Pathology in Practice

In collaboration with the American College of Veterinary Pathologists

History

An 8.5-year-old 6.5-kg spayed female Miniature Schnauzer was presented because of an approximately 6-month history of signs of painful footpads affecting all 4 feet. A chemical burn was initially suspected, and the footpads were treated with antiseptic wipes without improvement. Treatment with prednisone (0.7 mg/kg, PO, q 24 h for 3 days then tapered) and cefpodoxime proxetil (7.3 mg/kg, PO, q 24 h for 8 days) resulted in partial improvement; however, clinical signs returned once the medications were finished. Over the next 5 months, the dog received 4 additional courses of prednisone without meaningful improvement. All medications were discontinued. The dog became anorectic, had high activities of liver enzymes, and was referred for suspected liver-induced necrolytic migratory erythema (NME; hepatocutaneous syndrome).

Clinical and Clinicopathologic Findings

On physical examination, the dog was quiet, mildly tachycardic (160 beats/min), and had mild peripheral lymph node enlargement. Erythema, erosions, and crusting were present periorally and on the ventral aspect of the vulva. Severe crusting, edema, and hyperkeratosis affected footpads of all 4 feet; the feet were painful, and there was severe interdigital erythema on the ventral aspect of all 4 feet. A serum liver profile revealed mild hypoalbuminemia (3.1 g/dL; reference range, 3.3 to 4.2 g/dL) and mildly high activities of alkaline phosphatase (142 U/L; reference range, 13 to 95 U/L). Findings on abdominal ultrasonography were unremarkable. Biopsy specimens were obtained from the focal perioral skin lesions and submitted for histologic examination.

Histopathologic Findings

Skin biopsies were characterized by subcorneal pustules and crusts spanning several hair follicles with mild epidermal hyperplasia in between (Figure 2). Pustules were roofed by a thin layer of keratin and contained well-preserved neutrophils admixed with single round to polygonal acantholytic...
or fungal organisms were seen on Gram or Grocott methenamine silver staining, respectively. Immunohistochemistry staining for canine IgG demonstrated IgG between cells in the upper layers of the stratum spinosum of developing pustules, surrounding acantholytic cells in pustules, and intercellularly in the roof of crusts (Figure 3). Rafts of acantholytic keratinocytes in crusts stained intensely for canine IgG.

**Morphological Diagnosis and Case Summary**

Morphological diagnosis: multifocal neutrophilic subcorneal pustular dermatitis with acantholytic keratinocytes and crusting.

Case summary: pemphigus foliaceus restricted to the footpads and mucocutaneous junctions in a dog.

**Comments**

Taken together the dog’s history, the clinically distinctive skin lesions affecting predominantly footpads with mucocutaneous junction involvement, and the histopathologic findings led to the diagnosis of pemphigus foliaceus (PF).

Pemphigus foliaceus is the most common clinical variant within the pemphigus complex in dogs.\(^1,2\) The trunk, ears, and face are typically affected in canine PF with rare reports of solitary footpad lesions and mucocutaneous junction involvement.\(^2\) In canine PF, autoantibodies target the desmocollin-1 protein within the intercellular junctions between keratinocytes called desmosomes, which results in loss of cell-to-cell adhesion and subsequent separation of keratinocytes within the superficial epidermis with infiltration of neutrophils and rarely eosinophils.\(^2-4\)

These keratinocytes are called acantholytic cells; on cytology, they appear as rounded epithelial cells with nuclei and basophilic (deep blue) cytoplasm.\(^5\) The outcome of desmosome disruption is the formation of large pustules that rapidly progress into crusts or erosions as the pustules rupture. The dog’s skin lesions in this report are dominated by crusting rather than pustules as the active areas are subjected to constant friction, which results in easy pustule rupture. Direct immunofluorescence has been shown to be helpful in the diagnosis of PF by detecting tissue-bound autoantibodies.\(^5,6\) In this case, indirect immunohistochemistry was used similarly to demonstrate canine IgG-positive staining in skin lesions (Figures 2 and 3).

Initially, the dog in this report was thought to have NME due to liver disease because of the high activities of liver enzymes and the extensive hyperkeratosis of all footpads. Necrolytic migratory erythema in dogs is clinically and histologically identical to NME in humans and can be associated with glucagonoma or liver disease (hepatocutaneous syndrome).\(^7\) Severe hyperkeratosis, crusting, and fissuring of footpads as well as erosions and crusting around mucocutaneous junctions are characteristics

**Figure 2**—Photomicrographs of a section of a perioral skin biopsy sample from the dog in Figure 1. A subcorneal pustule (arrow) merges into a thick crust (C) overlying moderate hyperplastic epidermis. H&E stain; bar = 200 μm. Inset—Pustule at arrow contains well-preserved neutrophils and acantholytic cells detaching from stratum spinosum. H&E stain; bar = 100 μm.

**Figure 3**—Photomicrographs of sections of skin biopsy samples from the dog in Figure 1. The thick crust has a keratin roof (K) and is composed of serum, degenerate neutrophils (N), and a large raft of degenerating acantholytic keratinocytes (A). H&E stain; bar = 100 μm. Inset—A section of the same crust shows a large, brown staining IgG-positive raft of acantholytic cells (asterisk) and brown staining IgG-positive cells in the overlying keratin roof (arrow). Immunohistochemistry staining (3,3′-diaminobenzidine [DAB]) for canine IgG; bar = 100 μm.

cells characterized by abundant eosinophilic cytoplasm and viable nucleus.

Acantholytic cells were seen detaching from the stratum spinosum with a few clinging to the overlying roof. Thick crusts with a roof of keratin were composed of serum, large amounts of neutrophilic debris, and rafts of degenerating acantholytic keratinocytes. The underlying superficial dermis was mildly edematous with perivascular to interstitial infiltrations of low numbers of mast cells, lymphocytes, plasma cells, and neutrophils. No bacterial
of NME. Histologically, dogs with NME have the characteristic red, white, and blue epidermal pattern representing parakeratotic hyperkeratosis, edema of the stratum granulosum, and spinosum and basal cell hyperplasia. Elevated liver enzyme activities and hypoalbuminemia are common findings, and on abdominal ultrasonography, the liver-associated NME shows a distinctive honeycomb pattern or in the glucagonoma-associated NME nodules can be observed in the pancreas. The dog of the present report had high activities of liver enzymes but no liver abnormalities on abdominal ultrasonography; high activities of liver enzymes were likely caused by prolonged glucocorticoid administration. Furthermore, there were no characteristic red, white, and blue NME epidermal changes observed in the skin biopsy of this patient presented in this report.

Canine PF is an autoimmune antibody-driven skin disease and treatment consists of systemic and topical immunosuppressive medications; glucocorticoids, cyclosporine, mycophenolate mofetil, and azathioprine are commonly utilized for the treatment of PF. Phases of treatment include induction of remission defined as no new lesion formation and maintenance that focuses on preventing the patient from developing new lesions after successful clinical remission. Although the prognosis for dogs with PF can vary, 71% of dogs in 1 study were alive after a mean follow-up period of 2.7 years. Dogs may relapse following cessation of medication; however, extended periods of remission of over 1 year have been reported. To the authors’ knowledge, there are no prospective controlled veterinary studies comparing the various immunosuppressive medications used in canine PF. In dogs, oral corticosteroids continue to be the most commonly prescribed first-line treatment in PF mainly because of their rapid onset of action. Induction dosages of oral administration of prednisone or prednisolone range from 2.2 to 4.2 mg/kg every 24 hours for a minimum of 10 days. Once disease remission is achieved, the dose is slowly tapered over a number of months to the lowest effective dose that results in no new lesion formation. Glucocorticoids are not recommended as the sole long-term treatment due to their numerous undesirable adverse effects such as polyuria, polydipsia, polyphagy, skin atrophy, and iatrogenic hyperadrenocorticism.

The dog of this report was initially treated with 1 mg/kg/day of prednisone with 7 mg/kg/day of cyclosporine and responded well to treatment with tapering of the prednisone beginning on day 35 and finishing on day 101. Cyclosporine, a calcineurin inhibitor that blocks the activation and proliferation of T-cells, has been used successfully in the management of PF. Cyclosporine is typically combined with prednisone initially with the goal of weaning and then discontinuing the prednisone. The most common adverse effects of cyclosporine include vomiting, diarrhea, and anorexia, with gingival hyperplasia and psoriasiform-lichenoid-like dermatitis being observed less commonly. The dog remained solely on cyclosporine for approximately 60 days before being discontinued due to financial constraints. As reported by the referring veterinarian, the dog relapsed 30 days later and was restarted on prednisone. Unfortunately, the patient was lost to follow-up.

In summary, PF is a pustular disease that in some dogs can predominantly affect the footpads and mucocutaneous junctions and mimic other diseases (ie, NME) that cause crusting of footpads and mucocutaneous junctions. Skin biopsy is helpful to differentiate PF from NME. Treatment consists of immunosuppression typically using a combination of prednisone and a steroid-sparing immunosuppressant such as cyclosporine.

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References