In 1942, a cutaneous disorder accompanying malignant tumors of internal organs was described in humans. It was called necrolytic migratory erythema (NME). The distinct skin eruption that accompanies NME is usually associated with a glucagon-secreting tumor but has also been described in patients with chronic pancreatitis, micronodular hepatic cirrhosis, and protein-losing enteropathies. In 1986, Walton et al reported a condition similar to NME in diabetic dogs. Since then, nondiabetic dogs have been identified with the disease. The canine disease has since been called hepatocutaneous syndrome, superficial necrolytic dermatitis (SND), metabolic epidermal necrosis, and NME. Similarities between the human and veterinary diseases include patient age (i.e., middle-aged or older), lesion distribution, morphology of both gross and microscopic lesions, and therapeutic options. Unlike humans with NME, dogs with SND are much more likely to have an underlying vacuolar hepatopathy.

**PRESENTATION**

Patients with SND most often present with persistent skin lesions. Affected dogs are usually 4 to 16 years of age. No breed or sex predilection has been proven; however, some clinicians believe terriers are overrepresented. SND is characterized by an erosive, crusting, and scaling dermatopathy distributed symmetrically over the face, distal paws, and inguinal area as well as in areas of constant friction (Figure 1). Mucocutaneous junctions, the genital area, and pressure points are often affected (Figure 2). Secondary bacterial colonization frequently develops. There may also be marked hyperkeratosis, fissuring, and ulceration of the footpads (Figure 3). Common owner complaints include lethargy, anorexia, weight loss, and difficulty or painful walking in affected dogs. The skin lesions frequently wax and wane in severity, making evaluation of therapy and definitive diagnosis difficult.

Signs of the underlying condition, usually a hepatopathy, might also be seen. However, not all dogs have signs of severe hepatic disease at the time of skin lesion development.

**PATHOPHYSIOLOGY**

The pathogenesis of SND in dogs is unknown. NME in humans is usually associated with a glucagon-secreting neoplasm; therefore,
Canine Superficial Necrolytic Dermatitis

Canine superficial necrolytic dermatitis is most often associated with a hepatopathy, the cause of which is usually unknown.

zinc and fatty acids) in patients with liver dysfunction may also be partially responsible for the skin lesions.12 Few studies have been conducted to assess the role of glucagon in dogs with SND. In cases in which it was evaluated, glucagon levels often did not correlate with development of skin lesions. Furthermore, the disease in animals is associated with a glucagon-secreting tumor in fewer than 10% of cases. In fact, of the 64 cases of SND reported in the veterinary literature from 1986 through 1997, only four were found to have a pancreatic tumor.13 Various hepatopathies have more commonly been associated with SND in dogs.5 Some clinicians have postulated that peripheral glucagon concentrations measured in these studies are not a reliable or sensitive index of increased pancreatic glucagon secretions. In dogs, a tripling of pancreatic glucagon secretion can occur without a significant increase in peripheral glucagon concentration.14 Therefore, it is possible that increased portal glucagon levels could be responsible for increased hepatic gluconeogenesis and hypoaminoacidemia without a concurrent increase in peripheral glucagon levels due to hepatic extraction and peripheral dilution.15 In a report of 42 cases of SND, 90.5% were associated with advanced liver disease.16 Liver lesions may be secondary to an underlying metabolic, hormonal, or toxic insult.4 The severe vacuolar liver disease present in some dogs with SND may support the theory of an underlying metabolic or hormonal dysfunction rather than primary liver disease.15 Hypoaminoacidemia or persistent elevations of glucagon may be responsible for the hepatic changes that occur. This is supported by the observation that dogs fed a protein-deficient diet for a prolonged period of time may develop hypoaminoacidemia and have increased glucagon levels.

Glucagon is a 29 amino acid polypeptide produced primarily by pancreatic alpha cells. It enhances the liver’s capability for gluconeogenesis.4 The biologic significance of several immunoreactive fractions of glucagon has not been determined.10 It has been hypothesized that an elevation in glucagon or one of its immunoreactive fractions is responsible for causing NME in humans.5 Increased production of glucagon by a glucagonoma or its diminished degradation by a dysfunctional liver may result in abnormal ratios of circulating immunoreactive glucagon. Hypoaminoacidemia develops secondarily to the catabolic gluconeogenic effects of excessive glucagon.11 Because of the skin’s continuous growth and requirements for histidine and lysine-rich keratohyalin granules in the stratum granulosum, the epidermis is susceptible to this amino acid deficiency.8,12 Increased glucagon levels may also stimulate arachidonic acid synthesis in keratinocytes, causing increased arachidonic acid release and, therefore, inflammation and necrosis in the areas of skin most frequently traumatized.2 Others have theorized that abnormal zinc or fatty acid metabolism caused by lower levels of albumin (which carries the role of glucagon in the development of NME in humans has been studied. Glucagon is a 29 amino acid polypeptide produced primarily by pancreatic alpha cells. It enhances the liver’s capability for gluconeogenesis.4 The biologic significance of several immunoreactive fractions of glucagon has not been determined.10 It has been hypothesized that an elevation in glucagon or one of its immunoreactive fractions is responsible for causing NME in humans.5 Increased production of glucagon by a glucagonoma or its diminished degradation by a dysfunctional liver may result in abnormal ratios of circulating immunoreactive glucagon. Hypoaminoacidemia develops secondarily to the catabolic gluconeogenic effects of excessive glucagon.11 Because of the skin’s continuous growth and requirements for histidine and lysine-rich keratohyalin granules in the stratum granulosum, the epidermis is susceptible to this amino acid deficiency.8,12 Increased glucagon levels may also stimulate arachidonic acid synthesis in keratinocytes, causing increased arachidonic acid release and, therefore, inflammation and necrosis in the areas of skin most frequently traumatized.2 Others have theorized that abnormal zinc or fatty acid metabolism caused by lower levels of albumin (which carries
period may develop similar hepatic changes; however, the typical skin lesions are not seen. In dogs, an underlying cause for the liver dysfunction is usually not found.

**DIFFERENTIAL DIAGNOSIS**

Appropriate diagnostic differentials for skin lesions associated with SND include bacterial pyoderma, pemphigus foliaceus, erythema multiforme, systemic lupus erythematosus, zinc-responsive dermatosis, vitamin A-responsive dermatosis, toxic epidermal necrolysis, and drug eruptions. If underlying liver pathology is suspected, causes of liver disease (e.g., copper storage disease, mycotoxicosis, long-term anticonvulsant therapy) should be ruled out.

**DIAGNOSIS**

Common blood work abnormalities in dogs with SND include increases in liver enzymes and hypoalbuminemia. In one study, alkaline phosphatase activity was increased in all 22 animals and elevated alanine transaminase activity occurred in 18 of the 22 animals. Other serum biochemistry abnormalities may include elevated aspartate aminotransferase levels, fluctuating hyperglycemia, nonregenerative to mildly regenerative anemia, and hypoalbuminemia. Affected dogs may also have hyperglucagonemia, hyperinsulinemia, and hypoaminoacidemia. Many dogs have concurrent diabetes mellitus (DM) and/or hyperadrenocorticism. Bile acids have reportedly been elevated, but this finding is inconsistent.

Abdominal radiography may be helpful in ruling out other underlying diseases or demonstrating hepaticomegaly. Ultrasonography of the liver may reveal diffusely abnormal liver parenchyma with a mottled appearance. The marginal echoes of the intrahepatic branches of the portal vein may appear prominent, which is suggestive of periportal fibrosis. The liver has been described as having a classic “honeycomb” appearance because of variably sized hypoechoic regions surrounded by hyperechoic borders. Ascites has not been reported with SND. The pancreas should be thoroughly evaluated during ultrasonographic examination. Dogs with pancreatic glucagon-producing alpha cell tumors are not reported to have the characteristic honeycomb liver changes.

Hypoaminoacidemia is a common, but not universal, abnormality in patients with SND. In one study, all eight dogs tested had severely decreased (i.e., usually 30% to 50% of normal values) serum concentrations of amino acids. It was found that concentrations of hydroxyproline, threonine, glutamine, proline, alanine, citrulline, and arginine were the most severely reduced. Amino acid levels can be determined at the University of California, Davis Veterinary Teaching Hospital. Plasma glucagon levels were not elevated in the dogs in this study, although documented increases in serum glucagon levels have been noted in some dogs with SND. Other diseases that have been shown to increase glucagon levels include DM, pancreatitis, and chronic...
hepatic insufficiency. Glucagon is considered to be unstable; therefore, it is recommended to use an enzyme inhibitor such as aprotinin when submitting a blood sample for measurement of glucagon to a laboratory. Assays for human glucagon have been determined to be useful in most other species, and glucagon levels can usually be obtained at a local human hospital. Plasma zinc levels are usually normal.

Skin biopsies are needed to confirm a diagnosis of SND. The histologic lesions on skin biopsy specimens are virtually pathognomonic and include diffuse parakeratotic hyperkeratosis, intracellular edema of the granular epithelial cells, and basal cell hyperplasia. This is known as the red, white, and blue pattern; the superficial layer of keratin stains red, the middle layer of vacuolated pale keratinocytes stains white, and the deep layer of hyperplastic basal cells stains blue with hematoxylin and eosin. 

Changes in the dermis are minimal but, when present, usually consist of a superficial, diffuse infiltrate of lymphocytes, plasma cells, and neutrophils. It is important to examine multiple skin biopsy samples because these characteristic findings may not be uniformly present. Biopsy samples should be taken from the periphery of an ulcerating skin lesion or a crusting, scaling lesion. Biopsies of the footpad are recommended but can be less helpful based on the degree of hyperkeratosis present.

In patients with an underlying liver condition, a liver biopsy can confirm the unique histologic findings in patients with SND; however, fine-needle aspiration and ultrasound-guided biopsy can be misleading if only a vacuolar hepatopathy is reported. Histopathology of hepatic biopsy samples reveals distinct regenerative nodules bordered by severely vacuolated hepatocytes, numerous bile ductules, and a network of reticular and fine collagen fibers that represent remnants of collapsed hepatic lobules. This severe lobular collapse and nodular regeneration are evidence of ongoing hepatocellular regeneration and necrosis with resultant parenchymal collapse.

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**Palliative therapy with amino acid supplementation may improve skin lesions in some patients.**

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**THERAPY AND PROGNOSIS**

Therapy for SND is symptomatic and has shown only limited success. Secondary infections should be treated appropriately. If a glucagonoma is found, removal of the mass may lead to remission of signs and increased amino acid concentrations. However, some dogs have not improved, even with discontinuation of phenobarbital. Palliative therapy with parenteral and/or oral amino acid supplementation as well as zinc (i.e., zinc methionine [2 mg/kg/day]) and fatty acid supplementation has improved some cutaneous lesions in dogs. Omega-3 fatty acids at twice the bottle dose is recommended. Supplementation with cooked or raw egg yolk (i.e., 3 to 6 per day) as a source of amino acids and a high-quality, high-protein diet are recommended. Intra-venous administration of amino acid solution (Aminosyn 10% Crystalline Amino Acid Solution, Abbott Laborato-
ries) at 25 ml/kg over 8 to 10 hours and repeated every 7 to 10 days has been recommended; however, definitive studies on the efficacy of this treatment are lacking. In humans, somatostatin analogues have resulted in remission of NME lesions. The somatostatin analogue octreotide (Sandostatin, Novartis) is a potent inhibitor of glucagon release and has been administered subcutaneously. It has been shown to be potentially beneficial when a glucagonoma is present. Colchicine, an antifibrotic agent, has been used with mixed success in humans to inhibit the advancement of possible cirrhosis. Prednisone therapy must be used cautiously because it may promote glucose intolerance and DM.

The prognosis for SND is poor. In one study, mean survival time from the onset of skin lesions was 5.3 months and from the time of diagnosis was 1.6 months. With further research and evaluation, the length and quality of life of affected dogs may improve.

**SUPERFICIAL NECROLYTIC DERMATITIS IN CATS**

To our knowledge, only four cases of feline SND have been published. One cat had a pancreatic adenocarcinoma, and one had thymic amyloidosis. The two other cases involved cats with hepatopathies and a similar cutaneous reaction, as seen in dogs. However, distribution of skin lesions in cats has been different than in dogs, with lesions present on the inguinal and ventral abdominal skin as well as the interdigital region in cats. Cats are also more likely to have increased alanine transaminase and aspartate aminotransferase activity as well as bile acids with normal alkaline phosphatase activity. This may be due to differences in isoenzyme release or induction or differences in the severity or cause of the hepatopathy. Hyperalimentation, zinc, or fatty acid supplementation or intravenous amino acid therapy has not been attempted in cats.

**CONCLUSION**

SND is an uncommon dermatopathy in dogs and is rare in cats. It is frequently associated with underlying liver pathology. A definitive diagnosis can usually be made from skin biopsies, and treatment is supportive. Amino acid supplementation, oral fatty acid and zinc supplementation, and feeding a high-protein, high-quality diet and egg yolks may help ameliorate the skin lesions. Antifibrotic agents and somatostatin analogues have also been used with mixed success in dogs. The long-term prognosis for patients with SND is poor.

**REFERENCES**

1. SND in dogs is most commonly associated with
   a. kidney disease.
   b. liver disease.
   c. pancreatic tumors.
   d. DM.

2. Definitive diagnosis of SND requires
   a. skin biopsies.
   b. pancreatic biopsies.
   c. serum chemistries.
   d. glucagon measurements.

3. SND is similar to ______ in humans.
   a. Crohn's disease
   b. lupus
   c. NME
   d. none of the above

4. Which is not a treatment option in dogs with SND?
   a. egg yolk
   b. amino acid infusions
   c. immunosuppressive steroid therapy
   d. somatostatin analogues

5. Which is not a histopathologic component of skin biopsy specimens obtained from patients with SND?
   a. basal cell hyperplasia
   b. parakeratotic hyperkeratosis
   c. increased numbers of acantholytic cells
   d. intracellular edema

6. Secondary pyoderma and/or __________________ is often present in dogs with SND.
   a. Malassezia spp infection
   b. candidiasis
   c. histoplasmosis
   d. blastomycosis

7. Ultrasonographic findings in patients with SND often include
   a. normal echogenicity of the liver parenchyma.
   b. ascites.
   c. diffusely hyperechoic liver parenchyma.
   d. a "honeycomb" appearance of the liver parenchyma.

8. Gross skin changes in patients with SND do not include
   a. hyperkeratosis of the footpads.
   b. ulceration of the footpads.
   c. pustular dermatopathy.
   d. erosive, scaling, and crusting dermatopathy.

9. NME in humans is usually associated with a tumor that produces
   a. somatostatin.
   b. glucagon.
   c. calcium.
   d. epinephrine.

10. SND is more common in
    a. cats.
    b. dogs.
    c. mice.
    d. monkeys.