

“Just a Crusty, Ole’ Bull”

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Introduction:

Immune-mediated skin disease in small animal veterinary medicine is uncommon. Although uncommon, pemphigus foliaceus is categorized as being one of the more common immune-mediated skin disorders of the canine and feline. (1,4) There are reports in other species including goats, horses, and sheep. (2,6,7) However, there are no published reports in bovine. The main lesions associated with pemphigus foliaceus are erythematous macules and pustules or vesicles which tend to occur in waves. Other differentials for pustules should also be considered, such as those associated with bacterial pyoderma. Ulceration and crust formation occur as pustules rupture. Epidermal collarettes may be noticed as ulcerative lesions heal. Alopecia and secondary pyoderma are also common consequences of pemphigus foliaceus. Pruritus is variable and mildly present in animals affected. The clinical course of the disease is gradual but progressive, with episodes of acute exacerbation and partial remission. (1)

Species reportedly affected by pemphigus foliaceus include dogs, cats, horses, goats, and sheep. (1,2,5,6,7) A recent editorial mentioned a report of one cow being affected. (4) However, no case report has been published regarding this disease in cattle. The lesion distribution of pemphigus foliaceus in dogs is often over the bridge of the nose, the periorbital area, ears, and footpads. Most dogs with pemphigus foliaceus develop generalized lesions within 6 months of developing initial lesions. It typically occurs in middle-aged dogs, with no sex predilection. Genetic predispositions include the Akita, Bearded Collie, Chow Chow, Dachshund, Doberman Pinscher, Finnish Spitz, Newfoundland, Chinese Shar-pei, English Springer Spaniel, and the Schipperke. Feline breeds affected by pemphigus foliaceus vary from short-long haired breeds. Anatomical regions most frequently affected are similar to those affected in the dog, although in cats there will often be involvement of the skin around nipples and mammary glands, nail beds,

and unguis folds. Pruritus and systemic signs of disease are also evident and common in cats. (5) Pemphigus foliaceus lesions in the goat include widespread pustules and scaling along with diffuse alopecia and crusts on the head, neck, dorsum, perianal area, and occasionally the udder and ventral abdomen. Pruritus is also typically a common clinical sign. (6) In one case report of suspected pemphigus foliaceus in a ram, the lesions included a three-month history of pruritus, crusting, and exudative dermatitis that was primarily on the face and in the interdigital space of all feet. Crusts are the most common lesion noted in horses affected by pemphigus foliaceus. Anatomical areas affected by crusts include the head, extremities, ventrum, and sheath. Evidence of pain, pruritus, ventral edema, and pyrexia are also clinical signs that can be seen in the horse. Unlike in other species, pustules and vesicles are not commonly seen in horses. (7)

Diagnosis of pemphigus foliaceus is performed by cytologic or histologic examination of intact pustules. Cytologic findings reveal large numbers of keratinocytes either singularly or in rafts, termed acantholytic keratinocytes or acanthocytes. Keratinocytes break free from each other due to the immune-mediated breakdown of intercellular bridges. On histopathology the lesions are characterized by subcorneal clefts containing keratinocytes and inflammatory cells with acantholytic cells. Immunostaining on skin biopsy samples demonstrates intercellular deposition of immunoglobulin, particularly in subcorneal regions. (1,2,5,6)

Therapy for pemphigus foliaceus in small animals includes treating secondary pyoderma with antibiotics, utilizing immunosuppressive doses of systemic glucocorticoids (prednisone), and implementing other immunosuppressive agents such as azathioprine, chlorambucil, cyclosporine, mycophenolate mofetil and leflunomide in severe cases. In one study, corticosteroid monotherapy was sufficient to obtain complete remission of pemphigus foliaceus in cats. However, the disease course and its management had negative impacts on the patient

and client's quality of life due to receiving/administering medications, attending veterinary appointments, and financial commitments. (5) If treatment is pursued in felines, several oral corticosteroids, either as a monotherapy, or in combination with adjunctive cyclosporine or chlorambucil are recommended. Due to the incidence of severe adverse effects, long-acting injectable glucocorticoids are no longer suggested for long term management of feline pemphigus foliaceus. (5) Successful treatment options for caprine pemphigus foliaceus include intramuscular prednisolone, intravenous and intramuscular dexamethasone, intramuscular triamcinolone and topical corticosteroid ointment. Once remission is achieved in the goat, non-steroidal immunosuppressive drugs can be implemented for further chronic maintenance therapy rather than chronic immunosuppressive steroids. (6) Similar to the treatment course for goats, treatment for sheep affected by pemphigus foliaceus includes glucocorticoids. However, regular observation of clinical parameters, such as a serum chemistry, should be performed throughout treatment. (2) Treatment for horses with pemphigus foliaceus requires high doses of glucocorticoids as a monotherapy or with adjunctive immunomodulatory drugs to induce remission. Reportedly, horses that do not respond to oral prednisone will respond to orally administered prednisolone or dexamethasone at similar doses. However, laminitis subsequent to glucocorticoid administration is a common adverse effect due to the corticosteroids altering the blood flow in the horse's hooves, causing hypoxia in the lamina. Therefore, if horses do not improve with glucocorticosteroid administration, or if adverse effects are too severe, steroid-sparing drugs, such as azathioprine, may be added. The end goal is to slowly taper and discontinue the drugs and for disease relapse to not occur. (7)

History and Presentation:

Bull #7288 was an approximately 2 year old, Jersey, breeding Bull from the MSU MAFES Dairy Unit. He presented to Mississippi State University, College of Veterinary Medicine (MSU CVM) Food Animal department on 12/28/2018 due to the concern that he was doing poorly and was anorexic. He had been losing weight consistently beginning 10 days prior to presentation to MSU CVM and began exhibiting alopecia (primarily along dorsum, orbits, and muzzle) beginning 12-14 days prior. It was noted that the bull had also been coughing consistently. The cough was described as a dry, heaving, non-productive cough. Bull #7288 was housed on pasture with another bull and 10 heifers. He and the other bull were used as cleanup bulls for the dairy. When the bull was loaded to come to MSU-CVM there were areas of skin that sloughed off when he gently brushed against some bushes in the pasture.

Upon presentation Bull #7288 was irritable. He weighed 524 kilograms, had a temperature of 105.8 degrees fahrenheit, a pulse of 120 beats per minute, a respiratory rate of 48 breaths per minute, and had a body condition of 3/5. He was noted to be dehydrated as indicated by a prolonged skin tent. He had bilateral subconjunctival hemorrhage and injected sclera along with multiple raised, red, nodules on the cornea of his right eye. There were areas of scaling, hyperkeratinization along his whole body, including multiple ulcerations and crusts, under his tail head, dewlap, ventral abdomen, distal aspect of the forelimbs and hindlimbs, and around his orbits and muzzle. He presented with multiple ulcerated lesions along his shoulders (scapula), thorax, and hindquarters. There was a mild odor to the skin lesions (yeast or necrotic smell). Harsh lung sounds were auscultated bilaterally, and a dry cough could be appreciated periodically. His heart rate was elevated and bounding. No dental pad ulcerations were noted upon presentation. The remainder of the physical exam was unremarkable.

A complete blood count and serum chemistry were performed which revealed a mild hypochloremia (93.4 mmol/L with normal being 97.0-111.0 mmol/L), a mildly elevated anion gap (32 mmol/L with normal being 11-27 mmol/L), a mild hyperglycemia (glucose of 143 mg/dl with normal being 61-102 mg/dl), a moderate-severely elevated AST (185 U/L with normal being 64-76 U/L), a mildly decreased GGT (7U/L with normal being 10-35 U/L) a mild hyperproteinemia (9 g/dl with normal being 7.0-8.9g/dl), a mild hypoalbuminemia (2.2 g/dl with normal being 2.4-3.7 g/dl), a mild hyperglobulinemia (6.8 g/dl with normal being 2.5-4.4 g/dl), a severe hypophosphatemia (1.9 mg/dl with normal being 4.0-7.1 mg/dl), a moderate hypomagnesemia (1.1 mg/dl with normal being 2.0-2.8 mg/dl), and a moderate hypocholesterolemia (29 mg/dl with normal being 78-142 mg/dl).

Pathophysiology:

Pemphigus foliaceus is the most common form of pemphigus in small animals and possibly the most common of all immune-mediated skin diseases in the dog. It is considered a rare autoimmune dermatosis in small ruminants, such as sheep and goats, where only three cases have been reported in the goat to date. (2,6) In the horse, pemphigus foliaceus is the most common autoimmune disease. There have been cases reported in the horse ever since the early 1980's. (7) Pemphigus foliaceus is an acquired autoimmune disease in which the body's immune system produces immunoglobulins against keratinocyte desmosomal proteins, resulting in a loss of adhesions between keratinocytes. In the dog the major autoantigen is desmocollin-1 (DSC-1) which is involved in intracellular adhesion. The minor autoantigen in dogs is desmosomal cadherin, and desmoglein-1 (DSG1), which is the main pemphigus foliaceus autoantigen in humans. (3,9,10) The binding of these immunoglobulin autoantibodies to the keratinocytes results in the loss of the intercellular connections between keratinocytes and causes the formation

of subcorneal blisters, pustules, or vesicles within the epidermis. These lesions result in ulceration and crusts. The keratinocyte is the major cell type of the epidermal skin layer. Keratinocytes are connected to each other by desmosomes and attached to the underlying basement membrane that separates the epidermis and dermis. Keratinocytes originate from division of stem cells in the stratum basale epidermal layer of the skin. Next, they push up through all the layers of the epidermis, slowly differentiating until they reach the outermost layer of the skin, the stratum corneum. Here, they form a layer of dead, compressed, keratinized cells. The outermost layers of the stratum corneum continuously shed and are replaced by the new cells being generated underneath. Therefore, dermal lesions seen in pemphigus foliaceus occur in a “wave-like” or transient manner. Definitive diagnosis of pemphigus foliaceus is based on histological findings, ruling out other causes of pustule formation and sometimes demonstration of antibody deposition with the epidermis. Neutrophils or eosinophils are usually also present within pustules. (3,9,10)

Diagnostic Approach/Considerations:

Considerations for Bull #7288’s condition includes an autoimmune skin disorder (pemphigus foliaceus), bullous impetigo, superficial pustular drug reaction, or a superficial pustular dermatophytosis. Four skin biopsies were taken on 1/3/2019 from the left scapula region and left thoracic region and were submitted for evaluation. Intraepithelial vesicles and pustules with acantholysis were evident which is most consistent with autoimmune disease. The other differentials can be ruled out due to the presence of acanthocytes, no history of drug administration prior to presentation, and the fact that special stains for infectious agents performed on the skin biopsies were negative. On histopathology, the epidermis was diffusely hyperplastic and there were multifocal pustules and vesicles containing degenerate neutrophils,

scattered eosinophils and clusters of acantholytic keratinocytes within the epidermis. These findings indicate an intraepidermal pustular dermatitis. There were varying stages of pustule formation which was transient and lead to thick crusts with variable scaling due to pustules rupturing and forming a thick inflammatory crust that contained acantholytic cells. In some areas there was loss of the superficial epidermis and the remaining epidermis, along with some areas having partial to complete epidermal necrosis/loss with an overlying serocellular crust. The histopathology findings were highly suggestive of pemphigus foliaceus. With no other causes of pustular dermatitis and disease progression, a diagnosis of pemphigus foliaceus was made. (3,5)

Treatment and Management:

As stated previously, the standard treatment of pemphigus foliaceus is immunosuppressive therapy for all species that have been discussed. Treatment for bull #7288 included Nuflor (florfenicol) antibiotic administration at a 20mg/kg dose for a total of 35 mls subcutaneously in the neck once on presentation, then given at a 40mg/kg dose for a total of 70 mls subcutaneously in the neck q96h according to Beef Quality Assurance guidelines (no more than 10 mls were injected at each injection site at one time). He also received Meloxicam 15 mg tablets - 1 mg/kg orally for a total of 39 tablets supplemented in his grain daily for the first three days, then every other day for the remaining thirteen days that he was in hospital. Lastly, he received a Predef 2x corticosteroid injection (isoflupredone acetate) intramuscularly for a total of 10 mls (20mg) in the neck every other day according to Beef Quality Assurance guidelines. During the entirety of his stay, he had a decent appetite and drank water well. He consistently developed new skin lesions, mostly where he would lie down to rest. Skin lesions were red and ulcerative due to epidermal sloughing at areas of pressure. His dry, non-productive cough did not improve with the administration of Nuflor antibiotic. Towards the end of his hospital stay, it was

noted that he exhibited forelimb, leg shifting lameness. This was presumed that he was painful and probably had laminitis along with edema formation in his extremities. He also was moderately pruritic which was exemplified by him rubbing his body and head on the stall walls which created more regions of epidermal ulceration.

Case Outcome:

Unfortunately, due to Bull #7288's poor prognosis and worsening of clinical signs, humane euthanasia and necropsy was elected. Bull #7288 had cranioventral, suppurative, bilateral, severe, chronic bronchopneumonia. *Trueperella pyogenes* was cultured from the lungs. He also had a lymphoplasmacytic, fibrotic, chronic interstitial nephritis with moderate tubular dilation indicating that he has had progressive scarring of the tubulointerstitium. Important considerations for causes of interstitial nephritis in cattle includes, but is not limited to leptospirosis, immune-mediated diseases, and idiopathic causes. Necropsy skin histopathology was similar to the skin biopsy findings. There were also intermittent areas in which the epidermal inflammatory cell infiltrate was mostly eosinophilic, which has been reported in dog's affected by pemphigus foliaceus. (1) As stated previously, the diagnosis of autoimmune disorder (pemphigus foliaceus) was made based on histopathology findings and due to the ruling out of other causes of pustular dermatitis and disease progression.

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