“The Undeniable Itch”

Pemphigus Foliaceus in a Dog

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Introduction:

Pemphigus foliaceus is one of the most common autoimmune skin disorders in dogs and cats, and it is the most common form of the pemphigus complex disorders, which also include pemphigus erythematosus, pemphigus vegetans, pemphigus vulgaris, and paraneoplastic pemphigus. Pemphigus foliaceus is characterized by acantholysis of the skin cells, resulting in the separation of the keratinocytes from each other. Most cases of pemphigus foliaceus are idiopathic, but there are cases of drug-induced iatrogenic pemphigus. The disease starts as erythematous macules and papules that create pustules, which rupture to form ulcers with crusts and erosions with epidermal collarettes. Alopecia and scaling ensue, and secondary bacterial pyoderma is common (1). This disease typically occurs in middle aged to older dogs, with Akitas and Chow Chows having a possible predisposition. With pemphigus foliaceus, the head, face, and ears are affected in over 80% of cases, and eventually the lesions can become generalized over the body. The skin lesions may wax and wane and can be variably pruritic (1,2). Pemphigus foliaceus that is widespread across the truncal skin with or without facial or pedal lesions may occur more commonly in Cocker Spaniels and Chihuahuas (5). For the following case, Sally Jane demonstrated a complex example of pemphigus foliaceus that was complicated by other disease processes.

History and Presentation:

Sally Jane is an approximately 6.5 year-old female spayed tri-colored Cocker Spaniel that presented to the Mississippi State University College of Veterinary Medicine (MSU CVM) Dermatology Department on March 14, 2018, for worsening of skin issues. Sally Jane first presented to her referring veterinarian six weeks prior for an inflamed vulva and was diagnosed with and treated with Clavamox (250mg every 12 hours; 20mg/kg/dose) for a urinary tract

infection. Two weeks later, Sally Jane's owners noticed several small sores on Sally Jane's body, thought she was having an allergic reaction, and returned to their referring veterinarian. The veterinarian confirmed that the previously diagnosed urinary tract infection was cleared, and she biopsied the affected skin regions. The biopsies were sent to the MSU CVM Research and Diagnostic Laboratory in Pearl, Mississippi, which resulted in the diagnosis of pemphigus foliaceus. Sally Jane was started on cephalexin (150mg every 12 hours; 12mg/kg/dose), prednisone (20mg every 12 hours; 1.5mg/kg/dose), and hydroxyzine (25mg every 24 hours; 2mg/kg/dose). Her energy level then began to slightly decrease, while her food and water intake increased. On March 12, 2018, Sally Jane presented again to her referring veterinarian because her skin lesions were worsening. While at the referring veterinary clinic, Sally Jane began pulling out her hair, and acepromazine (10mg as needed; 0.8mg/kg/dose) and trazodone (50mg every 12 hours; 4mg/kg/dose) were prescribed to help calm Sally Jane. Azathioprine (25mg every 12 hours; 2mg/kg/dose) was added to the regimen for her pemphigus foliaceus. At this point, Sally Jane was referred to the MSU CVM Dermatology Department. The owners reported that Sally Jane has a habit of constant panting, circling in both directions, and tracing figure-8 patterns, especially when storms are approaching. Sally Jane was wearing an e-collar when unsupervised, due to her constantly licking and scratching her body to the point where her hair falls out in clumps. About 4-5 years ago, Sally Jane had a similar episode of skin sores, but they were much less severe. She was switched to a grain-free dog food, and her skin sores resolved with no other skin issues until this recent episode. Sally Jane was spayed at 1.5 years-old following a possible heat cycle or false pregnancy, and she is a primarily outdoor dog. Sally Jane currently eats Diamond Natural Grain Free Salmon and Potato dog food, which she began eating about 1 year prior, and receives Heartgard and Nexgard.

On presentation, Sally Jane was bright, alert, and responsive, but she was severely pruritic and scratching her body on anything in sight. Her vital parameters were within normal limits, with a temperature of 101.6F, pulse of 130 beats per minute, and respiration of 30 breaths per minute. Sally Jane weighed 12.5 kg with a body condition score of 5/9 (4-5 being ideal). There was a severe buildup of dental tartar on her teeth, and her nictitating membranes were protruding bilaterally. On cardiothoracic auscultation, no murmurs or arrhythmias were detected, and no wheezes or crackles were detected from her lungs. There was severe inflammation and erythema of the vulva and tissues surrounding the vulva. Plaques with crusts, epidermal collarettes, erosions, severe scaling, and alopecia were diffuse across her body, especially on the bridge of the nose, ears, forelimbs, dorsum, rump, perianal area, and inguinal area. Sally Jane did not appear painful, just severely pruritic and uncomfortable. No other abnormalities were detected on physical exam.

Pathophysiology:

The layers of the epidermis from most superficial to deep are the stratum corneum, stratum granulosum, stratum spinosum, and stratum basale. Within the skin layers, desmosomes are the cell adhesion structures, which contain transmembrane cadherins, such as desmogleins and desmocollins, and linker proteins, such as desmoplakin, plakoglobin, and plakophilins, to maintain the keratinocyte connections (9). In human pemphigus foliaceus, IgG autoantibodies are formed within the body that target the adhesion molecule glycoprotein desmoglein-1 (DSG-1), which is located primarily in the stratum granulosum of the epidermis. This deposition and binding of autoantibodies in the intercellular spaces creates a loss of intercellular connections between the keratinocytes, as DSG-1 is a prominent component of the desmosomes. This results in acantholysis, or the detachment of cells from each other in the uppermost epidermal layers,

and subcorneal blisters forming within the epidermis (3,4,5). In dogs with pemphigus foliaceus, there are antikeratinocyte IgG autoantibodies present, but the DSG-1 is only rarely targeted by IgG (4,5). In one study using immunofluorescence analysis on 83 dogs with canine pemphigus foliaceus sera, 82% of these dogs contained "detectable circulating anti-keratinocyte autoantibodies" (8). Only 6% of the 83 dogs tested contained IgG autoantibodies that recognized the DSG-1 antigen, therefore suggesting that DSG-1 is only a minor autoantigen in canine pemphigus foliaceus (8). However, in another study, immunomapping was used to compare the expression profiles of the main desmosomal and nondesmosomal proteins to the staining patterns of the canine pemphigus foliaceus serum IgG. In 80% of canine pemphigus foliaceus sera, the staining profile closely resembled the expression profile of desmocollin-1 (DSC-1), which is a calcium-dependent cadherin expressed significantly in the superficial epidermal layers. These DSC-1 IgG autoantibodies were detected in the majority of canine sera with pemphigus foliaceus but not detected in normal canine sera or the sera of canines affected by non-pemphigus foliaceus autoimmune blistering skin diseases (9). Subcorneal clefts, or superficial pustules, are the primary lesions of pemphigus foliaceus, as the autoantibodies mainly target the granulosum layer, but these lesions are often hidden by hair coat and are easily ruptured. Superficial erosions, crust, scales, epidermal collarettes, and alopecia are all secondary lesions that may be more readily observed. (2). While the majority of cases of pemphigus foliaceus are idiopathic, there are reported cases of this disorder developing due to a sequela of a chronic inflammatory skin disease, due to the use of various antibiotics, such as trimethoprim-potentiated sulfonamides and cephalexin, or due to the ectoparasiticide drug Promeris, which is no longer on the market but contains the active ingredients of metaflumizone and amitraz (2,4,5). If induced by a drug reaction, pemphigus foliaceus may present very early in age, have an unusually rapid onset, or

produce oral lesions, which are all atypical for the idiopathic version of this disease (5). In this case, the patient had no known history of treatment with these reported drugs prior to the signs of disease, therefore her pemphigus disorder was likely idiopathic.

Diagnostic Approach/Considerations:

While the lesions of pemphigus foliaceus typically involve the dorsal muzzle, planum nasale, pinnae, periorbital skin, and pawpads, visualization is not enough to confirm a definitive diagnosis (5). Cytology of intact pustules often reveals acantholytic cells with neutrophils and eosinophils present, but biopsies are the most efficient way to confirm the presence of this autoimmune skin disorder. Histopathology of skin biopsies from primary intact pustules are the ideal samples specimens, and subcorneal pustules containing acantholytic keratocytes and neutrophils are characteristic for pemphigus foliaceus. The acantholytic cells are often partially adhered to one another and free floating in 'rafts' or adhered to the overlying stratum corneum. Immunofluorescence or immunohistochemical testing from the skin biopsies can also be submitted to detect the deposition of intercellular antibodies, however this is typically not necessary for diagnosis (1,2,5). Differential diagnoses may include demodicosis, bacterial pyoderma, dermatophytosis, other autoimmune skin diseases that affect the nasal planum (i.e. discoid lupus), drug reactions, erythema multiforme, or sterile pustular diseases (2). To rule out differential diagnoses or determine conditions that may be complicating unmanaged pemphigus foliaceus, further diagnostics may be performed. Superficial and deep skin scrapings can identify parasitic infections, while impression smears and tape preparations may detect bacterial or fungal organisms. Dermatophyte fungal cultures and Wood's Lamp examination may detect the presence of dermatophytes, while bacterial cultures can detect secondary bacterial infections (6).

Treatments and Management:

Multimodal approaches to treat pemphigus foliaceus are generally more efficacious and result in minimizing the adverse side effects of one therapy alone. In order to transition this disease into remission, an induction phase of higher dosages of glucocorticoids are started, with slowly tapering dosages typically occurring over 2-3 months to determine the lowest effective dose. Multimodal approaches may include the following: topical therapy with steroid-containing products or tacrolimus, conservative systemic treatments, steroid therapy, and nonsteroidal immunosuppressive drugs (2). Conservative systemic treatments may include essential fatty acids (180mg EPA/10pounds/dose every 24 hours), vitamin E (400IU/dose every 24 hours), doxycycline (5-10mg/kg/dose every 12 hours for induction), niacinamide (250 or 500mg/dose, if <10kg or >10kg, respectively, every 8 hours for induction), or cyclosporine (5-12.5mg/kg/dose every 12-24 hours for induction) (2). Steroid therapy commonly includes prednisolone (1-3mg/kg/dose every 12-24 hours for induction and reduced to 0.5-2mg/kg/dose every 48 hours). At times alternatives may be needed, such as triamcinolone (0.1-0.6mg/kg/dose every 12-24 hours for induction and reduced to 0.1-0.2mg/kg/dose every 48-72 hours) or dexamethasone (0.1-0.2mg/kg/dose every 12-24 hours for induction and reduced to 0.05-0.1mg/kg/dose every 48-72 hours). Nonsteroidal immunosuppressive drugs may include azathioprine (1.5-2.5mg/kg/dose every 24 hours for induction and reduced to 1.5-2.5mg/kg/dose every 48-72 hours) or chlorambucil (0.1-0.2mg/kg/dose every 24 hours for induction and reduced to 0.1-0.2mg/kg/dose every 48 hours). Caution must be taken to monitor for myelosuppression when using azathioprine or chlorambucil, and monitoring for hepatotoxicity should occur when using azathioprine. Systemic antibiotics are recommended as a preemptive measure during immunosuppression therapy to treat secondary bacterial pyoderma, which is a common

occurrence with pemphigus foliaceus (1,2).

With autoimmune skin disorders, flare-ups can occur, however "the goal of therapy is to control 90% of the symptoms 90% of the time while minimizing the adverse effects of treatments" (2). Antibiotic therapy during the induction phase of immunosuppressive regimes result in higher survival rates. Prognosis for pemphigus foliaceus is fair to good for reaching remission with treatment, but most dogs will require lifelong therapy for remission to be maintained (2,7).

Case Outcome:

To determine the underlying reason for the unmanaged pemphigus foliaceus and to determine if any other diseases had developed, a series of diagnostic tests were performed on Sally Jane. On deep and superficial skin scrapings, no mites were detected. A Wood's Lamp exam had no positive fluorescence, and the dermatophyte culture was negative for growth at four weeks. Skin cytology through tape preparations from multiple lesions were obtained. No yeast were detected, but varying amounts of cocci bacteria were detected from the perivulvar skin and hip lesions. Impression smears from multiple lesions showed a large number of neutrophils and eosinophils, with some cocci bacteria and acantholytic cells. Sally Jane was then sedated with dexmedetomidine (5mcg/kg) and butorphanol (0.2mg/kg). A swab sample for bacterial culture was obtained from underneath a crust, and biopsies were acquired from 6 different site lesions. Biopsies were repeated due to concerns of appropriate dosing and duration of prednisone not resolving the pemphigus lesions and the concern for other disease development, such as a drug reaction, erythema multiforme, and cutaneous T-cell lymphoma. Upon waiting for the biopsy and culture results, Sally Jane was started on cefpodoxime (100mg every 24 hour; 8mg/kg/dose), and continued on prednisone (20mg every 12 hours; 1.5mg/kg/dose), hydroxyzine (25mg every

24 hours; 2mg/kg/dose), trazodone (50mg every 12 hours; 4mg/kg/dose), and acepromazine (10mg as needed; 0.8mg/kg/dose). The azathioprine dosage was decreased to 25mg every 24 hours (2mg/kg/dose, which was previously 2mg/kg every 12 hours), and the cephalexin was discontinued. Before leaving the MSU CVM, Sally Jane received a Cytopoint injection (30mg; 2.4mg/kg), which is a monoclonal antibody against interleukin 31 (IL31) to decrease the itch sensation. This is commonly used in dogs with atopic dermatitis. Sally Jane was also sent home with a sample bag of Hill's Prescription Diet Z/D in case an underlying food allergy was complicating her pemphigus foliaceus signs.

On March 22, 2018, Sally Jane's skin biopsies and bacterial culture returned. The biopsies confirmed the diagnosis of pemphigus foliaceus with no other disease processes detected. A pattern of follicular epithelium involvement and follicular rupture was noted on the pathology. The bacterial culture returned with growth of *Staphylococcus intermedius* and *Corynebacterium* species, which were resistant to the previously prescribed cefpodoxime. Therefore, Sally Jane was switched to clindamycin (150mg every 12 hours for 21 days; 12mg/kg/dose). Upon calling Sally Jane's owners to notify them of these result, her owner relayed that Sally Jane was more comfortable and had less inflamed skin, however, she had an episode of inappetence, depression, and labored breathing the night before. Sally Jane was taken to her regular veterinarian, where a region of consolidated lung lobe was detected on thoracic radiographs. Sally Jane was referred to the Animal Emergency & Referral Center (AERC) on March 28, 2018, where they detected elevated liver enzymes, a mild non-regenerative anemia, and a mild stress leukogram from bloodwork. Sally Jane was started on ursodiol (12mg every 24 hours; 1mg/kg/dose), SAMe and Milk Thistle or Denamarin (225mg every 24 hours; 18mg/kg/dose), and Douxo Chlorhexidine Shampoo. No abnormalities were noted on her

thoracic radiographs. Her prednisone was decreased to 20mg (1.6mg/kg/dose) in the morning and 10mg (0.8mg/kg/dose) in the evening, while her azathioprine dose remained the same. On April 10, 2018, Sally Jane had an appointment at AERC with dermatology for a recheck of her pemphigus foliaceus. At that time her bloodwork remained abnormal, but her skin lesions were resolving. Sally Jane received another Cytopoint injection (30mg; 2.4mg/kg). On April 24, 2018, Sally Jane returned to AERC for a dermatology recheck. Bloodwork revealed resolution of her previous anemia and leukocytosis. Her liver enzymes, however, remained elevated. Due to the improvement of her skin, the prednisone dose was decreased again, with the azathioprine dose remaining the same. On July 10, 2018, Sally Jane returned once more for a recheck at AERC with dermatology. The owners reported that Sally Jane's active skin lesions have resolved, with only patches of alopecia remaining. Hair growth had occurred on her ears, and no active lesions were noted. Sally Jane's diet remained as Hill's Prescription Diet Z/D. Blood work was repeated and revealed continued elevated liver enzymes and return of a mild anemia with mild lymphopenia and eosinopenia. A urinalysis revealed a specific gravity of 1.005 and pH 6.0, with no other concerns. A urine culture and susceptibility was submitted and revealed no growth at 24 hours but growth from enrichment broth of *Klebsiella pneumoniae ssp pneumoniae*. This will be treated with antibiotics and rechecked with a follow-up urine culture. The prednisone doses were tapered further with a plan for a recheck in 1 month. Other medications remained the same.

The secondary bacterial infection in combination with atopy or food allergy may have been the culprits causing Sally Jane's intense pruritus, complicating her pemphigus foliaceus. While Sally Jane's pemphigus foliaceus is now well managed, unfortunately, Sally Jane was diagnosed with heartworm disease in June 2018. Her owners plan to treat her heartworm disease and hope to have many more years to enjoy Sally Jane's company.

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