Cutaneous Manifestations of Internal Diseases

Catherine A. Outerbridge, DVM, MVSc

KEYWORDS

• Cutaneous markers of internal disease • Paraneoplastic skin disease
• Metabolic skin disease • Endocrine skin disease

KEY POINTS

- The skin's appearance and integrity is influenced by internal factors, such as hormonal levels and overall health of the animal. Consequently, changes in the skin can be a critical sentinel for internal disease.
- Recognizing those skin changes that are clinical markers for internal disease can expedite the diagnosis and timely management of certain systemic diseases.
- The skin changes seen with endocrine disease are good examples of the connection between the skin and internal disease.
- Paraneoplastic skin diseases, such as feline paraneoplastic alopecia, provide clinically distinct, cutaneous clues to the clinician about internal neoplasia.
- Several systemic infectious diseases can be associated with skin lesions, and biopsies of the skin can, in some cases, provide the diagnostic information to confirm the diagnosis.

INTRODUCTION

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 internal disease. Some cutaneous changes are so intimately associated with a particular underlying organ dysfunction or disorder that they are immediate visual clues to evaluate for specific diseases. Evaluation for disturbances in hemostasis or vascular integrity is clearly indicated when petechiations 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 multisystemic, 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. These factors include the nutritional status, hormonal levels and interactions,

Department of Veterinary Medicine and Epidemiology, William Pritchard Veterinary Medical Teaching Hospital, University of California Davis, One Shields Avenue, Davis, CA 95616, USA
E-mail address: caouterbridge@ucdavis.edu

Vet Clin Small Anim 43 (2013) 135–152
http://dx.doi.org/10.1016/j.cvsm.2012.09.010 **vetsmall.theclinics.com**
0195-5616/13/$ – see front matter

perfusion and vascular integrity, and the overall health and systemic organ function of the individual animal. The skin is also readily accessible for diagnostic sampling and can in some cases provide the necessary information for making the diagnosis of internal disease.

CUTANEOUS CHANGES ASSOCIATED WITH HORMONAL DISTURBANCES

Endocrine diseases provide excellent examples of the connection between internal disease and the skin. Hypothyroidism, hyperadrenocorticism (HAC), and sex hormone imbalances from testicular neoplasia, ovarian tumors, or adrenal tumors (see later discussion) can alter the skin's appearance and function.

Hypothyroidism

Thyroid hormones are important to the skin and promote the initiation of the anagen phase of the hair follicle cycle.[1,2] Consequently, many hypothyroid dogs have some degree of alopecia. This alopecia is often first noted in areas of wear (neck under collar, dorsal tail, pressure points, lateral trunk). The extent and pattern of alopecia can vary among breeds of dogs and individual animals. For example, Rhodesian Ridgebacks can develop a pronounced striping pattern (**Fig. 1**).[2] The persisting hair coat is often dry and brittle and can be dull or faded.[3] Failure to regrow hair coat after clipping is sometimes a presenting complaint of hypothyroid dogs.[2,3] Hypothyroidism results in disturbances in cornification and melanosis, an increase in the number of hair follicles in telogen, and accumulation of glycosaminoglycans in the dermis.[2,3] Clinically, this results in alopecia, a dull, dry hair coat, variable hyperpigmentation, scaling, and myxedematous changes. Pinnal margin seborrhea may be seen in some dogs (**Fig. 2**).[2] In hypothyroidism, the normal barrier function of the epidermis is likely impaired, and in animal models impaired neutrophil and lymphocyte function has been reported. Consequently, recurrent pyoderma and otitis externa often occur.[3] In some cases, recurrent or refractory otitis externa or recurrent pyoderma may be the only presenting clinical signs in a dog with hypothyroidism.

Hyperadrenocorticism

Dermatologic changes seen in dogs with HAC occur because glucocorticoids cause cornification abnormalities, inhibition of fibroblast proliferation and collagen production, and pilosebaceous gland atrophy. Clinically, excessive cortisol (endogenous or exogenous) also results in disturbances in cornification, dermal thinning, and delayed

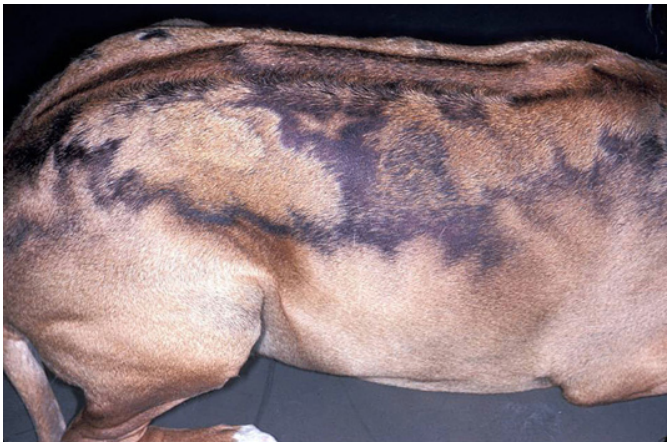

Fig. 1. A Rhodesian ridgeback with striking, striping pattern of alopecia secondary to hypothyroidism. (*Courtesy of* Dr. Stephen White.)

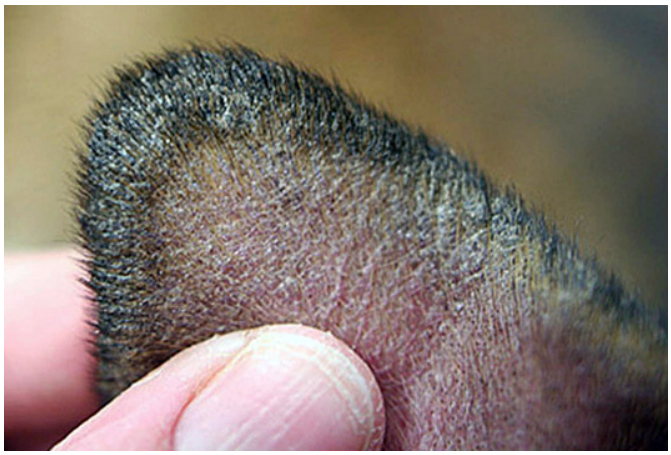

Fig. 2. A hypothyroid dog with pinnal margin seborrhea characterized by follicular casting and adherence of keratinized debris along the pinnal margin. (*Courtesy of* University of California Davis, Veterinary Dermatology Service.)

wound healing. Dogs with HAC or iatrogenic hypercortisolism can develop bilaterally symmetric alopecia, thin hypotonic skin susceptible to bruising, easily visible dermal vasculature, phlebectasias, comedones, calcinosis cutis, increased susceptibility to recurrent pyoderma and adult onset demodicosis.[3]

Calcinosis cutis

This is a broad term and includes all forms of dystrophic or metastatic calcification of the skin. More specifically, the term is often used for the dystrophic calcification seen in dogs secondary to hyperadrenocorticism or iatrogenic hyperglucocorticoidism. Erythematous papules coalesce into firm, gritty plaques that may ulcerate and develop hemorrhagic crusts. Lesions often develop in areas prone to chronic flexure movement, and the dorsal cervical, axillary, or inguinal areas are common lesional sites (**Fig. 3**). 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.[2] The author has documented calcinosis cutis lesions in the inguinal region of a dog supplemented chronically with calcitriol postparathyroidectomy. Lesions of calcinosis cutis typically resolve in time if the underlying metabolic disturbance can be removed. In some cases, osseous metaplasia can occur. The resulting osteoma cutis lesions will not regress.

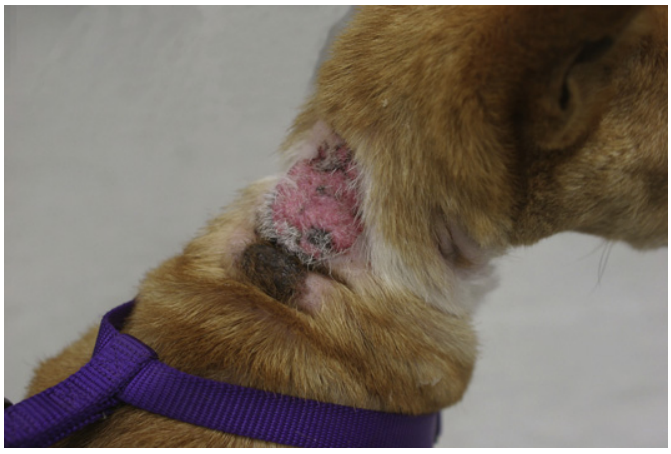

Fig. 3. Calcinosis cutis lesion is present in the dorsal cervical region of this dog. Erythematous plaque was indurated on palpation and had some hemorrhagic crusting associated with it. (*Courtesy of* University of California Davis, Veterinary Dermatology Service.)

Feline-acquired skin fragility

Acquired skin fragility in cats is associated with hyperadrenocorticism (often 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 hepatic lipidosis and hepatic neoplasia.[2]

CUTANEOUS PARANEOPLASTIC MARKERS

Paraneoplastic skin diseases represent a group of skin disorders that, if recognized, alert the clinician to underlying internal neoplastic disease. These disorders include cutaneous changes and feminization seen with testicular tumors, feline paraneoplastic alopecia, feline thymoma-associated exfoliative dermatitis, nodular dermatofibrosis, paraneoplastic pemphigus, and superficial necrolytic dermatitis associated with glucagonoma.

Testicular Tumors (Hyperestrogenism)

Increased estrogen can arise from cystic ovaries, granulosa cell tumors, or testicular tumors (Sertoli cell tumors most commonly) or iatrogenically from estrogen supplementation for urinary incontinence or chronic exposure to human topical estrogen products. Estrogen inhibits anagen initiation of hair follicles, which results in alopecia. Hyperpigmentation often is present and can be diffuse or macular. In male dogs with testicular tumors (with presumed hyperestrogenism), a visually distinctive lesion of linear preputial hyperpigmentation with varying degrees of erythema often is seen (**Fig. 4**). Hyperestrogenism can also cause feminization in the male dog and in severe cases bone marrow suppression and aplastic anemia. Intact animals should be neutered. Already neutered animals should be evaluated for possible exogenous sources of estrogen (diethylstilbestrol) as may be used for urinary incontinence or exposure to human use of estrogen topical therapy.

Fig. 4. Linear preputial erythema present along the midline of the prepuce in a dog with testicular neoplasia (sertoli cell tumor and seminoma). (*Courtesy of* University of California Davis, Veterinary Dermatology Service.)

Feline Paraneoplastic Alopecia

There is an association with pancreatic adenocarcinoma and a bilaterally symmetrical, ventrally pronounced distribution of alopecia in which the skin appears shiny but is not fragile (**Fig. 5**). Some of these cats may also have dry, scaly, or fissured footpads (**Fig. 6**). On necropsy, exocrine pancreatic adenocarcinoma with hepatic metastases is the most common tumor found, but bile duct carcinoma has been reported in 2 cases.[4] 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. Secondary *Malassezia* infections are common and may contribute to why some affected cats groom excessively. Histopathology of a skin biopsy shows epidermal hyperplasia with marked follicular and adnexal atrophy. Any cat with a tentative diagnosis of paraneoplastic alopecia should undergo an abdominal ultrasound scan to evaluate for the presence of a pancreatic or hepatic mass. Temporary resolution of the cutaneous disease was reported in one cat after the primary pancreatic tumor had been removed; the lesions recurred with development of metastatic disease.[5]

Feline Thymoma-associated Exfoliative Dermatitis

A rare, exfoliative dermatitis has been described in middle-age to older cats with thymomas.[4] The exact pathogenesis is not known but is thought to be immunologic with an erythema multiforme or graft-versus-host type of reaction having been proposed. 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 shows a cell-poor, hydropic interface with apoptosis (single cell necrosis) of basal cell keratinocytes. If detected and diagnosed, removal of the thymic tumor will lead to resolution of the dermatologic clinical signs.[4,6,7]

Nodular Dermatofibrosis

A syndrome characterized by the development of a generalized nodular dermatofibrosis with associated renal cystadenocarcinomas or cystadenomas has been described

Fig. 5. A cat with marked ventral alopecia characteristic of feline paraneoplastic alopecia. The skin has a shiny appearance to it yet is not fragile. There are excoriations present that indicate self trauma. Cat had concurrent *Malassezia* dermatitis. (*Courtesy of* University of California Davis, Veterinary Dermatology Service.)

Fig. 6. A cat with feline paraneoplastic alopecia that has dry, scaling foot pads that have a shiny appearance to the epidermal surface. (*Courtesy of* University of California Davis, Veterinary Dermatology Services.)

most often in German Shepherd dogs and their crosses.[4] There does not seem to be a sex predilection, and the syndrome is diagnosed in middle-age dogs, typically between 6 and 8 years of age. In the German Shepherd dog, the development of this syndrome is suggested to have an autosomal dominant mode of inheritance.[8] 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 finds dense collagenous hyperplasia. Ultrasonography is warranted in all cases of nodular dermatofibrosis. If the original ultrasound scan 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 have clinical signs of renal dysfunction within 2.5–5 years after skin lesions are first noticed.[9] Cutaneous lesions that are problematic for the dog can be surgically excised.

Paraneoplastic Pemphigus

Paraneoplastic pemphigus (PNP) is a rare and severe blistering disease that involves mucosal surfaces (oral, urogenital), mucocutaneous junctions, and haired skin seen in association with internal neoplasia. There are rare reports of this disease in the dog.[10] It has been reported in association with thymic lymphoma and splenic sarcoma.[2] The lesions are clinically similar to those of pemphigus vulgaris. Human patients have autoantibodies that target a variety of proteins responsible for connections between keratinocytes: specifically, plakin and desmoglein (Dsg) proteins.[2] It has been shown in the dog that antibodies target desmoplakin, envoplakin, periplakin, and Dsg 1 and Dsg 3.[10,11] Histologic lesions include suprabasilar clefting (as seen in pemphigus vulgaris) with intraepidermal keratinocyte apoptosis (as seen in erythema multiforme) and intraepidermal pustulation with acantholytic keratinocytes (as seen in pemphigus foliaceus).[10] This unusual mixture of lesions is the key to making the diagnosis and warrants a full evaluation of the patient for underlying neoplasia. Immunopathologically compatible cases in which neoplasia was not found have been recognized,

and, in those cases, drug reactions were suspected.[10] PNP associated with neoplasia carries a grave prognosis. Definitive diagnosis of actual PNP is made with compatible histopathology in an animal with concurrent neoplasia and immunologic studies to identify the targeted antigens.

CUTANEOUS MANIFESTATIONS OF NUTRITIONAL OR METABOLIC PERTURBATIONS

The skin can develop lesions secondary to nutritional deficiencies; however, this is 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, whereas 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.[12] 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 (periocular, perioral), pressure points (elbows, hocks), and footpad margins (**Fig. 7**). Dogs with this disease manifest signs even on well-balanced diets. Diagnosis is based on signalment, typical cutaneous lesions, and histopathology of skin biopsies that shows marked follicular and

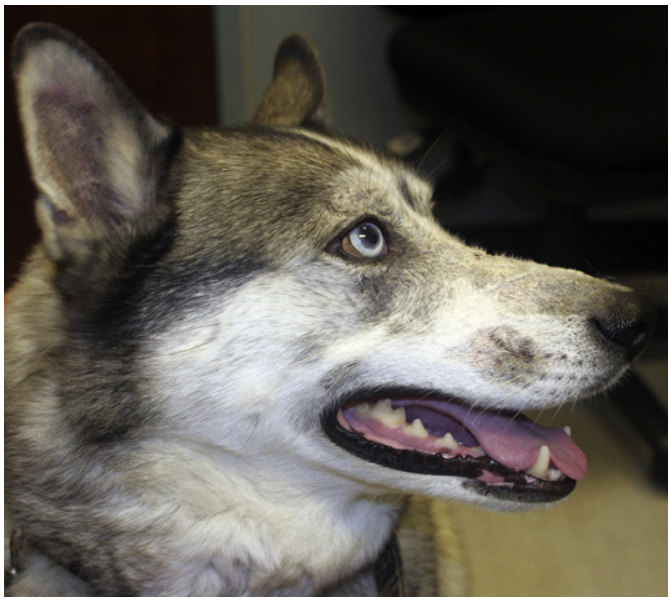

Fig. 7. A Husky dog with zinc responsive dermatosis. The dog has focal areas of partial alopecia with adherent fine, silvery scale present on the dorsal and lateral muzzle, commissure of the lip, upper eyelid, and beneath the eye. (*Courtesy of* University of California Davis, Veterinary Dermatology Service.)

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[13] 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 oversupplemented 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 those of syndrome I). Response to Zn supplementation is dramatic but is not needed once the dog has reached maturity, unlike most syndrome I dogs. Many dogs will respond to a higher quality diet.

There has been a recent report of zinc-responsive dermatitis in related Pharaoh hound puppies.[14] 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.

Generic Dog Food Dermatosis

A dermatosis associated with the exclusive feeding of a poor-quality dog food was reported in the mid to late 1980s.[15,16] This disease is seen less commonly in North America since the institution of pet food certification programs. Many affected dogs were typically less than a year of age and undergoing a period of rapid growth. Affected dogs develop well-demarcated, thick, crusted plaques with fissures and erosions.[16] These lesions are typically located on the muzzle, on mucocutaneous junctions, over pressure points, and on distal extremities. Histopathology of representative skin lesions shows an acanthotic epidermis with parakeratosis, crusting, and spongiosis.[2] Diagnosis is based on compatible dietary history and histopathologic evaluation of skin biopsies. Anecdotal reports of a similar disease occurring in dogs fed vegan diets have also surfaced. Lesions resolve with feeding a better-quality diet.

Lethal Acrodermatitis

Lethal acrodermatitis (LAD) is an autosomal recessive disease seen in white bull terriers. The disease has some clinical similarities to the human disease acrodermatitis enteropathica.[2,17–19] The homozygously affected puppies show clinical signs in the first few weeks of life and have a median survival of 7 months, typically succumbing to bronchopneumonia and sepsis. Bull terriers that are heterozygously affected may have increased risk for pyoderma.[2]

Affected dogs are characterized by a progressive crusting dermatitis of the distal extremities and mucocutaneous junctions. Abnormal keratinization of paw pads can result in splaying of the feet. Claw dystrophy and paronychia may also be present. Secondary infections of the skin with bacteria and *Malassezia* yeast are common.[2,18] Dogs with LAD also often have an abnormally arched hard palate, retarded skeletal growth, abnormal mentation, diarrhea, and bronchopneumonia. In a report of 28 affected dogs, all had difficulty eating, stunted growth, splayed digits, and developed skin lesions by 12 weeks of age.[18] Dogs with LAD have been shown to have significantly lower IgA levels than a control group of dogs.[20] A diagnosis of LAD can be strongly suspected in any bull terrier showing a combination of the aforementioned signs from an early age. Skin biopsy results show a marked parakeratotic

hyperkeratosis. Although many of the clinical signs and the histopathology of this condition suggest Zn deficiency, Zn supplementation is of little benefit. There is no effective therapy. A recent report of a proteomic analysis of liver tissue in 2 affected bull terriers documented that 13 proteins involved in a variety of cellular functions were abnormally expressed in affected pups compared with a normal bull terrier.[18] Diagnosis is based on compatible signalment, physical examination findings, and skin biopsy results.

Superficial Necrolytic Dermatitis

Superficial necrolytic dermatitis (SND) (synonym, metabolic epidermal necrosis) is an uncommon skin disease associated with systemic metabolic disease(s). Affected dogs most commonly have a characteristic concurrent hepatopathy, thus, the popular use of the term *hepatocutaneous syndrome* (HCS) to describe the skin condition. However, other disease processes, including glucagonoma of the pancreas, vacuolar hepatopathy, phenobarbital administration, and intestinal disease have been reported to cause similar histologic skin lesions. Therefore, it may be more appropriate to refer to the skin disease as *SND* and to reserve the term *HCS* for cases with the characteristic liver pathology. The disease is typically diagnosed in older dogs. The mean age of reported cases is 10 years, with a range of 4–16 years[21] Sixty-four percent of all reported cases are male dogs,[21] Shetland sheepdogs, West Highland white terriers, Cocker spaniels and Scottish terriers may have a predisposition to HCS because they seem to be overrepresented in the literature.[21]

Footpads develop marked crusting, fissuring, and ulcerations (**Fig. 8**). 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, often are present in dogs with SND. Lameness secondary to footpad lesions, inappetance, and weight loss can also be associated with SND. Polydipsia and polyuria may be present when there is concurrent diabetes mellitus or if significant liver dysfunction is present. Diabetes mellitus has been reported to occur in 25%–40% of dogs with the hepatic form of SND.[21]

Diagnosis of SND is based on obtaining skin biopsies with the typical histopathologic changes of a marked parakeratotic epidermis with striking intercellular and intracellular edema in the upper epidermis and hyperplastic basal cells, creating the red,

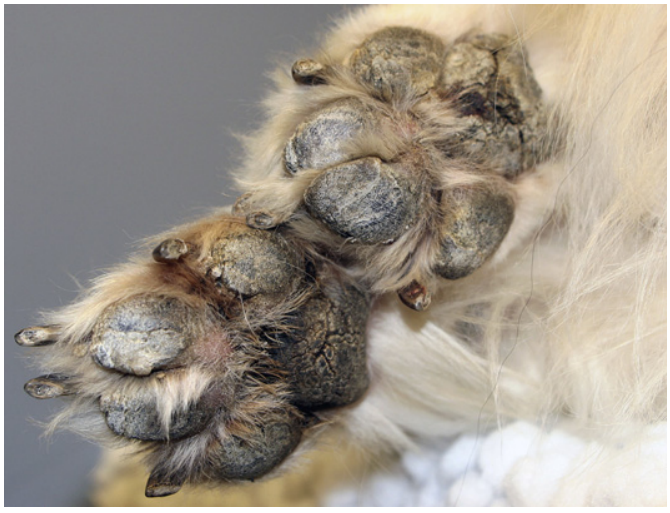

Fig. 8. Marked hyperkeratosis and fissuring that is affecting all foot pads and is characteristic of the foot pad lesions seen in dogs with superficial necrolytic dermatitis. (*Courtesy of* University of California Davis, Veterinary Dermatology Service.)

white and blue lesion that is diagnostic of this disease. Abdominal ultrasound scan can provide further support for the diagnosis if the characteristic honeycomb pattern consisting of variable-sized hypoechoic regions surrounded by hyperechoic borders is documented. If this ultrasonographic pattern to the liver is not visualized in a dog with a confirmed histologic diagnosis of SND on skin biopsy, evaluation for a possible pancreatic tumor or protein-losing enteropathy is warranted. Pancreatic tumors may not be readily visible with an abdominal ultrasound examination; therefore, measurement of plasma glucagon is also recommended. Elevation of liver enzymes and hypoalbuminemia are the most common clinicopathologic changes in one retrospective study.[22] Glucosuria and hyperglycemia may be documented if diabetes mellitus is present. Plasma amino acids, if measured, should document a characteristic severe hypoaminoacidemia. Because severe hypoaminoacidemia is documented to occur in all cases of SND in which plasma amino acids have been measured, regardless of associated disease, it is likely that this metabolic derangement is directly contributing to the cutaneous lesions seen in affected dogs. The liver plays a critical role in amino acid balance. With both chronic and acute hepatitis, compromised hepatic metabolism results in increased concentrations of many plasma amino acids, but this is not seen in dogs with SND, because most individual plasma amino acid concentrations are less than 60% of normal.[22] These differences suggest that the pathogenesis of hypoaminoacidemia in dogs with SND cannot be explained by compromised hepatic metabolism. It seems probable that an as yet unexplained increase in hepatic catabolism of amino acids might account for the severity of hypoaminoacidemia documented in the dogs with SND.

The most effective symptomatic or palliative therapy for dogs with the hepatic form of SND seems to be the administration of intravenous (IV) amino acids. Several crystalline amino acid solutions are commercially available that vary in their concentration and the inclusion of electrolytes. Although there are minor differences in the amounts of essential and nonessential amino acids between manufacturers, there are no data to suggest that one product is more efficacious than another. Solutions without additional electrolytes are preferred. Ten percent Aminosyn solution (Abbott Laboratories, Abbot Park, North Carolina), Travasol 8.5% without electrolytes (Baxter Healthcare Corp, Clintec Nutrition Company, Deerfield, IL), and ProcalAmine (B. Braun Medical Inc, Irvine, CA), 3% amino acids with 3% glycerine and electrolytes, have all been used for IV infusions in treating dogs who have SND. These hypertonic amino acid solutions should ideally be administered via a central vein to diminish the chance of thrombophlebitis. Inducing a hyperosmolar state is possible if administration is too aggressive. Dogs should be monitored for neurologic signs and the infusion discontinued if these occur. If compromised hepatic or renal function is present, the administration of intravenous amino acids may exacerbate hepatic encephalopathy or augment increases in blood urea nitrogen. Such dogs warrant close monitoring with serial measurements of ammonia, blood urea nitrogen, and osmolality during IV amino acid administration. 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 these dogs, and repeat infusions are performed bimonthly, monthly, or when clinical signs return.

Oral nutrition should include a high-quality protein diet that can be supplemented additionally with an amino acid powder. Unless significant hepatic dysfunction with hyperammonemia has been documented, suggesting the presence of some other concurrent liver disease and necessitating a low-protein diet, most dogs with SND cannot be fed enough protein to overcome the hypoaminoacidemia occurring in this disease. Zinc, essential fatty acid supplementation, and egg yolks have been

recommended in the literature to be beneficial.[23,24] These supplements might provide micronutrients that have some as-yet unknown role in this disease, but to maximize additional protein from an egg source, egg whites should be included. 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 manage secondary infections. Therapy with glucocorticoids is not recommended. Although antiinflammatory 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 was palliative in one case report.[25]

The prognosis for dogs with SND is generally poor and most dogs have survival times of less than 6 months. However, 20% of dogs in one study were maintained for 12 months or more with oral protein hyperalimentation and periodic parenteral IV amino acid infusions.[22]

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 with hereditary hyperchylomicronemia, megestrol acetate–induced diabetes mellitus, or naturally occurring diabetes mellitus. Cutaneous xanthomas have been reported in a dog with diabetes mellitus.[26] Often affected animals are consuming a diet rich in fats or triglycerides at the time lesions develop.

Clinically, cutaneous xanthomas present as multiple pale yellow to white plaques, papules, or nodules with erythematous borders. They often are located on the head, particularly the preauricular area or pinnae. Lesions can develop in paw pads and over boney prominences on limbs (**Fig. 9**). Lesions may bruise readily, and larger masses may, in rare cases, ulcerate and exude inspissated necrotic material.[2] Cats with inherited hyperchylomicronemia may also show peripheral neurologic signs because of nerve compression from subcutaneous xanthoma formation. Histologic evaluation of skin biopsies shows large foamy macrophages and giant cells. Serum biochemistry evaluations for diabetes mellitus, hypercholesterolemia, and hypertriglyceridemia should be obtained. Feeding of a low-fat diet and identification and correction of the underlying disturbance in lipid metabolism is recommended for patients that have had cutaneous xanthomas identified.

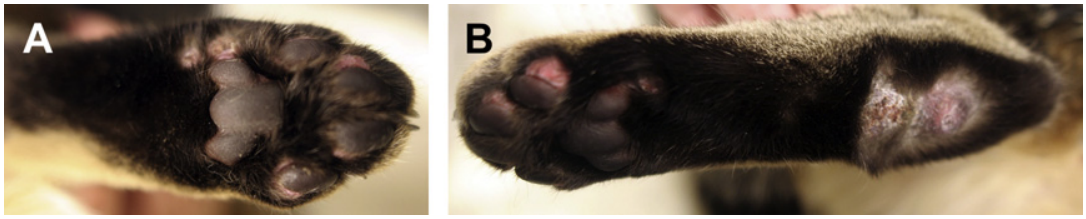

Fig. 9. (*A*) Cutaneous xanthomas present as multifocal nodular pinkish plaques on multiple feet in this cat that had an underlying disturbance in lipid metabolism. (*B*) Lesions over the metatarsal regions are inflamed and developing serocellular crusting caused by pressure and compromised integrity of the overlying skin. (*Courtesy of* University of California Davis, Veterinary Dermatology Service.)

CUTANEOUS MANIFESTATIONS OF SYSTEMIC INFECTIOUS DISEASES

Leishmaniasis

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 (*Leishmania chagasi*) but also from autochthonous foci in many states and 2 provinces in Canada.[27] In North America, foxhounds seem to be predisposed. The first signs of this disease noticed by owners are often skin lesions. Alopecia, erythema, and scaling with ulceration are common lesions involving the pinnae, dorsal muzzle, and mucocutaneous junctions. Affected dogs may be systemically unwell with concurrent lymphadenopathy, hyperproteinemia, hyperglobulinemia, nonregenerative anemia, azotemia, and proteinuria. Diagnosis is made by demonstration of the organism in aspirates of lymph nodes, bone marrow or synovial fluid, or histology of skin biopsies or culture, or looking for evidence of the infection via a variety of immunologic or serologic tests or polymerase chain reaction (PCR).[28] Recommended therapy is antimonial compounds, such as meglumine antimoniate in Europe and sodium stibogluconate in the United States (available from the CDC for use in dogs) along with oral administration of allopurinol.[29] Treatment failures and relapses are common.

Systemic Mycosis

Many systemic or deep mycoses (blastomycosis, coccidioidomycosis, cryptococcosis, histoplasmosis, aspergillosis) can present with cutaneous lesions. These lesions include papules, nodules, draining tracts, and ulceration and typically result from hematogenous dissemination of the fungal organism to the skin. Although rare, 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 of these fungal infections. Typically, there are other systemic clinical signs. Nasal aspergillosis can cause depigmentation and ulceration often beneath the nares as a result of a drainage board effect from the chronic nasal discharge (**Fig. 10**). Diagnosis of any of the fungal infections is based on demonstration of the organism within

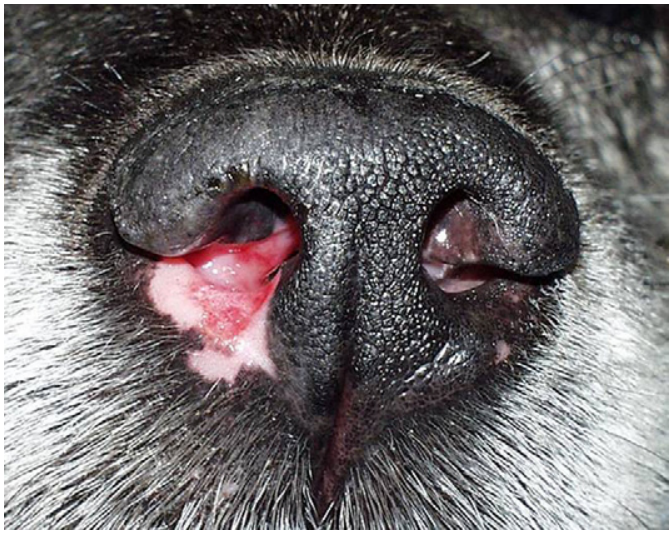

Fig. 10. Drainage board effect with depigmentation and erosions, and ulceration is present on the rostral muzzle and nares on the side of the nasal cavity that had pronounced nasal discharge resulting from nasal aspergillosis. (*Courtesy of* University of California Davis, Veterinary Dermatology Service.)

biopsied tissue or fungal culture. Suspicious cutaneous lesions can provide easy and rapid diagnostic information in the evaluation of animals with systemic mycoses. Appropriate antifungal therapy is chosen based on type of organism and overall health of the animal.

Viral Diseases

Canine distemper virus

Distemper virus has long been associated with hard pad disease. Hard pad disease represents an uncommon manifestation of canine distemper virus infection with a still unknown pathogenesis. 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 canine distemper virus. Canine distemper is an epitheliotropic virus that initially targets the gastrointestinal system, then respiratory tract, and then the central nervous system. Diagnosis can be confirmed by immunohistochemical demonstration of the virus within skin biopsies.[30]

Feline retroviruses

Opportunistic skin infections, oral ulcerations, and gingivitis have been associated with feline leukemia virus (FeLV) and feline immunodeficiency virus. 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 show the presence of the virus within a skin biopsy. Cutaneous lymphoma and giant cell dermatosis have also been reported in FeLV positive cats.[31]

Feline herpes virus

Feline herpes virus ulcerative dermatitis typically involves the dorsal muzzle, but lesions may extend to involve the nasal planum (**Fig. 11**). 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

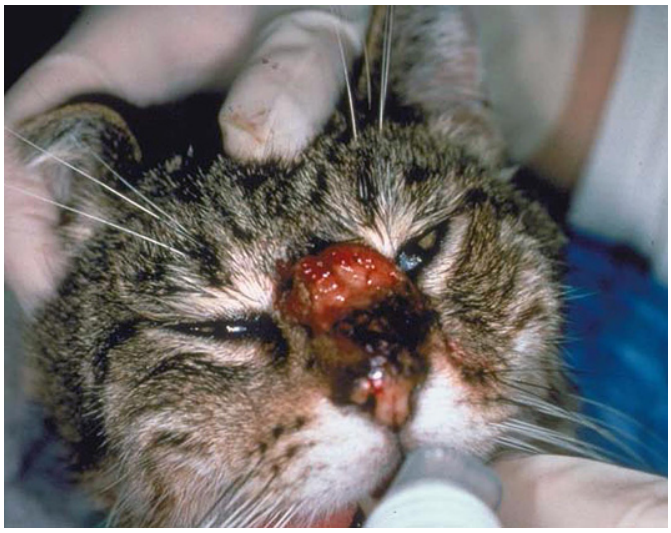

Fig. 11. Ulcerative dorsal muzzle lesion with marked hemorrhagic crusting and extension to involve the nasal planum in a cat. Lesion location and appearance is typical for the ulcerative dermatitis seen secondary to feline herpes virus 1 ulcerative dermatitis. Intranuclear inclusion bodies were seen on histopathology of a skin biopsy, and PCR from the biopsied skin sample was positive for feline herpes virus 1. (*Courtesy of* University of California Davis, Veterinary Dermatology Service.)

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. PCR has been shown to be a sensitive test to detect the presence of the virus within skin biopsies.[32] Treatment can include subcutaneous administration of α-interferon (1,000,000 units/m^2, 3 times a week), oral famciclovir (Famvir, Novartis Pharmaceuticals Corp, East Hanover, NJ, USA) (90 mg/kg),[33] or lysine.

AUTOIMMUNE 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.[3] They often are clinically impressive and can even be life threatening. Definitive diagnosis requires timely biopsy of appropriate representative skin lesions and cannot be based solely on clinical impression or appearance.

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a multisystemic autoimmune disease. The collie, Shetland sheepdog, German shepherd dog, spitz, and poodle are reported to be at increased risk.[3] Skin disease occurs in less than 20% of SLE cases. Fever, polyarthritis, protein-losing nephropathy, anemia, and thrombocytopenia are more common clinical signs seen with SLE. Organ-specific and non–organ-specific autoantibodies target a variety of tissue antigens in SLE. Resultant tissue damage occurs when there is immune complex deposition (as occurs in glomerulonephritis) or can occur because of direct cytotoxic effects or cell-mediated immunity.

Cutaneous lesions are variable and can 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, because an intact epidermis is needed to make a definitive diagnosis. The histopathologic findings are variable, but classic lesions include apoptosis of basal cells and basal cell vacuolation, which lead to dermo-epidermal separation and consequent ulceration.

Diagnosis of SLE requires demonstration of concurrent autoimmune disease in 2 organ systems in addition to the presence of antinuclear antibodies (ANAs). There are published criteria for the diagnosis of SLE in dogs, and diagnosis requires the presence of at least 3 or more criteria.[3] SLE 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 with and without protein-to-creatinine ratio, 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 level, although this may not always be present. Prognosis depends in large part on the organ systems involved. Immunosuppressive therapy with corticosteroids with or without other immunosuppressive drugs (azathioprine, chlorambucil, cyclosporine) is used.

Erythema Multiforme

Erythema multiforme (EM) terminology has been confusing. More recent nomenclature categorizes EM clinically based on severity of lesions. In EM minor, characteristic lesions involve only one mucosal surface and affect 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.[2] It has been documented that the cell-mediated immune response in EM has a Th1 cytokine pattern.[34] The T cell–mediated response is directed at keratinocytes that may express antigens in a novel way because of drug administration, infection, or neoplasia resulting in apoptosis (single cell necrosis) of keratinocytes. The more severe the clinical presentation of EM, the more likely it is to be related to adverse drug reaction.[35] There is a report of EM associated with parvovirus in a dog,[36] and herpes virus has been implicated in the cat.[37]

Lesions are often pleomorphic with an acute onset of erythematous plaques and macules that often become annular or serpiginous as they coalesce or they may appear targetoid. Progression to ulcerations is common, and lesions may become variably crusted (**Fig. 12**). Lesions often are generalized but are most commonly found on the ventrum, axillae, inguinal region, mucocutaneous junctions, oral cavity, and pinnae. Biopsies should be obtained from areas of erythema without ulceration or crusting because an intact epidermis is needed for the diagnosis. Histologically, apoptosis with lymphocyte satellitosis is the characteristic microscopic lesion of EM.

Prognosis for EM depends on the severity of the disease and identification of underlying triggers. In about 50% of canine cases, an underlying trigger cannot be found. Use of immunosuppressive drugs in human medicine is controversial because EM often is induced by herpes simplex virus.[34] In veterinary medicine, EM patients should be evaluated for underlying triggers: drugs, infection, or neoplasia. EM is often treated with immunosuppressive therapy using glucocorticoids with or without concurrent azathioprine (Imuran). Severe generalized mucocutaneous EM (EM major) often requires aggressive supportive care in addition to removal of underlying triggers and immunosuppressive therapy.

Sterile Nodular Panniculitis

Sterile nodular panniculitis typically presents with ulcerated or draining nodular lesions or nonulcerative subcutaneous nodules (**Fig. 13**). Dogs often are febrile when lesions

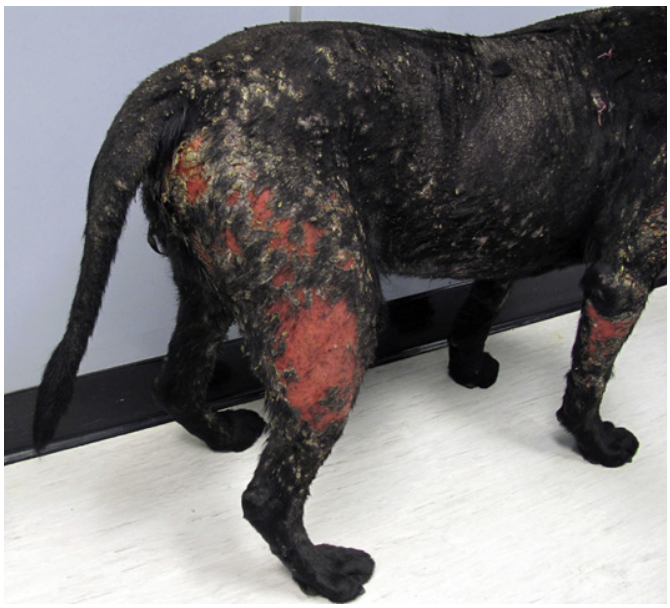

Fig. 12. Multifocal coalescing discrete erosions and ulcerations create large geographic erosive lesions. There are also generalized, multifocal crusting lesions evident in this dog with erythema multiforme. (*Courtesy of* University of California Davis, Veterinary Dermatology Service.)

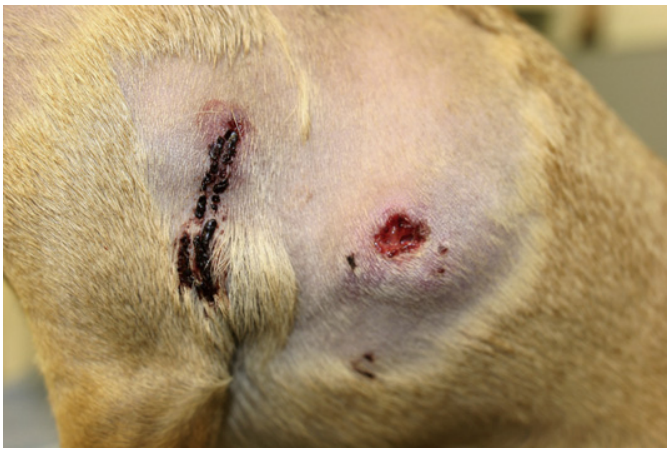

Fig. 13. A dog with discrete nodular lesions, lesions progress in size and then ulcerate and drain. Histopathology of a skin biopsy confirmed sterile nodular panniculitis. (*Courtesy of* University of California Davis, Veterinary Dermatology Service.)

are present, and a peripheral neutrophilia may be present. Lesions most commonly are seen on the trunk but can be present on the head, cervical area, or perineum or can be generalized (see **Fig. 11**). 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. In some cases, concurrent pancreatic disease (pancreatitis and pancreatic neoplasia) or immune-mediated disease in other organ systems (polyarthritis, SLE, rheumatoid arthritis) have been identified.[38] Sterile nodular panniculitis, if associated with pancreatitis, often resolves when the underlying pancreatic disease is managed successfully. Often, sterile nodular panniculitis requires a tapering course of immunosuppressive therapy, most often glucocorticoids, unless underlying or concurrent diseases make this contraindicated.

REFERENCES

1. Credille KM, Slater MR, Moriello KA, et al. The effects of thyroid hormones on the skin of beagle dogs. J Vet Intern Med 2001;15:539–46.
2. Gross TL, Ihrke PJ, Walder EJ, et al. Skin diseases of the dog and cat. Clinical and histopathologic diagnosis. 2nd edition. Ames (IA): Blackwell Science Ltd; 2005.
3. Scott DW, Miller WH, Griffin DE. Muller and Kirk's small animal dermatology. 6th edition. Philadelphia: Elsevier Health; 2001.
4. Turek MM. Cutaneous paraneoplastic syndromes in dogs and cats: a review of the literature. Vet Dermatol 2003;14:279–96.
5. Tasker S, Griffon DJ, Nuttal TJ, et al. Resolution of paraneoplastic alopecia following surgical removal of a pancreatic carcinoma in a cat. J Small Anim Pract 1999;40:16–9.
6. Forster-Van Hijfte MA, Curtis CF, White RN. Resolution of exfoliative dermatitis and Malassezia pachydermatis overgrowth in a cat after surgical thymoma resection. J Small Anim Pract 1997;38:451–4.
7. Rivierre C, Olivry T. Dermatite exfoliative paraneoplasique associee a un thymoma chez unchat: resolution des symptoms après thymectomie. Pract Med Chir Anim Comp 1999;34:533–7.
8. Lium B, Moe L. Hereditary multifocal renal cystadenocarcinomas and nodular dermatofibrosis in the German shepherd dog: macroscopic and histologic changes. Vet Pathol 1985;22:447–55.

9. Moe L, Lium B. Hereditary multifocal renal cystadenocarcinomas and nodular dermatofibrosis in 51 German shepherd dogs. J Small Anim Pract 1997;38:498–505.
10. Olivry T, Linder KE. Dermatoses affecting desmosomes in animals: a mechanistic review of acantholytic blistering skin diseases. Vet Dermatol 2009;20:313–26.
11. Elmore SA, Basseches J, Anhalt G, et al. Paraneoplastic pemphigus in a dog with splenic hematopoietic neoplasia. Vet Pathol 2003;40:609.
12. Lansdown AB, Sampson B. Trace metals in keratinizing epithelia in beagle dogs. Vet Rec 1997;141:571–2.
13. White SD, Bourdeau P, Rosychuk RA, et al. Zinc-responsive dermatosis in dogs: 41 cases and literature review. Vet Dermatol 2001;12:101–9.
14. Cambell GA, Crow D. Zinc responsive dermatosis in a litter of pharaoh hounds. J Vet Diagn Invest 2010;22:663–6.
15. Sousa C, Ihrke P, Reinke S, et al. Generic dog food and skin disease. J Am Vet Med Assoc 1983;182:198–9.
16. Sousa CA, Stannard AA, Ihrke PJ, et al. Dermatosis associated with feeding generic dog food 13 cases (1981-1982). J Am Vet Med Assoc 1988;192:676–80.
17. Jezyk PF, Haskins MF, MacKay-Smith WE, et al. Lethal acrodermatitis in bull terriers. J Am Vet Med Assoc 1986;188:833–9.
18. Grider A, Mouat MF, Mauldin EA, et al. Analysis of the liver soluble proteome from bull terriers affected with inherited lethal acrodermatitis. Mol Genet Metab 2007; 92:249–57.
19. McEwan NA, McNeil PE, Thompson H, et al. Diagnostic features, confirmation and disease progression in 28 cases of lethal acrodermatitis of bull terriers. J Small Anim Pract 2000;41:501–7.
20. McEwan NA, Huang HP, Mellon DJ. Immunoglobulin levels in bull terriers suffering from lethal acrodermatitis. Vet Immunol Immunopathol 2003;96:235–8.
21. Outerbridge CA. Hepatocutaneous syndrome. In: Ettinger SJ, Feldman EC, editors. Textbook of veterinary internal medicine, vol. 1, 7th edition. St Louis (MO): Saunders Elsevier; 2010. p. 112–5.
22. Outerbridge CA, Marks S, Rogers Q. Plasma amino acid concentrations in 36 dogs with histologically confirmed superficial necrolytic dermatitis (SND). Vet Dermatol 2002;13:177–87.
23. Gross TL, Song MD, Havel PJ, et al. Superficial necrolytic dermatitis (necrolytic migratory erythema) in dogs. Vet Pathol 1993;30:75–81.
24. Byrne KP. Metabolic epidermal necrosis-hepatocutaneous syndrome. Vet Clin North Am Small Anim Pract 1999;29:1337–55.
25. Oberkirchner U, Linder KE, Zadrozny L, et al. Successful treatment of canine necrolytic migratory erythema (superficial necrolytic dermatitis) due to metastatic glucagonoma with octreotide. Vet Dermatol 2010;21:510–6.
26. Chastain CB, Graham CL. Xanthomatosis secondary to diabetes mellitus in a dog. J Am Vet Med Assoc 1978;172:1209–11.
27. Duprey ZH, Steurer FJ, Rooney JA, et al. Canine visceral leishmaniasis, United States and Canada, 2000-2003. Emerg Infect Dis 2006;12:440–6.
28. Maia C, Campino L. Methods for diagnosis of canine leishmaniasis and immune response to infection. Vet Parasitol 2008;158:274–87.
29. Denerolle P, Bourdoiseau G. Combination allopurinol and antimony treatment versus antimony alone and allopurinol alone in the treatment of canine leishmaniasis (96 cases). J Vet Intern Med 1999;13:413–5.
30. Haines DM, Martin KM, Chelack BJ, et al. Immunohistochemical detection of canine distemper virus in haired skin, nasal mucosa, and footpad epithelium: a method for antemortem diagnosis of infection. J Vet Diagn Invest 1999;11:396–9.

31. Favrot C, Wilhelm S, Grest P, et al. Two cases of FeLV-associated dermatoses. Vet Dermatol 2005;16:407–12.
32. Holland JL, Outerbridge CA, Affolter VK, et al. Detection of feline herpes virus 1 DNA in skin biopsy specimens from cats with or without dermatitis. Am J Vet Res 2006;229:1442–6.
33. Thomasy SM, Lim CC, Reilly CM, et al. Evaluation of orally administered famciclovir in cats experimentally infected with feline herpesvirus type-1. Am J Vet Res 2011;72:85–95.
34. Caproni M, Torchia D, Schincaglia E, et al. Expression of cytokines and chemokine receptors in the cutaneous lesions of erythema multiforme and Stevens–Johnson syndrome/toxic epidermal necrolysis. Br J Dermatol 2006;155:722–8.
35. Hinn A, Olivry T, Luther P, et al. Erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis in the dog: clinical classification, drug exposure, and histopathological correlations. J Vet Allergy Clin Immunol 1998;6:13–20.
36. Favrot C, Olivry T, Dunstan SM, et al. Parvovirus infection of keratinocytes as a cause of canine erythema multiforme. Vet Pathol 2000;37:647–9.
37. Scott D, Miller W. Erythema multiforme in dogs and cats: literature review and case material from the Cornell University College of Veterinary Medicine (1988–1996). Vet Dermatol 1999;10:297–309.
38. O'Kell AL, Inteeworn N, Diaz SF, et al. Canine sterile nodular panniculitis: a retrospective study of 14 cases. J Vet Intern Med 2010;24:278–84.