reveals dense collagenous hyperplasia. Ultrasonography is warranted in all cases of nodular dermatofibrosis. If the original ultrasound is normal, it should be repeated at serial intervals. Female dogs should be spayed to avoid development of uterine leiomyomas. Renal function should be monitored. Affected dogs usually develop clinical signs of renal dysfunction within 2.5 to 5 years after skin lesions are first noticed[16]. Cutaneous lesions that are problematic for the dog can be surgically excised.

Cutaneous Manifestations of Systemic Infectious Diseases

Sometimes the skin provides valuable clues to underlying infectious disease. Skin lesions can develop in association with systemic mycosis, viral diseases, and *Leishmania*. In these diseases, the organism can sometimes be found within the lesional skin. Infectious diseases can also cause skin lesions as a consequence of the systemic vasculitis or thrombocytopenia that are associated with those infectious diseases as is the case for rickettsial diseases such as Rocky Mountain Spotted Fever or ehrlichiosis, or the protozoal disease canine babesiosis.

Leishmaniosis

This protozoal disease has been reported in dogs in the United States that have been imported or spent time in the Mediterranean basin/southern Europe (*Leishmania infantum*) or South America but there are also reports from autochthonous foci in many states and 2 provinces in Canada[17]. In North America, foxhounds seem to be predisposed. The first signs of this disease that owners notice are often skin lesions. Alopecia, erythema, and scaling with ulceration are common skin lesions often involving the pinnae, dorsal muzzle and mucocutaneous junctions. Affected dogs may be systemically unwell with concurrent lymphadenopathy, uveitis, hyperproteinemia, hyperglobulinemia, nonregenerative anemia, azotemia and proteinuria. Diagnosis is made by demonstration of the organism in aspirates of lymph nodes, bone marrow or splenic aspirates, histology of skin biopsies, isolating organism on culture, or looking for evidence of the infection via immunohistochemistry of tissue samples, serologic tests, or PCR[18,19]. Recommended therapy is antimonial compounds such as meglumine antimonate (Glucantime), along with oral administration of allopurinol[,20]. Treatment failures and relapses are common. Maintenance therapy with allopurinol (10 mg/kg) decreases parasitemia, maintains treated dogs in an asymptomatic state, and decreases the likelihood of direct or vector transmission. Prevention involving the use of insect repellents against the sand fly vector is advised in endemic regions. Domperidone (Leisguard®,Ecuphar), a dopamine D2 receptor antagonist with an immunomodulatory effect is prescribed to prevent and control leishmaniosis in dogs. A recent study evaluated preventative use in dogs and reported use of insect repellents was preventative and there was an additive effect when domperidone was also used[21]. There are lectures at WCVD10 including the presentation of the WAVD Clinical Consensus Guidelines that can speak in more detail about Leishmaniosis.

Systemic Mycosis

Many systemic or deep mycoses (blastomycosis, coccidioidomycosis, cryptococcosis, histoplasmosis, aspergillosis) can present with cutaneous lesions. These lesions can include papules, nodules, draining tracts and ulceration and typically result from hematogenous dissemination of the fungal organism to the skin. Direct inoculation of fungal organisms into a cutaneous wound could result in a

solitary lesion. Skin lesions are seen most commonly in feline cryptococcal infections and in canine blastomycosis and are reported to occur in approximately 20-40% of cases with these fungal infections. Typically, there are other systemic clinical signs. Nasal aspergillosis can cause depigmentation and ulceration often beneath the nares because of a "drainage board" effect from the chronic nasal discharge. Diagnosis of any of the fungal infections is based on demonstration of the organism within biopsied tissue and/or fungal culture of tissue samples or lesional exudate. Suspicious cutaneous lesions can provide easy and rapid diagnostic information in the evaluation of animals with systemic mycoses as skin lesions are readily accessible to obtain samples for fungal cultures. Appropriate antifungal therapy is chosen based on type of organism and overall health of the animal.

Systemic Viral Diseases

Several viral diseases in addition to the systemic clinical signs they cause can have associated cutaneous lesions. These include in dogs, canine distemper and pseudorabies and in cats the retroviruses FELV/FIV, feline herpesvirus, feline calicivirus, and feline coronavirus causing FIP. Both canine and feline papillomavirus cause cutaneous lesions but not systemic disease, although they can develop more readily, become more severe or difficult to manage in patients with underlying immunosuppression.

Canine distemper virus has long been associated with "hard pad disease". Hard pad disease represents an uncommon manifestation of canine distemper virus (CDV) infection whereby dogs develop excessive keratinous material on the foot pads and nasal planum. Diagnosis is suspected when the cutaneous lesions develop in a dog that shows other systemic signs of CDV (GI, respiratory and neurologic signs). Affected pups may develop impetigo. Diagnosis can be confirmed by immunohistochemical demonstration of the virus within skin biopsies of affected nasal planum or foot pads[22].

Opportunistic skin infections, oral ulcerations and gingivitis have been associated with the feline retroviruses FeLV and FIV. Cutaneous horns can develop on the paw pads of cats with FeLV. In severe cases lameness and discomfort can be marked. Diagnosis is confirmed with a positive FeLV status and skin biopsy. Immunohistochemistry can demonstrate the presence of the virus within a skin biopsy. Cutaneous lymphoma and giant cell dermatosis have also been reported in FeLV positive cats[23].

Feline herpesvirus ulcerative dermatitis typically involves the dorsal muzzle but may extend to involve the nasal planum. Cats do not have to have concurrent ocular or upper respiratory tract signs. Histologically the lesion is a necrotizing, ulcerative dermatitis most often with a concurrent marked eosinophilic inflammation, but the inflammatory pattern may be strongly neutrophilic in some cases. The presence of eosinophilic inflammation and the clinical appearance of the lesions make it difficult to differentiate from mosquito bite hypersensitivity or other feline eosinophilic ulcerative lesions. Unless intranuclear viral inclusions can be identified it is not possible to definitively diagnose the virus as the etiologic agent for the ulcerative dermatitis. Polymerase chain reaction (PCR) has been shown to be a sensitive test to detect the presence of the virus within skin biopsies[24]. Treatment can include subcutaneous administration of alpha interferon (1,000,000 units/m^2, 3 times a week), oral famciclovir (Famvir, Novartis Pharmaceuticals) (60-90 mg/kg)[25], and/or lysine.

Cutaneous Manifestations of Nutritional or Metabolic Perturbations

The skin can develop lesions secondary to nutritional deficiencies, however this is very uncommon in a patient that has a good appetite and is eating a well-balanced commercial food. Some cutaneous manifestations of nutritional deficiencies are recognized in particular breeds suggesting perhaps an alteration in absorption or metabolism while others have been linked to inadequate or unbalanced diets. Superficial necrolytic dermatitis can be a paraneoplastic skin marker if associated with glucagonoma but it is more commonly associated with some yet to be determined alterations in metabolism that causes depletion of amino acids. Underlying disturbances in lipid metabolism can result in the development of cutaneous xanthomas.

Zinc Responsive Dermatosis

The skin contains approximately 20% of the total body zinc (Zn) stores and the highest concentrations of Zn are found in the keratinized tissue of the nasal planum, tongue and footpad[26]. There are several recognized syndromes associated with either Zn deficiency or disturbances in Zn assimilation that present with cutaneous signs.

Syndrome I has been identified in Siberian huskies, Alaskan malamutes and occasionally other breeds. Affected dogs typically present with erythema followed by variable alopecia with fine silver scale that becomes adherent or develops into crusting involving the mucocutaneous junctions of the face (peri-ocular, peri-oral), pressure points (elbows, hocks), and footpad margins. Dogs with this disease will manifest signs even on well-balanced diets. Diagnosis is based on signalment, typical cutaneous lesions and histopathology of skin biopsies which shows marked follicular and epidermal parakeratotic hyperkeratosis. Therapy requires Zn supplementation with a recommended dosage of 2-3 mg/kg of elemental Zn in the form of zinc sulfate, zinc gluconate, or zinc methionine. There was not a detected difference between the different Zn salts in one study[27]. Clinical signs are typically improved within 4-6 weeks.

Syndrome II occurs in rapidly growing puppies that are being fed a poor-quality dog food or are being over-supplemented with calcium. These dogs are thought to have a relative Zn deficiency caused by a combination of low Zn intake and calcium or cereal phytate binding of Zn. Affected dogs have generalized crusting plaques with extensive crusting and fissuring of the foot pads. Diagnosis is based on compatible history, clinical signs, and histopathology (similar to Syndrome I). Response to Zn supplementation is dramatic but is not needed once dog has reached maturity, unlike most Syndrome I dogs. Many dogs will respond to a higher quality diet.

There has been a report of zinc responsive dermatitis in related Pharaoh hound puppies[28]. Dogs developed cutaneous lesions including exfoliative, erythematous lesions of the foot pads in the first months of life that histologically were suggestive of an underlying Zn deficiency. Affected puppies also had systemic signs of lethargy, poor growth, and mental dullness. Dogs did not respond to oral supplementation and intravenous supplementation with zinc sulfate was required to ameliorate clinical signs.

Superficial Necrolytic Dermatitis (SND)

Superficial necrolytic dermatitis is an uncommon skin disease reported in the dog, cat, and black rhinoceros. SND or also referred to in dogs as hepatocutaneous syndrome (HCS) or canine necrolytic migratory erythema (NME) or metabolic epidermal necrosis (MEN). Affected dogs most commonly

have a characteristic concurrent hepatopathy, thus the popular use of the term hepatocutaneous syndrome (HCS). As different disease processes (glucagonoma, vacuolar hepatopathy, phenobarbital administration, or intestinal disease) have been reported to cause similar histologic skin lesions it might be more correct to refer to the skin disease as SND or metabolic epidermal necrolysis (MEN). Recently the term aminoaciduric canine hypoaminoacidemic syndrome (ACHES) has been proposed to describe those dogs that have characteristic hepatic pathology and hypoaminoacidemia that can develop before the onset of skin lesions[29]. The term canine necrolytic migratory erythema if used should only be utilized in those cases with a confirmed glucgonoma.

The disease is typically diagnosed in older dogs. The mean age of reported cases in a literature review was 10 years, with a range of 4 to 16 years[30]. Male dogs and Shetland sheepdogs, West Highland white terriers, Cocker spaniels and Scottish terriers may have a predisposition to develop HCS as they appear to be over- represented in the literature[30] and there is a report of related Shih Tzus all developing SND.[31]

Cutaneous lesions typically involve footpads that develop marked crusting, fissuring and ulcerations. Erythema, crusting, exudation, ulceration and alopecia can also involve the periocular or perioral regions, pressure points on the limbs and scrotum. Secondary cutaneous infections with bacteria, yeast (*Malassezia, Candida*) or dermatophytes, particularly involving the feet, are often present. Lameness secondary to footpad lesions, inappetence and weight loss can also be associated with SND. Polydipsia and polyuria may be present when there is concurrent diabetes mellitus. Diabetes mellitus has been reported to occur in 25 to 40% of dogs with the hepatic form of SND.[30,32] Publications about ACHES propose that skin lesions develop later in the disease.[29]

Diagnosis of SND is based on obtaining skin biopsies with the typical histopathologic changes with parakeratosis and epidermal necrolysis. Abdominal ultrasound can provide further support for the diagnosis if a characteristic 'honeycomb' or "Swiss cheese" pattern is documented in the liver. Plasma amino acids, if measured, should document a characteristic moderate to severe hypoaminoacidemia.[32] Plasma levels of 1-methylhistidine and cystathionine have been proposed as ACHES biomarkers as has urine lysine and methionine levels.[29.]

The most effective symptomatic or palliative therapy for dogs with the hepatic form of SND appears to be the administration of intravenous (IV) amino acids. These hypertonic amino acid solutions should ideally be administered via a central vein to diminish the chance of thrombophlebitis although depending on the concentration (less than 3%) a peripheral venous access is possible but potential phlebitis should be monitored for. Some dogs show dramatic improvement in attitude with resolution of skin lesions after receiving amino acid infusions. There are no defined protocols for the administration of amino acid infusions in SND dogs and repeat infusions are needed by most dogs. Oral nutrition should include a high-quality protein diet that can be additionally supplemented with an amino acid powder, many dogs with SND cannot be fed enough protein to overcome their hypoaminoacidemia. Zinc, essential fatty acid supplementation and feeding egg yolks have been recommended in the literature to be beneficial[33,34]. Secondary infections should be treated with appropriate antibiotic and antifungal therapy with careful consideration of those drugs that may be hepatotoxic or require hepatic metabolism. Topical therapy with antimicrobial shampoos can also be of benefit in some dogs in helping to manage secondary infections. Therapy with glucocorticoids is not recommended. Although anti-inflammatory therapy for the skin lesions may be helpful to improve comfort, the risk of precipitating or exacerbating diabetes mellitus in these dogs makes the use of glucocorticoids contraindicated. Diabetes mellitus if present requires appropriate

management. Surgical removal of a glucagonoma has been reported to result in resolution of lesions in one dog. Serial treatments with octreotide in a dog with glucagonoma associated SND (canine necrolytic migratory erythema (NME)) was palliative for several weeks in one case report[35].

The prognosis for dogs with SND without intervention is generally poor and the majority of dogs have survival times of less than 6 months in original retrospective studies[32]. However, 20% of dogs in one study were maintained for 12 months or more with oral protein hyperalimentation and periodic parenteral IV amino acids infusions.[32] A more recent retrospective reported that optimal treatment for dogs that did best based on survival times (> 3 years) received multiple amino acid infusions, SAMe and other supplements and were fed a home cooked diet.[36] Some dogs have been reported to resolve skin and liver pathology with this support.[36] Two dogs at UC Davis were managed for close to 2 years with repetitive amino acids infusions, diet modification and supplements.

Cutaneous Xanthomas

Cutaneous xanthomas are rare and occur when there is underlying hereditary defects in lipid metabolism or acquired dyslipoproteinemia secondary to diabetes mellitus, or use of megestrol acetate. These skin lesions result from the accumulation of lipid-laden macrophages within the dermis. Feline cutaneous xanthomas may develop in cats affected with hereditary hyper-chylomicronemia, megestrol acetate induced diabetes mellitus or naturally occurring diabetes mellitus. Cutaneous xanthomas have been reported in a dog with diabetes mellitus[37]. Often affected animals are consuming a diet rich in fats or triglycerides at the time they develop lesions.

Clinically, cutaneous xanthomas present as multiple pale yellow to white plaques, papules, or nodules with erythematous borders. They are often located on the head, particularly the preauricular area or pinnae. Lesions can develop in paw pads and over boney prominences on limbs. Lesions may bruise readily, and larger masses may in rare cases ulcerate and exude inspissated necrotic material.[37] Cats with inherited hyperchylomicronemia may also demonstrate peripheral neurologic signs due to nerve compression from subcutaneous xanthoma formation. Diagnosis is made by histologic evaluation of skin biopsies and serum biochemistry evaluations for diabetes mellitus, hypercholesterolemia and hypertriglyceridemia should be obtained. Treatment involves feeding a low-fat diet, identification, and correction of the underlying disturbance in lipid metabolism.

Vasculitis

Vasculitis can occur as a primary disease but is more commonly secondary to some other underlying disease process such as an infectious disease, neoplasia, immune-mediated connective tissue diseases or adverse drug reactions. There are both immunopathogenic and non-immunopathogenic mechanisms that can induce vasculitis. Non-immunopathogenic mechanisms that result in vasculitis do not attack components of the vascular wall but weaken its integrity due to invasion of neoplastic cells or microbial agents and influences of burns, trauma, endotoxin, or hemodynamic factors. Immunopathogenic mechanisms for vasculitis include in situ formation or deposition of immune complexes, antibodies directed against vascular wall components, anti-neutrophilic antibody-mediated vessel damage, cytotoxic T cells directed against vascular components and cytokine induced mechanisms. Vasculitis can be categorized using a variety of classification schemes that are based on pathologic appearance and the inflammatory infiltrate

that is present or by the size and type of vessel involved. Although this classification is, useful to the pathologist it does not always correlate with a specific etiology and its clinical usefulness has limitations. The included table serves as a guide of particularly infectious etiologies to consider in the patient with vasculitis lesions and systemic signs.

Vasculitis may involve only one organ system such as the skin or may involve multiple organ systems and consequently clinical signs can be variable. Cutaneous vasculitis typically results from small vessel vasculitides with lesions of swelling, erythema, hemorrhagic macules, plaques, or bullae. Ischemic necrosis and ulceration are often present in lesional areas often located on extremities or over pressure points. Footpads if affected often have depressed areas of central pallor.

Perhaps the most important information to ascertain when evaluating a patient with vasculitis is the possibility of an underlying infectious etiology. If infectious vasculitis is not occurring, the clinician needs to evaluate for exogenous or endogenous antigens that may be triggering the disease. In one study, greater than 50% of the cases were deemed to be idiopathic[38]. Therapy is dictated by identification of any underlying triggers. Infectious etiologies need to be treated appropriately, possible inciting drugs should be discontinued, identification of any concurrent underlying diseases should be undertaken, and immunosuppressive or immunomodulatory therapy may be warranted.

There are breed associated primary vascular syndromes that cause regional vasculitic lesions that are not associated with underlying systemic disease. These include familial cutaneous vasculopathy of German shepherd dogs and proliferative arteritis of the nasal philtrum seen in Saint Bernard dogs. The vasculopathy of greyhounds can be associated with concomitant renal disease.

TABLE 1: POTENTITAL ETIOLOGIES OF VASCULITIS

INFECTIOUS VASCULITIS	EXAMPLES
Bacterial	Bacterial endocarditis, septicemia, bartonella
Fungal	Disseminated fungal infections
Viral	FIP, herpes, coronavirus
Rickettsial	Ehrlichiosis, Rocky Mountain Spotted Fever
Parasitic	Dirofilariasis
Protozoal	Leishmaniasis, babesiosis, trypanosomiasis, toxoplasmosis
NON-INFECTIOUS VASCULITIS	
Exogenous antigen	Drugs, vaccines (Rabies vaccine)
Endogenous antigen	Neoplasia, immune-mediated (Systemic Lupus Erythematosus)
Unknown antigen	Classify histologically by cell type involved and type of vessel

Immune-mediated Skin Diseases Associated with Systemic Disease

Canine autoimmune skin diseases are uncommon skin disorders and are reported to account for less than 2% of all skin diseases seen in small animal practice[39]. They are often clinically impressive and can even be life threatening. Definitive diagnosis requires timely biopsy of

appropriate representative skin lesions and should not be made solely on clinical impression or appearance. That said most are not cutaneous markers for underlying systemic disease but SLE if the affected animal has skin targeted is an example of a disease where the same immunologic pathogenesis may be targeting multiple tissues. Erythema multiforme in people is a marker for underlying herpetic disease and in the minority of veterinary cases the EM lesions may be alerting the clinician about an infectious disease or adverse drug reaction.

Systemic Lupus Erythematosus (SLE)

SLE is a multi-systemic autoimmune disease. The German shepherd dog is reported to be at increased risk[39]. Skin disease occurs variably with percentages as high as 40 to 50% of cases of SLE having skin lesions[39]. Fever, polyarthritis, protein-losing nephropathy from glomerulonephritis, anemia, and thrombocytopenia are the more common clinical signs seen with SLE. Tissues damage in SLE results from immune complex deposition (as occurs in glomerulonephritis) or can occur because of direct cytotoxic effects.

Cutaneous lesions are variable and include erythema, scaling, crusting, depigmentation, alopecia and ulcerations. Lesions often involve the face, pinnae and distal extremities. Lesions may be present on mucocutaneous junctions and within the oral cavity. Ulcers and erosions are rarely diagnostic lesions to biopsy, as an intact epidermis is needed to make a definitive diagnosis.

There are published criteria for the diagnosis of SLE in dogs and diagnosis requires the presence of at least three or more criteria[40]. These criteria include identification of immune-mediated disease targeting various organs systems/tissues +/- a positive ANA. Definitive diagnosis requires involvement in at least 2 or more organ systems and a positive ANA. Systemic lupus erythematosus is a progressive disease and evidence of immunologic involvement in multiple organ systems may not always be evident on the initial presentation. A thorough systemic evaluation including a complete blood cell count, serum biochemistry, urinalysis, +/- protein to creatinine ratio, antinuclear antibody (ANA), arthrocentesis and evaluation of joint fluid cytologically may be indicated in patients suspected of having SLE. Most patients with SLE have an elevated ANA although this may not always be present. Prognosis depends in large part on the organ systems involved. Immuno- suppressive therapy with corticosteroids with or without other immunosuppressive drugs (azathioprine (Immuran), chlorambucil (Leukeran), cyclosporine (Atopica)) is utilized.

Erythema Multiforme (EM) / SJS/ TEN

The terminology has been, over the years, confusing in both human and veterinary medicine in regards to EM and Steven-Johnson's syndrome (SJS)/toxic epidermal necrolysis(TEN) (SJS/TEN). The human disease EM is typically associated with herpes viral infections (>90%) which is very different from EM in small animals which is often idiopathic (40%)[41]. In veterinary species, EM has been attributed to adverse drug reactions, but this is often difficult to prove and confirm and if it occurs, it should respond to drug withdrawal. In both humans and domestic animals SJS/TEN are life-threatening skin diseases associated with necrosis and loss of the epidermis. They are highly linked to adverse drug reactions. EM and SJS/should be considered as separate etiologies. Clinical nomenclature categorizes EM based on severity of lesions. In EM minor, characteristic lesions involve only one mucosal surface and affects less than 10% of body surface. EM major has clinically similar lesions with more than one mucosal surface affected, 10-50% of body surface affected and less than 10% epithelial detachment[41,42]. Either direct cytotoxicity

against keratinocytes or the effects of soluble mediators such as Fas ligand, granzymes or perforin result in apoptosis of keratinocytes[41]. The more severe the clinical presentation of EM the more likely it is to be related to adverse drug reaction[43].

Lesions of EM are pleomorphic with an acute onset of erythematous plaques and macules that can become annular, serpiginous as they coalesce, or they may appear targetoid. Progression to ulcerations is common and lesions may become variably crusted. Lesions are often generalized and can involve the ventrum, axillae, inguinal region, mucocutaneous junctions, oral cavity and pinnae. Biopsies should be obtained from areas of erythema without ulceration or crusting as an intact epidermis is needed for the diagnosis. Histologically, apoptosis with lymphocyte satellitosis is the classic histologic lesion of EM.

Prognosis for EM depends on the severity of the lesions and identification of underlying triggers. In about 50% of canine cases, an underlying trigger cannot be found and it is termed idiopathic EM. In veterinary medicine, EM patients should be evaluated for underlying triggers: drugs, infection or neoplasia. Erythema multiforme minor may resolve on its own but more severe EM cases are often treated with immunosuppressive therapy with glucocorticoids with or without other corticosteroid sparing immunosuppressive drugs (azathioprine, cyclosporine, mycophenolate, chlorambucil). Severe generalized mucocutaneous EM (EM major) requires aggressive supportive care in addition to removal of underlying triggers and immunosuppressive therapy. Intravenous immunoglobulin therapy or plasmapheresis, if available, might be useful in cases of SJS/TEN.

Sterile Nodular Panniculitis

Sterile nodular panniculitis (SNP) typically presents with ulcerated or draining nodular lesions and/or non-ulcerative subcutaneous nodules. Dogs are often febrile when lesions are present, and a peripheral neutrophilia may be documented. Lesions are commonly seen on the trunk but can be present on the head, cervical area, perineum, conjunctiva, or can be generalized. Diagnosis is made based on appropriate clinical history, compatible histology of deep tissue biopsies with negative special stains and negative cultures for any infectious organisms. One study proposed that SNP was a dermatologic marker for underlying internal disease[44]. Concurrent pancreatic disease (pancreatitis and pancreatic neoplasia) or immune- mediated disease in other organ systems (polyarthritis, SLE, rheumatoid arthritis) have been identified in conjunction with SNP. A recent retrospective study failed to find association with systemic disease except polyarthritis[45]. Often SNP requires a tapering course of immunosuppressive therapy, typically glucocorticoids, unless underlying or concurrent diseases make this contraindicated. If associated with pancreatitis, SNP often resolves once the underlying pancreatic disease is successfully managed.

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