Skin There, Done That: A "Maddy"-ning Experience

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Introduction

Since the description of pemphigus foliaceus in a dog approximately 30 years ago, immune-mediated dermatoses have become more well-recognized.[7] Though their presentations remain uncommon and complete understanding of their pathophysiology has not been obtained, for many of the disease, knowledge of them, as well as treatment options have grown. Immune-mediated dermatoses can be divided into two categories: autoimmune and immune-mediated. The autoimmune subtype occurs when immunological self-tolerance is lost and an immune response is mounted towards normal body structures or functions. However, the immune-mediated subtype occurs due to antigens foreign to the body such as drugs, bacteria, and viruses. Ages at which dogs become inflicted with these diseases vary by type and cause and no studies have shown a sex predilection for any of the diseases.[6] The following paper is a case report of a dog with clinical signs highly suggestive of an immune-mediated dermatosis. The paper will review the history, presentation, clinical signs, diagnostic approach, pathophysiology of the strongest differentials and treatment options available. The clinical outcome of the patient will also be discussed.

History and Presentation

Maddy is a 12-year-old, female spayed mixed breed dog that presented to the MSU-CVM Emergency Service on 8/16/21. Her presenting complaint was for progression of a skin condition that began on approximately 6/26/21. Maddy's owners first noticed her front left paw was hyperkeratotic and sloughing. Similar lesions soon spread to her other paws while areas of crusting appeared on her stomach, neck, and nose. Maddy presented to her rDVM several times as her lesions progressed and was treated with NSAIDs, Clavamox for several weeks' duration, terbinafine, and gentamicin spray. She also received a Depo-Medrol injection that seemed to worsen her clinical signs. After several weeks of little to no significant improvement, Maddy

became lethargic and anorexic as well as very painful due to the lesions on her paws. It was then that Maddy's owners decided to seek further treatment and diagnostics at MSU-CVM.

On presentation on August 16, 2021, Maddy was quiet, alert, and responsive. She weighed 35 kilograms with a body condition score of 7/9. Her vital parameters were within normal limits with a temperature of 103.2F and a heart rate of 184 beats per minute. A respiratory rate was not obtained as she was panting. Her mucous membranes were tacky and she had a prolonged skin tent; she was estimated to be 6-8% dehydrated. Cardiopulmonary auscultation revealed no murmurs, crackles, or wheezes. Her peripheral lymph nodes were small, smooth, and symmetrical. Maddy's hair coat was very dull diffusely and there was a circumferential area of alopecia around her neck that was suspected to be secondary to prolong wear of her e-collar. Bilaterally, her ears were inflamed with multifocal papules and crusts with excessive discharge. On her nasal planum, there was a large region of dry crusting with depigmentation and loss of normal architecture on the dorsal surface. The crusting extended from the junction of the nasal planum and haired skin caudally and even appeared on the sides of her muzzle. All four of Maddy's paw pads were hyperkeratotic and sloughing with blood and purulent discharge present. The lesions were malodorous and very painful to the touch. Her interdigital spaces were also very inflamed. Her anus, vulva, and the surrounding area were very exudative and inflamed with a grey-brown purulent discharge in some areas.

As Maddy had presented through the emergency service, she was admitted to the ICU and started on IV fluids, methadone, and Unasyn. Her paws were bandaged and she rested comfortably overnight to be transferred to the Internal Medicine service the next morning.

Diagnostic Approach

With Maddy's clinical signs and the distribution of her lesions, a lengthy list of differentials was generated that included pemphigus foliaceus, systemic and discoid lupus, adverse drug reaction/erythema multiforme, and bacterial pyoderma. Clinical diagnosis of some immune mediated diseases can be supported by results from laboratory tests. While testing for abnormal antibody or immune complex deposition is of great value in human medicine, these are of less value in veterinary medicine with positive results in canine disorders varying from about 25% to 90% for direct immunofluorescence testing. As such, for many cases, these tests are still not accurate enough[3] and a diagnosis must be made based on clinical findings of characteristic dermatopathological changes.[6]

As Maddy's anorexia and lethargy were more suggestive of a systemic illness, a complete blood count (CBC) and serum chemistry panel were performed. CBC revealed a mild neutrophilia and lymphopenia with an increased plasma protein. Blood chemistry revealed mild increases in ALP and ALT with ALP being greater than ALT. It was suspected that the increase in ALP could have been secondary to her recent corticosteroid injection. Also present on the blood chemistry was a mild hypercholesterolemia, hypernatremia, and hyperchloridemia. Creatine kinase was mildly increased, and the sample was noted to be mildly icteric. Urinalysis submitted showed an alkalotic pH as well as moderate proteinuria.

As Maddy's bloodwork was free from any highly concerning values suggestive of systemic illnesses that would cause her anorexia and lethargy, further investigation and treatment of her dermatological condition was commenced. Prior to a consult from the dermatology service, cytology of her paws and nose was collected as well as an aerobic culture and sensitivity of the purulent discharge from her paw. Cytology of her nose and paws revealed a septic, suppurative inflammation with moderate to marked eosinophilic inflammation.

A dermatology consult was requested, and several diagnostic procedures were performed. Clinically and histologically, lesions due to dermatophytosis caused by *Trichophyton mentagrophytes* can look similar to those of pemphigus foliaceus. Elimination of dermatophytosis as a cause of Maddy's lesions was important due to the negative consequences that immunosuppression could have on a dermatophyte infection.[2] In order to rule out this differential, hairs were collected for dermatophyte culture with no growth seen at 4 days, 2 weeks, or 4 weeks. Tape prep cytology of her interdigital spaces as well as an impression smear of a crusted lesion on her dorsum showed large numbers of neutrophils and cocci which indicated inflammation or infection. An ear swab was performed for cytology with high numbers of rods, cocci, and yeast found bilaterally confirming a concurrent otitis externa. As the sample most important in the initial diagnosis of an immune-mediated dermatosis is a skin biopsy and subsequent histopathologic examination[2], biopsies of several lesions were taken including a crusting lesion on her dorsum, a pustule on her ventrum, the periphery of a foot pad, and the nasal planum.

The results of the biopsies revealed several ongoing disease processes. Of those processes, the most notable was a bacterial epidermitis with numerous cocci, intense suppurative inflammation and profound crusting. Concurrently, there was a more chronic, mixed interface dermatitis that was primarily lymphoplasmacytic and eosinophilic with a neutrophilic component. Interface dermatitis refers to a reaction pattern in which the junction between the epidermis and dermis is obscured by either degeneration of basal cells or a cellular infiltrate or both. It is seen with drug eruptions, lupus erythematous, pemphigus erythematosus, erythema multiforme and a host of other primarily immune-mediated diseases.[1] Other components included basal cell degeneration and apoptosis, and pigmentary incontinence. Acantholytic cells

were also present on histopathological examination, however, the classical intact intraepidermal pustules filled with acantholytic cells typical of pemphigus foliaceus and erythematosus were not found. The present basal cell degeneration and apoptosis is a histological finding common with lupus erythematosus which increased our suspicion of the disease. Although Maddy's histopathology could not definitively diagnose pemphigus foliaceus or lupus, the combination of her histopathology report and clinical signs helped to narrow our differentials down to either pemphigus foliaceus or systemic lupus erythematous with a secondary bacterial pyoderma.

Pathophysiology of Pemphigus Foliaceus

Pemphigus foliaceus (PF), the most common autoimmune skin disorder, is within a group of autoimmune skin diseases characterized by pustules, papules, crusts, vesicles, bullae, erosions, and ulcers, and histologically by loss of adhesion between keratinocytes (acantholysis).[5] These mechanisms are not fully understood; however, several hypotheses have been proposed. One hypothesis proposes that a type II immune reaction occurs that causes proinflammatory cytokines to be released from keratinocytes. Urokinase-type plasminogen activator is then induced that could indirectly induce the cleaving of intercellular contacts causing the characteristic acantholysis. Another hypothesis proposes that the structural integrity of the adhesion molecule is disrupted by the binding of autoantibodies to keratinocyte antigens.[4] In canine PF, the major autoantigen is desmocollin 1 while the minor autoantigen is desmoglein 1. This differs from PF in humans where desmoglein 1 is the major autoantigen. [6]

Genetic factors are likely to predispose to the development of PF while environmental factors are suspected to induce flares of the disease. Many causes of PF have been investigated with the more common causes being drug-induced, idiopathic, or chronic inflammatory skin disease. While evidence supporting an association between PF and allergic skin disease has not

been proven, a study from California reported that a history of flea allergy dermatitis was the most common skin disease reported in dogs later diagnosed with PF.[7] Canine PF is more commonly seen in middle-aged to older dogs and Chows and Akitas are overrepresented as breeds.[8]

Though pemphigus foliaceus is a pustular disease, it commonly begins with papules that progress rapidly to the pustular stage. These pustules can span several follicular units and widespread erosions and yellow crusting is not uncommon due to the pustules rupturing. Alopecia secondary to inflammation commonly develops and, in some cases, may be extensive. Predisposed sites include the head, face, and ears and the lesions can be strikingly symmetrical.[6] In one third of dogs with PF, the footpads are affected with fissures and crusting and the disease can even be restricted to only the footpads.[7] A secondary staphylococcal infection is commonly acquired during PF and can complicate the clinical picture as well as histopathology results.[8]

A presumptive diagnosis of PF can be made based on clinical signs. Major differentials such as bacterial pyoderma, demodicosis, and dermatophytosis must be excluded. Cytology of an intact pustule may display nondegenerative neutrophils with acantholytic keratinocytes and can be used to tentatively diagnose PF while biopsy results are pending. However, the gold standard for diagnosing pemphigus foliaceus is a biopsy with subsequent histopathologic examination. Ideally, biopsy would be performed on pustules, but a biopsy of a crust is another option. When severe bacterial skin infections are present concurrently with pemphigus foliaceus, it can be difficult to determine which histological changes are due to PF and which are due to the inflammatory processes from the infection. Biopsies can also be submitted for direct immunofluorescence and immunohistochemistry, but these diagnostics are not routinely used in veterinary medicine as of now due to varied sensitivities and dependability.[6]

Pathophysiology of Systemic Lupus Erythematosus

Whereas PF is a disease confined to mostly dermatologic lesions, systemic lupus erythematosus (SLE) is a multisystemic disease with a multitude of clinical signs. As with PF, the exact cause of the disease in unknown. At the root of the disease is a type III hypersensitivity reaction as antigen-antibody complexes are produced and lodge in small vessels, the basement membrane zone of the skin, and in various organ systems.[4] Genetic, hormonal, and environmental factors have been found to all contribute to the development of SLE.

The most common presenting sign of canine SLE is lameness caused by joint disease and distinguishing SLE from other types of immune mediated polyarthritis can be difficult. SLE usually causes a symmetrical, multiarticular arthritis that is non-deforming and nonerosive. Although these joints may be swollen and painful, little to no radiographic changes are usually observed apart from some soft-tissue swelling. Skin lesions are in seen in 40-50% of SLE cases and their appearances are highly variable. Patients can present with lesions that range from mild alopecia to a more severe ulcerative dermatitis.[5] Loss of pigment from the nose or periocular region, presentations commonly observed with discoid lupus erythematous, may occur as well as focal ulcerations of the footpads suggestive of a vasculitis. Though there is no definitive dermatologic lesion seen only with SLE, symmetry of the lesion is often a striking feature of the disease.

Anemia is often present in patients with SLE and is usually immune-mediated or an anemia of chronic disease. Thrombocytopenia may be present as well as a leukopenia or leukocytosis. Profuse proteinuria is evident in 50% of cases and can proceed to azotemia and renal failure. Less common, but still observed in some cases of SLE are serositis, neurological changes and other less specific signs such as a cyclic fever.

As with PF, the diagnosis of SLE is not an easy one and is typically more challenging. As there are a varied range of clinical signs, each with a long list of differentials, the diagnosis of SLE is one of exclusion. Diagnostics most specific to SLE include histopathology and antinuclear antibody by immunofluorescence. Histopathologic findings of the skin include a lichenoid or hydropic interface dermatitis in close contact with the dermoepidermal junction. Apoptosis of basal or suprabasal cells may be present as well as subepidermal vacuolar alteration, focal thickening of the basement membrane, and pigmentary incontinence.[5] Though these findings are commonly seen in cases of SLE, it is important to remember that they are only supportive of SLE and rarely diagnostic when performed alone.[4]

Antinuclear antibody immunofluorescence (ANA) is the preferred test for routine use to detect autoantibodies to nuclear antigens. Sensitivity varies based on the laboratory performing the test as well as the substrate utilized. High titers are not specific to SLE and positive titers, even at high levels, can be found in sera from normal dogs and dogs in varied disease states. Chronic diseases of microbial and parasitic etiology can also cause high titers. The value of the ANA in diagnosing SLE comes from the detection of antibodies towards histones or ribonucleoproteins found to be specific for canine SLE. Histones are nucleoproteins associated with DNA and the presence of antibodies towards them is highly correlated with a positive diagnosis of SLE. Subsequently, antibodies detected towards heterogenous nuclear ribonucleoprotein G, found to be the most specific marker for canine SLE, can also be detected.[6]

Ultimately, diagnosis of SLE depends on the fulfillment of certain criteria adapted from diagnosis of the disease in humans, modified to better fit the disease in dogs. These criteria are as follows: erythema, discoid rash, photosensitivity, oral ulcers, arthritis, serositis, renal disorders, neurologic disorders, hematologic changes, immunologic, and the presence of antinuclear

antibodies. Definitive diagnosis of SLE can be made only when at least 4 of the criteria are observed during any period of the disease. A probable diagnosis can be obtained when three criteria are present. In most cases, however, as the clinical signs can develop at any time within the course of the disease, clinicians will often be left to treat signs as they come without a definitive diagnosis.[6]

Treatment

While awaiting biopsy results, efforts were made to improve Maddy's appetite and lethargy as well as treat her bacterial pyoderma. She remained on intravenous fluids and gabapentin was added to further control her pain. Entyce was prescribed to stimulate her appetite and her paws were bandaged and changed every 24 hours. Unasyn was continued as well, but as little to no improvement was seen with it alone, marbofloxacin was added for additional antimicrobial coverage while awaiting the results of her culture and sensitivity. Maddy began to eat and her attitude continued to improve. After her biopsy results returned highly suggestive of an immune-mediated dermatosis, more specific treatment was implicated. With both pemphigus foliaceus and systemic lupus erythematous, immunosuppression is imperative and oral glucocorticoids are the mainstay of treatment.[9] Maddy was started on prednisone and transitioned to all oral medications in preparation for discharge. Results of her culture and sensitivity revealed growths of Klebsiella pneumoniae, E.coli, and Enterococcus faecium that were sensitive to doxycycline. On August 20th, 2021, Maddy was discharged with the medications above as well as otic suspensions for treatment of her otitis externa. It was suggested that an astringent be used at home to further dry out her paws as well as utilizing Pawz rubber dog boots.

Case Outcome

On September 2nd, 2021, Maddy returned for her 1st recheck appointment. Her appetite and lethargy were much improved as well as the areas of her nasal planum. Most improved were her paws that were no longer purulent and malodorous. She did, however, have new areas of irritation on her neck, abdomen, and genital areas. Douxo shampoo was prescribed for use in these areas. Ear cytology showed an improvement in her otitis externa as rods and cocci were no longer present and clotrimazole was prescribed to treat the remaining yeast. A skin scrape revealed no mites and impression smears revealed little improvement as numerous cocci and neutrophils remained. As suspicions were high that previous swabs had missed a Staphylococcal species, cefpodoxime was added to her treatment plan to further eliminate her bacterial pyoderma. As the owners also reported that Maddy continued to be pruritic, a Cytopoint injection was given to help alleviate her itchiness.

Treatment of Maddy's condition included several recheck appointments with improvement as well as declines in her condition. At her second recheck appointment, improvement was noted after the addition of the cefpodoxime. However, a hyperemic exudative rash was present that extended from her abdomen to her vulva. Areas of alopecia and crusting remained, and a new wound was found on her left carpus after Maddy chewed away a scab. Skin cytology was repeated with large numbers of cocci and inflammatory cells present. Ear cytology was repeated with yeast noted and an aerobic culture and sensitivity was repeated but taken from the skin lesions as opposed to the paws. Maddy was continued on her previous medications as well as mupirocin for the wound on her carpus and Apoquel to combat her pruritus.

Maddy returned to MSU-CVM before her next scheduled recheck appointment on September 18th, 2021 for a swollen right hindlimb. As her culture and sensitivity results had returned with growth of a very resistant strain of *Staphylococcus intermedius*, her physical exam

was performed in isolation. Her right limb was diffusely swollen with pitting edema. There were no associated wounds noted on this limb. A CBC and chemistry were performed that revealed a neutrophilia, severely elevated ALT, ALP, and GGT, and a mildly increased BUN. As the owners declined further diagnostics at this time, Maddy was discharged with instructions to ice and massage the limb at home. Though the culture and sensitivity results showed that the Staph spp. grown was sensitive to rifampin and chloramphenicol, due to Maddy's elevated liver enzymes, there was hesitancy in starting her on these antibiotics.

When Maddy's right hindlimb did not improve with icing and massage, her owners returned wanting further answers. A complete and thorough diagnostic work-up was performed by the Internal Medicine service to determine to the cause of her swelling. Diagnostics performed included limb and abdominal radiographs, abdominal ultrasound with liver aspirates, aspirates of the subcutaneous swelling and lymph node aspirates and bacterial cultures. An ammonia tolerance test was also performed. At this time, cellulitis with drug-induced hepatopathy secondary to her doxycycline was suspected. The doxycycline was discontinued and the rifampin started at discharge.

At Maddy's subsequent rechecks with the internal medicine and dermatology service, improvement was noted as her swelling had resolved and her skin lesions were significantly better. However, as her bloodwork was being monitored while she was taking rifampin, a severe increase in her liver enzymes was noted. She was continued on her previous medications and prescribed Denamarin. Before her recheck on October 28th, Maddy's appetite had decreased and her owners discontinued the rifampin and her appetite returned shortly after. As Maddy had completed a four-week course of the medication and due to the improvement noted, the rifampin was not continued. Her bloodwork at this recheck continued to show elevated ALP and ALT

suspected to be secondary to the rifampin. A recheck on November 11th revealed that Maddy's liver enzymes were elevated but decreased from her last visit. As the rifampin had been discontinued, it was suspected that the decline would continue over time. The owners expressed concerns that though Maddy was much improved overall, her paws were reddened again and reminiscent of signs displayed when Maddy's disease first began.

On December 2nd, Maddy presented, once again, for a recheck. Her paws were cracked and scaly with erythema present. There were multiple scaly patches on her dorsum and her vulva was not as hyperemic as on her last visit. Despite these findings, Maddy seemed to be a happier dog with skin lesions of a static nature. The owners reported that Maddy was weak in her hindlimbs and groaned frequently when she laid down or moved. Her ALP and ALT continued to decrease. Osteoarthritis was suspected to be the cause of Maddy's mobility issues and a joint supplement was suggested. Instructions were given for Maddy's paws to be wiped when returning from outdoors and Vaseline applied to her paws.

During the week of December 10th, Maddy's lethargy returned as well as her anorexia. She began to have trouble walking and lesions similar to the ones present on her initial presentation returned. Due to these occurrences, Maddy's owners made the decision for Maddy to be humanely euthanized on December 14th, 2021.

Although a concrete diagnosis of Maddy's illness was unable to be obtained, treatment for an immune-mediated dermatosis and bacterial pyoderma significantly improved the condition of her lesions as well as her quality of life overall. It is not uncommon for treatment to be initiated for these diseases without a definitive diagnosis. Maddy's case was no different and can serve as a great example of prioritizing treatment over diagnostics. It is the hope that more

options for diagnosis and treatment of canine immune-mediated dermatoses can be developed in the future.

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