Mr. Moogoo's Tricky Issue

Hepatocutaneous Syndrome in the Canine Patient

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Introduction

Canine superficial necrolytic dermatitis is a progressive cutaneous disorder of dogs that is an erosive dermatopathy with multifocal distribution. Hepatocutaneous syndrome is the term used to describe the condition in which a concurrent hepatopathy is present (4). This disorder is similar to a cutaneous disorder that accompanies malignant tumors of internal organs of people, called necrolytic migratory erythema (3). There is no known sex predilection, but it often occurs in dogs older than 8 years old. Breed predilection includes Shetland Sheepdogs, Cocker Spaniels, West Highland White Terriers, and Shih Tzu's (4). One study also found that purebred dogs were more likely to develop Hepatocutaneous syndrome compared to mixed breed dogs, suggesting a genetic component (7). It is characterized by a crusting, ulcerative dermatosis that occurs on areas exposed to mechanical trauma, including the muzzle, mucocutaneous junctions, contact surfaces of appendages like the elbow joint and paw pads. The most problematic cutaneous complication includes the development of fissures along the paw pads, which leads to secondary infections and reluctance to walk. Diagnosis with skin biopsies and liver evaluation are the only ways to definitively identify this disease from other dermatologic conditions. Unfortunately, palliative treatment is the best option in the literature currently for hepatocutaneous syndrome and most commonly the survival duration after diagnosis is only 6 months (9).

History and Presentation

Moogoo, a 10-year-old male neutered Powderpuff Chinese Crested dog, presented to MSU-CVM on October 5, 2018 for a dermatology appointment after several months of having skin issues and weight loss. Over the past 6 months Moogoo had lost approximately 3.5kg. His

left front and back right paws had been reddened and painful, and Moogoo had been licking his feet. The owner had taken Moogoo to her local vet in August 2018, who prescribed Simplicef and topical ointment (Panalog). Moogoo had been taking Simplicef once a day and topical ointment was applied three times a day for 21 days with no improvement. He had also been getting bathed in Sebozole shampoo once a week. Moogoo was taken back to his rDVM at the end of September 2018, after no resolution in clinical signs and a complete blood count and chemistry panel were evaluated They showed elevated liver enzymes (ALT and ALP). At this time, Moogoo had become increasingly lethargic and would not want to walk. He was also continuing to lose weight. This is when the primary veterinarian noted the thickening paw pads on all four feet with fissures and bleeding. At this time, Moogoo was refereed to MSU-CVM Dermatology.

On presentation, Moogoo was bright, alert and responsive. His vital parameters were within normal limits for an anxious dog. His heart rate was 160 bpm, his respiratory rate was 44 bpm, and his temperature was 100.9. His prescapular and popliteal lymph nodes were moderately enlarged. There was some crusted debris around the commissure of the right side of his mouth, incorporating hair. There was irregular hyperkeratosis across the entire surface of the majority of the pads of all four feet with fissures/cracks present on some. On his front paws, paronychia was present as well as nail deformities. Several areas of darkly pigmented, crusted skin were found on the dorsal aspect of the caudal half of his back, with smaller crusts of similar nature along his ventral abdomen and inguinal regions and one over his right shoulder.

A full dermatology work was performed, starting with a CBC, neuro chemistry panel, and urinalysis. This lab work showed a mild leukopenia 6.46 K/ul (7.0-22.0), mild anemia 32% (34-60), and mild lymphopenia 1098 /ul (1200-6500). His platelets appeared adequate on blood

smear. The chemistry panel showed mildly decreased BUN 6 mg/dl (8-24), mildly decreased creatinine 0.44 mg/dl (0.50 - 1.40), as well as mildly low albumin 2.4 g/dl (2.5-3.9). The ALT was mildly elevated at 278 U/L (10-90), and ALP was mildly elevated at 355 U/L (11-140). The urine specific gravity was 1.034, and there were no other abnormalities noted on the urinalysis. A deep skin scrape of his right hind paw, dorsal back and left front paw showed that no mites were present. Multiple tape preps of the lesions showed yeast, too numerous to count. These tape preps were taken on his front right paw, back left paw, and right side of mouth. A dermatophyte culture was also performed, which yielded no growth.

Skin biopsies were taken on his left forelimb digital skin, right hindlimb digital skin, as well as a place on his back near the base of his tail. The biopsy taken from his back near the base of his tail showed mild epidermal hyperplasia with orthokeratotic hyperkeratosis, dermal fibrosis, and adnexal atrophy, indicating chronic sun damage. The left forelimb digital skin and right hindlimb digital skin showed similar characteristics histopathologically. They both showed papilliferous epidermal hyperplasia with basal epithelial cell hyperplasia, sub parakeratotic edema, marked parakeratotic hyperkeratosis, moderate lymphoplasmacytic and fibrosing superficial perivascular dermatitis, pigmentary incontinence, and multifocal deep dermal collagen lysis. The histologic appearance of the left forelimb digital skin and the right hindlimb digital skin displayed microscopic changes suspicious for superficial necrolytic dermatitis (hepatocutaneous syndrome).

With the diagnosis of superficial necrolytic dermatitis, it was advised to have an Internal Medicine workup for evaluation of the liver and pancreas. Moogoo was sent home on Tylenol 4 2 mg/kg, fluconazole 8 mg/kg, and cefpodoxime 8 mg/kg. He also had an appointment with Internal Medicine on October 15, 2018.

Pathophysiology

Superficial Necrolytic Dermatitis is an uncommon skin disease associated with systemic metabolic disease. Affected dogs have a characteristic concurrent hepatopathy, which is why most of these cases are called hepatocutaneous syndrome (5). Many disease processes have been reported to cause similar histologic skin lesions. The most common etiology of hepatocutaneous syndrome in dogs are various forms of vacuolar hepatopathy. There are several causes of vacuolar hepatopathy including the following ingestion of mycotoxins, chronic phenobarbital administration, cirrhosis, diabetes mellitus, glucagonoma, increased cortisol such as hyperadrenocorticism, or idiopathic (5). The most common clinical signs, besides the skin lesions, include lethargy, reluctance to walk, inappetence and weight loss (2). Rarely are these canine patients in hepatic failure at the time of presentation.

Hypoaminoacidemia is a central feature, however remains hard to interpret. Evidence that hyperglucagonemia is the driving mechanism for hypoaminoacidemia remains scarce, but there is a suspicion for a link. There is currently no standard diagnostic method for measuring glucagon concentrations in the canine due to multiple molecular glucagon isomers in plasma (9). Glucagon is produced by alpha cells in the pancreas, stomach, and duodenum, indicating all of these areas must be evaluated if glucagon levels are high or amino acids are low (6). In a normal patient, glucagon stimulates gluconeogenesis when blood sugar drops, and stimulates a catabolic state in the body, resulting in increased glucose concentration and ureagenesis, leading to a reduction in plasma amino acid concentration (11). Chronic elevation of glucagon promotes hepatic gluconeogenesis from amino acids obtained from body stores, which then results in hypoaminoacidemia (11). Glucagon may be the direct cause of hypoaminoacidemia, leading to

epidermal protein depletion and keratinocyte necrolysis (6). However, only a handful of cases of dogs with HCS had an identifiable glucagonoma (8). It some rare cases, hyperglucagonemia occurs in patients without a glucagon-secreting neoplasm. Consideration of alternative pathological mechanisms for hypoaminoacidemia have to be considered in the canine patient.

Other theories include a wasting aminoaciduria where amino acids are filtered through the kidney, depleting amino acids, or amino acid membrane transporters are not working appropriately (9). Glutamine and alanine are found in highest concentrations in the plasma, muscle, and skin, indicating that severe depletion of these amino acids could interfere with normal dermatologic metabolism. Proline, arginine, and glycine have dermatologic functions that include differentiation of keratinocytes, synthesis of matrix metalloproteinase, and formation of elastin and collagen (8). Reduced amounts of proline and hydroxyproline could possibly explain the cutaneous lesions by the limited reparative collagen synthesis. With these depletions of amino acids, it is unknown exactly how it happens.

Diagnostic Approach/Considerations

Most hepatocutaneous syndrome cases present with chronic dermatologic problems with the intensity of dermatitis waxing and waning. Due to the differential list of paw pad dermatosis, a workup should include full blood work, urinalysis, urine culture, as well as skin scrapes, tape preps, and a dermatophyte culture. The most common clinicopathologic abnormalities include non-regenerative anemia, high hepatic enzymes (ALP and ALT), and hyperglycemia. Inconsistently, a low albumin, blood urea nitrogen, and leukocytosis has been seen (2). Without a skin biopsy, Hepatocutaneous syndrome is somewhat differentiated from other dermatosis due to the elevation in liver enzymes, as well as hypoaminoacidemia (5).

Diagnosis of superficial necrolytic dermatitis is based on obtaining skin biopsies that show typical histopathologic changes and is often the only way to differentiate superficial necrolytic dermatitis from other possible diagnoses. Differentials for the skin lesions include cutaneous drug eruption, dermatophytosis, deep pyodermas, systemic lupus erythematosus, zinc responsive dermatitis, pemphigus foliaceus or vulgaris, and cutaneous epitheliotropic lymphoma (12). There is “diffuse hyperkeratosis, intracellular edema of the granular epithelial cells and basal cell hyperplasia” (3). These histologic changes are known as a “red, white, and blue” pattern. The superficial keratin accumulation would stain red (eosinophilic), the middle edematous, vacuolated pale layer would stain white, and the deeper hyperplastic basal cells would stain blue (basophilic) (7). There is often colonization of the keratin accumulation with bacteria and *Malassezia* yeast species.

After the diagnosis of superficial necrolytic dermatitis, the next diagnostic approach should be to find any underlying hepatopathy or metabolic issues. An abdominal ultrasound with evaluation of the liver and pancreas is recommended, either with fine needle aspirates, or surgical biopsies (1). Abdominal ultrasound shows a diffusely hyperechoic appearance of the hepatic parenchyma with hypoechoic nodules diffusely throughout. This has a Swiss cheese or honeycomb-like pattern (2). This is only a pattern seen on ultrasound and differentials for this pattern include nodular hyperplasia, regenerative nodules, infiltrative mass lesions, hepatic fibrosis/cirrhosis and vacuolar hepatopathy (10). Vacuolar hepatopathy is the underlying lesion found in dogs with hepatocutaneous syndrome. However, in dogs with idiopathic nodular hyperplasia, hepatic adenomas, hepatocellular carcinoma, and gallbladder mucoceles, abdominal ultrasound can look similar, and therefore, surgical biopsies are needed to rule out these conditions (10).

Hepatic biopsies are often needed to determine the specific underlying hepatopathy. Glycogen-vacuolated hepatocytes are a pathologic change common to several diseases and is often found on liver fine needle aspirates in dogs with hepatocutaneous syndrome (10). Histologic appearance of the liver shows multifocal to coalescing foci of hepatocytes with severe ballooning degeneration mixed with proliferation of hepatocytes and areas of parenchymal collapse. Glycogen-type hepatocyte accumulation can also be seen commonly. Vacuoles that are clear, rough bordered, and separated by thin wisps of cytoplasm are frequently present and may be , glycogen may be confirmed via periodic acid-schiff stain (2). Expansive proliferative foci of hepatocytes were present in roughly 50% of the samples of one study. These foci were disorganized and lacked the connective tissue that would be consistent with nodular regeneration (4).

Plasma amino acid concentrations are another diagnostic test that can help suggest hepatocutaneous syndrome. Glutamine, proline, alanine, arginine, threonine and glycine were proportionally the most severely affected amino acids in dogs that had their plasma amino acid concentrations measured (8). At this time, measuring plasma amino acid concentrations is rarely performed due to the cost, as well as equipment needed.

In some patients, often late in the disease course, dogs are diagnosed with diabetes mellitus. These patients often have common clinical signs of DM including drinking and urinating more frequently, vomiting and diarrhea, lethargy, and weight loss. Clinicopathologic features include hyperglycemia, persistently elevated liver enzymes, as well as glucosuria and ketonuria. Diabetes Mellitus is a cause of vacuolar hepatopathy, which is the hepatic pathology commonly found in hepatocutaneous syndrome.

The diabetes may often be due to a glucagonoma, which, as discussed earlier, may decrease amino acids. Glucagonomas are a neoplasm of alpha-pancreatic islet cells. These cells actively produce and secrete glucagon. The tumors are formed in the pancreas and will often metastasize to the liver (11). Glucagonoma can also been seen in multiple endocrine neoplasia syndrome, which is an inherited disorder affected multiple endocrine glands (12). These tumors are usually small and hard to find grossly, or on ultrasound (11). A CT scan is a warranted diagnostic tool if a glucagonoma is suspected. Tissue must be examined with a chemical staining for glucagon presence. Other types of imaging that might be warranted include thoracic radiographs to check for metastatic disease (1).

Treatment and Management

Parental amino acid supplementation is the treatment of choice for the skin lesions. There are currently two formulations of parental amino acid solutions. One is Aminosyn 10% that is hypertonic and should be administered through a central line. The other is a 3% amino acid and electrolyte solution, like Procalamine. These two are typically given at 25 ml/kg intravenous over 6-8 hours. Studies show that these infusions should be repeated every 7-10 days for the first 6 treatments and then spread out over time depending on the return of the skin lesions (12). Prior to intravenous amino acid supplementation, an ammonia tolerance test should be performed. In patients with compromised renal or hepatic function, the administration of intravenous amino acids may exacerbate hepatic encephalopathy by increasing blood urea nitrogen (5).

If a solitary, neoplastic glucagonoma is found, the treatment of choice is surgical removal. However, even with surgical resection of the main tumor, many human patients present with metastasis. In most cases, where a tumor is found, debulking and removing the tumor

results in significant palliation of symptoms in 75% of canine patients. There are several reports of dogs that describe improvement of the cutaneous lesions and an increase an overall patient comfort. Chemotherapy agents appear to have little antitumor activity against human glucagonoma; however, mild tumor regression has occasionally occurred in human patients using drug combinations that include streptozotocin, 5-fluorouracil, and dacarbazine (6). If metastatic disease is suspected, or surgery was not successful in removing the tumor, somatostatin, a hormone secreted in the pancreas and pituitary gland that inhibits gastric secretion and somatotropin release has shown some success (11).

Other recommended therapies include a high-quality protein diet that can be supplemented with amino acid powder and cooked egg whites. Zinc and essential fatty acid supplementation may also be beneficial. Secondary skin infections should be treated with appropriate antifungals or antibiotics, with careful consideration of drugs that are known to be hepatotoxic or may require hepatic metabolism. Topical shampoos may improve discomfort and help with the management of secondary infections. Glucocorticoids are not recommended due to the risk of inducing or exacerbating diabetes mellitus in these patients (5).

Increased production of free radicals has been shown as a mechanism for ongoing hepatic damage. Dogs with hepatocutaneous syndrome have ongoing and progressive liver damage. Studies have evaluated antioxidants and nutraceuticals in these patients, but unfortunately no specific research has been done on the effect of liver protectant drugs in dogs with hepatocutaneous syndrome. SAMe (S-Adenocylemethionine) is a glutathione indirect precursor, which is a cellular antioxidant. It may promote cell repair, tissue regeneration, DNA synthesis and influence inflammatory cascades. Milk thistle acts as a free radical scavenger and promotes hepatocyte regeneration. These therapies are usually worth trying, as they have not shown to

cause any harm to patients (3). The role of these therapies, as well as fatty acid, zinc and niacin supplementation needs to be more critically evaluated.

If a toxic or metabolic cause of hepatic dysfunction is identified and removed (such as phenobarbital or mycotoxins), occasionally resolution of the disease is possible. If no underlying disease is identified, then nutritional support and amino acid therapy are critical and may result in partial to complete improvement of skin lesions (11).

Case Summary and Outcome

Moogoo had an appointment with MSU-CVM Internal Medicine on October 17, 2018. At presentation, Moogoo was quiet, but alert and responsive. He weighed 6.7 kg and his vital parameters were within normal limits with a heart rate of 132, a respiratory rate of 36, and a temperature of 101.6. The only abnormalities noted during his physical exam was that there was irregular hyperkeratosis across the entire surface of the majority of the pads of all four feet with fissures/cracks present on some. There were also areas of erythema present in between each digit. The areas of darkly pigmented, crusted skin was found on the caudal dorsum back, abdomen and inguinal regions were still present, but improved significantly from the dermatology appointment. He also had sutures present from his previous skin biopsies that were removed during the visit. At this appointment, Moogoo had a full medicine work up that included a liver panel, ammonia tolerance test, abdominal radiographs, abdominal ultrasound as well as aspirates of his liver.

A small animal liver panel showed mildly elevated glucose 181 mg/dl (75-125), mildly elevated ALT 217 U/L (10-90), and moderately elevated ALP 526 U/L (11-140). These values had increased compared to the bloodwork ran on October 5, 2018. There was a mildly decreased

BUN 5 mg/dl (8-24), as well as mildly decreased Albumin 2.4 g/dl (2.5-3.9). The ammonia in his pre-sample was <0.10 umol/L. 5.4 ml (2 mg/kg) of Ammonium Chloride 5% solution was given rectally once. The 20 minute post sample was 67 umol/L (23.60-70.50), and the 40 minute post sample was 42.0 umol/L (23.60-70.50).

Thoracic radiographs showed age-related changes to the bronchi and lung pattern. There was no evidence of nodular pulmonary metastatic neoplasia at that time. Abdominal radiographs revealed an enlarged liver with undulating, rounded caudoventral margins with dorsal displacement of the pylorus. The cranial pole of the left kidney was also flattened, most likely due to hepatomegaly. Abdominal ultrasound showed an enlarged liver with rounded margins that extended beyond the right kidney. The liver was diffusely heterogeneous and coarse in echogenicity and echotexture with numerous hypoechoic ill-defined nodules. Fine needle aspirates of the liver showed mild, multifocal glycogen accumulation.

Many supportive treatments were discussed, and the decision was made that Moogoo would have the amino acid infusions. It was instructed to place Moogoo on a high protein diet and supplement his food with cooked egg whites. Gabapentin 7 mg/kg, Tylenol 4 1 mg/kg were prescribed for pain relief. Denamarin 20 mg/kg was prescribed as liver protectant and Aller G-3 Caps Liquid was prescribed as an omega 3/6 supplementation.

On Friday, October 19, 2018 Moogoo has his first amino acid infusion. Moogoo was 6.6 kg, with a temperature of 100.8 F, heart rate of 132 beats per minute, and respiratory rate of 36 breaths per minute. The owner reported that Moogoo had several episodes of vomiting since his workup two days prior but did eat cooked egg beaters and some of the other dog's dry Hill's Science diet prior to coming into hospital. An intravenous catheter was placed in the right cephalic vein. Moogoo received 165 ml of amino acid therapy over 8 hours, at 25 ml/kg.

Moogoo came in for his second amino acid infusion on October 26, 2018. Moogoo had begun vomiting more the past week but he had an increased appetite and was starting to follow his owner around the house more. With his history, it was decided to discontinue the Denamarin, Omega 3 and 6 supplements, and just give him the pain medications. Gastrointestinal upset is a common side effect of the Denamarin, and it was decided that each medication was going to be introduced gradually instead of all at one time. The third infusion was November 2, 2018; Moogoo was doing well at home. His owner reported that he was beginning to act like himself and was more willing to go for walks and explore outside. At each visit, his paws were starting to become less sensitive and less painful. The crusting lesions on his mouth and inguinal areas had improved greatly since the start of the amino acid infusions. Moogoo's fourth infusion was November 12, 2018.

On his 4th infusion, Moogoo was 6.4 kg, and had normal vital parameters (Temperature 101.6, pulse 124, and respiratory rate of 42). At this time the skin lesions were still present, with hyperkeratosis along the entire surface; however, his paws were less sensitive, and had less erythema. Moogoo's owner reported that his attitude has been changing at home and he was more lethargic, anorexic and starting to spit up clear, foam after he drinks water. Moogoo had also been drinking and urinating more frequently as well as having more accidents in the house. Moogoo had his amino acid infusion (25ml/kg) this day, and a small animal liver profile and urinalysis was performed. The liver profile showed severely elevated glucose 553 mg/dl (75-125), severely elevated ALT 473 U/L (10-90), and severely elevated ALP 2039 U/L (11-140). A urinalysis showed a USG of 1.041, with 4+ glucose and moderate ketones. A urine culture showed no growth at 48 hours. With these findings, Moogoo was diagnosed with diabetes and a blood gas was evaluated to check for acidosis. An elevated glucose and decreased ionized

calcium were noted. With these findings explained to the owner, and the possibility that a glucagonoma could be playing a part in this, the owner opted to pursue no further diagnostics. Moogoo was sent home with supportive care including maropitant 2 mg/kg, and lactulose (10gm/15ml) 0.3 ml/kg. On November 17, 2018 Moogoo was humanely euthanized after increasing lethargy, anorexia, and vomiting, as well as difficulty breathing.

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