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Dermatomyositis Disease in Dogs

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Abstract

Canine dermatomyositis is an inflammatory vasculopathy from skin and muscles, with cutaneous manifestations involving face, ears, tail and distal ends over bony prominences. The muscles involved include the muscles of the head, leading to difficulty in swallowing, reduction of reflex of vomit. Some animals have muscle changes that lead to the development of an atypical gait. Canine dermatomyositis is classified in familial canine dermatomyositis with an autosomal dominant pattern of inheritance, and the variant form called dermatomyositis-like. Familial canine dermatomyositis is the standard example of generalized ischemic skin disease, which occurs mainly in young dog's breed Collies and Shetland Sheepdogs. The scientific evidences appointed that canine dermatomyositis has genetic basis that involve the emergence of an immune-mediated disease, which can be triggered by environmental factors. Causes of focal or multifocal alopecia, such as demodicosis, bacterial folliculitis, and dermatophytosis, should be included in the differential diagnosis of disease. The genetic basis of canine disease is complex, and news studies revealed three loci associated with disease in canine breed Shetland sheepdog. The diagnosis is based on clinical history, physical examination findings, and skin biopsy of the affected muscle, electromyogram, and laboratory tests. The standard therapy instituted in canine dermatomyositis includes the use of glucocorticoids, pentoxifylline and vitamin E. Unfortunately, the treatment need news options to improve best quality of life in dogs affected.

Keywords: Canine Dermatomyositis; Familial Canine Dermatomyositis; Canine Dermatomyositis-Like Disease; Ischemic Skin Disease; DogsTamaulipas

Introduction

Canine dermatomyositis is an inflammatory vasculopathy of the skin and muscles, which includes the forms designated as canine familial dermatomyositis, with an autosomal dominant pattern of inheritance in breeds Collie and Shetland Sheepdog [1], and the similar dermatomyositis that affects the breeds Chow-Chow, Welsh Corgi, German Shepherd, Kuvasz, miniature Schnauzer, Dachshund, Fox Terrier and Rottweiler [2,3]. Familial canine dermatomyositis and dermatomyositis-like are clinically similar, and differ from other ischemic skin diseases such rabies vaccine–induced vasculitis with alopecia [4].

In humans, dermatomyositis is considered an immune-mediated inflammatory myopathy, whose molecular alterations suggest a strong association with a high production of type 1 interferon (IFN), especially IFN-beta, association with HLA DQA1 0501 and polymorphism for TNF in patients with photosensitization [5]. Because it is an immune-mediated myopathy whose primary target is the endothelium, occur deposition and activation of

complement system proteins, leading to inflammation and leukocyte infiltration with endofascicular hypoperfusion and perifascicular atrophy [6].

In dogs affected by disease, changes resulting from a true vasculitis are not observed microscopically such as hemorrhage and necrosis areas; but are observed follicular atrophy, interstitial collagen deposition, basement membrane fissures and epidermal hyperkeratosis. These findings are clinically accompanied by alopecia, hyperkeratosis and/or scaling of the skin, and ulcers that are difficult cicatrization [4].

In humans, there is juvenile and adult form, with the juvenile form classified as type I and II. The juvenile type I form has rapid and lethal progression, whereas type II is chronic and less severe [7]. The canine familial dermatomyositis is clinically similar to juvenile type II in humans. There is a common consensus that canine dermatomyositis is an immune-mediated disease that develops after an environmental trigger. Classically in canine dermatomyositis, the rabies vaccination is described as triggering events of the disease, the same way that parvovirus infection, trauma, stress, estrus, childbirth, lactation and excessive exposure to sunlight [8].

The canine dermatomyositis is classified in familial canine dermatomyositis with an autosomal dominant pattern of inheritance [1,9], or in the variant form called canine dermatomyositis-like [2,3], that are clinically similar and that develop mainly in young animals [4]. Familial canine dermatomyositis is recognized exclusively in breed Shetland Sheepdogs, Collies and their crossbreds, while canine dermatomyositis-like is recognized in any breed dog, and whose clinical and histopathological findings are identical to observed in familial canine dermatomyositis [2,3].

Animals presenting with familial canine dermatomyositis initially show clinical signs of erythema, alopecia, and skin scaling or crusts. With the evolution of the clinical picture, has the development of ulcerations and secondary pyoderma. Over time, scarring alopecia appears on the face, distal extremities, tip of the tail and other cutaneous parts of the body over bony prominences that are subject to mechanical trauma [4]. Muscle weakness and disturbances in food grasping, chewing and water intake are associated with myositis, with myositis most described in Collie breed dogs [9].

Pathophysiology

The exact pathophysiology of dog dermatomyositis remains unclear. Based on human analogous diseases whose genetic basis suggest an immune-mediated disease, canine dermatomyositis is described in association with autoimmune and environmental factors, where certain infections can trigger disease through molecular mimicry with microbial antigens, exposure of cryptic epitopes and break of peripheral tolerance [10].

The *post-mortem* findings found in adult and neonatal Collie dogs, crossbred dogs Collie Labrador Retriever and crossbred dogs with dermatomyositis, picornaviruses were isolated in the feces of young dogs, calicivirus in skin, and rotavirus or coronavirus in intestinal scrapings, reinforcing hypothesis of environmental factors involved [11].

A study in the 1980s suggested a deficiency of complement system proteins in Collie breed dogs. However, serum levels of C2 protein of the complement system were found to be altered in Collie dogs and also in non-Collie dogs, making it impossible to support this hypothesis [12]. In humans, dermatomyositis is considered an immune-mediated myopathy whose primary target is the endothelium, and the activation of complement system proteins leads to their consumption, especially in the active phase of the disease, phenomena observed in other autoimmune diseases [13], but not in canine dermatomyositis. Due to the familial nature of the disease in Collie and Shetland Sheepdogs, reproduction assays initially suggested an autosomal dominant inheritance with incomplete penetrance [14,15].

Already genetic screening studies involving the use of microsatellite markers involving the Shetland Sheepdogs appointed to linkage disequilibrium in chromosome 35, suggesting that it may be associated with Shetland sheepdog phenotypic dermatomyositis [9]. In a study that evaluated the gene profile in the Shetland Sheepdog, an increase in the expression of genes *KRT2A* (keratin 2A, a type II cytokeratin found largely in the upper spinous layer of epidermal keratinocytes, and defects in this gene cause ichthyosis bullosa of Siemens), *IGLV1-51* (immunoglobulin lambda variable 1–51, gene associated with immune response) *LY9* (lymphocyte antigen 9 or CD229, homophilic receptor predominantly expressed on the surface of B and T cells; acts as a cosignaling molecule, regulating lymphocyte homoeostasis and activation) was observed [1].

In breeds Collie dogs and Shetland Sheepdogs dermatomyositis was associated with canine MHC (*locus* C, *DLA-DRB1*). New *loci* were also identified on canine chromosomes 10 (*locus* A, *PAN2*) and 31 (*locus* B, *MAP3K7CL*) whose analyzes of MHC polymorphisms and haplotypes indicated that they are capable of conferring a high probability of disease occurrence [16].

The Orthopedic Foundation for Animals (OFA) provides a list of laboratories to perform genetic tests for canine

dermatomyositis based on these three genes together, *DLA-DRB1*, *PAN2* and *MAP3K7CL. Based on genotype of each animal, it is possible to assess the probability of a dog developing dermatomyositis, classified low (0%-5%), moderate (33%-50%) and high (90%-100%)* (http://www.ofa.org/dna_alltest.html).

Recently the genome sequencing of dogs with dermatomyositis identified a pathological variant of the gene *SLC25A12*, result of leucine for proline substitution at amino acid 349 in neuron and muscle-specific aspartate-glutamate transporter 1 (AGC1). The AGC1 participates in a range of cellular functions, such as mitochondrial respiration control, calcium signaling and antioxidant defenses. The mutation in *SLC25A12* can be support the installation of a highly oxidative and pro-inflammatory muscle environment, causing an inflammatory myopathy [17].

Clinical Manifestations

Clinical manifestations in dogs are established in variable age groups [11,18], and skin lesions typically involve the face, ears, tail tip and distal extremities over bony prominences [4,14,19]. In breeds Collie and Shetland Sheepdogs there is no association with sex, coat color or hair length. Taking into account family predisposition, lesions typically occur before six months of age. Skin lesions typically occur in areas of mechanical trauma and are observed in the face, especially around the eyes, ear tips, regions over bones such as carpus and tarsus, digits and tail. Oral and cushions injuries are rare, but are described in the literature [4,20]. Lesions are not pruritic unless secondary bacterial infection occurs [4].

Muscle involvement is associated with atrophy of the muscles of the head, difficulty in drinking water and in apprehending, chew and swallow food due to involvement of masticatory and esophageal muscles, in addition to reduced vomit reflex. Atrophy in the muscles of the head, mastication, and distal limbs are common findings [15,19]. Some animals have altered gait, rigid, megaesophagus and aspiration pneumonia [15].

Diagnostic

The diagnosis of canine dermatomyositis, as with any other ischemic skin disease, is based on the clinical history, physical examination findings, skin and muscle biopsy, electromyography and laboratory tests. The early age of onset of signs and symptoms and the race affected are useful in formulating the diagnosis [4].

The differential diagnosis for dermatomyositis should include demodicosis, staphylococcal folliculitis, dermatophytosis, discoid lupus erythematosus and epidermolysis bullosa. Canine dermatomyositis must be differentiated from marginal ear dermatosis [21] proliferative thrombovascular necrosis of pinna [4], fly bite dermatitis [22], leishmaniasis [23], ischemic juvenile skin disease [24], panniculitis after rabies vaccine application [25], vaccination-induced generalized ischemic skin disease [26], ischemic skin disease in an adult animal without association with vaccine reaction [4] and uveodermatological syndrome [27].

The diagnosis of canine dermatomyositis is based on the clinical history of the animal, confirmed by the result of dermatohistopathology [2,15,19]. A minimum of four samples with a minimum size of 6 mm in size of biopsy material must be collected, since not all samples can present the histopathological changes that confirm the diagnosis [4].

In dermatohistopathology, vacuolar changes are observed in the surface and the follicular basal cells, and individual keratinocyte necrosis. Apoptotic cells (Civatte's corpuscles), intrabasal or subepidermal slits, perivascular to interstitial dermatitis, presence of lymphocytes, plasma cells and histiocytes, and follicular atrophy and fibrosis are common findings [19].

In clinical practice, animals are often presented to veterinarian and biopsied during the chronic phase of disease. In chronic cases, histopathological features include follicular atrophy accompanied by varying degrees of inflammation, perivascular lymphocytic infiltration, melanophages and vacuolar degeneration in cells of basal layer (Figure 1) [4,19,28].

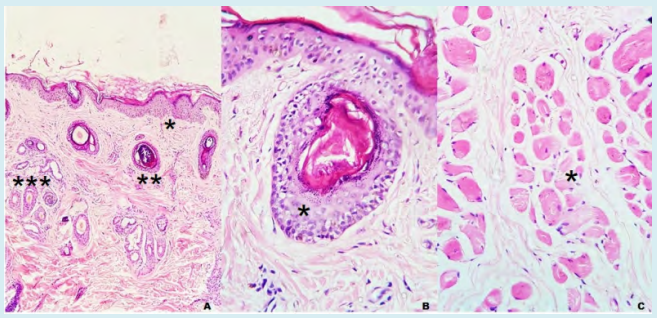

Figure 1: A. Skin (ear). Mild dermal edema (*), perivascular dermatitis (**) and interface folliculitis poor in cells, follicular atrophy (***) and moderate dermal fibrosis (hematoxylin/eosin staining, 40x). **B.** Skin (cephalic region). Perivascular and hyperplastic dermatitis, partially hyalinized vascular wall (*) (hematoxylin/eosin staining, 400x). **C.** Temporal muscle. Moderate fibrosis and varying degrees of muscle fiber atrophy (*) (hematoxylin/eosin staining, 400x). **Font:** Errante, et al. [28].

In routine clinical practice, muscle biopsy is not commonly performed. Histopathology demonstrates the presence of lymphocytic inflammation, inflammatory exudate accompanied by vasculitis, fragmentation, loss of crossed stretch marks, necrosis, fibrosis and muscle fiber [20,28].

Electromyogram changes include positive sharp waves and fibrillation potentials in the muscles of the head and distal extremities [3,15]. Neurological findings and nerve conduction studies are usually normal [29].

The hemogram and biochemical analysis of serum profiles are not altered, although some animals may exhibit increased serum creatine kinase levels (CK) and aspartate aminotransferase (AST) [29]. An increase in serum levels of immunoglobulins and immune complexes may occur in the active phase of the disease [11]. In some dogs with dermatomyositis-like specific autoantibodies can be detected. These antibodies are directed against an antigen called masticatory myosin-binding protein C (mMyBP-C) located inside the masticatory muscle fibers and cell surface [30], and also antibodies against type 2M fibers that constitute the muscles responsible for mastication [29].

Treatment

Skin lesions worsen after trauma or sun exposure, making management important in quality of life. Because the mechanical trauma component of the disease, clients should be educated about the management of affected dogs, how to bed on soft/cushioned surfaces, and include the use of protective footwear when the cushions are eroded/ulcerated [4].

When the disease is not serious, the combination of tetracycline or doxycycline and niacinamide can be used for their synergistic and immunomodulatory anti-inflammatory properties [27]. Animals with widespread skin lesions and generalized myopathy with difficulty swallowing and lameness can be treated with high doses of prednisolone (2 mg/kg every 24 hours) [28]. The continuous use of glucocorticoids should be discouraged due to the worsening of muscle atrophy, development of secondary bacterial infections and demodicosis. Some authors use pulse therapy with prednisone or methylprednisolone during severe disease attacks, especially in the presence of ulcerative lesions, but not indicate the prolonged use [4].

The use of cyclosporine, azathioprine and mycophenolate mofetil in combination with corticosteroids is indicated in refractory cases [27]. Corticosteroids are the first choice for treatment, and also xanthine derivatives with rheological action, such as pentoxifylline [4,27,31].

The pentoxifylline (25 mg/kg/ every 12 hours) is the drug indicated for the treatment of ischemic skin diseases. The pentoxifylline is a derivate of theobromine and belongs to the methylxanthines class, not showing cardiac and bronchodilator effects like other drugs of this class. The pentoxifylline reduces blood viscosity and promotes increased tissue oxygenation by increasing microvascular blood flow. It also has immunomodulatory properties that include inhibition of pro-inflammatory cytokine synthesis and leukocyte-mediated effects [4,32]. Its use has been described in different ischemic skin diseases, including canine rabies vaccine-associated skin disease and ear margin vasculopathy [31,33]. The response to pentoxifylline is slow, leading to two to three months before the effectiveness of the treatment can be determined [33].

The oclacitinib is a selective inhibitor of the enzyme janus kinase (JAK) present on cytokine receptors such as interleukin-2 (IL-2), interleukin-4 (IL-4), interleukin-6 (IL-6), interleukin-13 (IL-13) and interleukin-31 (IL-31), can be used as an immunosuppressive adjuvant along with oral glucocorticoids for the treatment of refractory or severe cases of ischemic skin disease [34]. Its use in animal models and humans has been shown to be objective in the treatment of lupus erythematosus and dermatomyositis [35].

The vitamin E (200 to 800 IU/day) is also be indicated by your antioxidant properties against oxygen-derived free radicals and other molecules that contribute to oxidative stress and by the anti-inflammatory characteristics, being beneficial for skin lesions but not muscle lesions. In humans, topical use of vitamin E is not effective, because the levels quickly deplete on exposure to UV-B radiation [36,37].

Its oral use in ischemic lesions in dogs in conjunction with pentoxifylline has been described with good results at doses of 200 UI (small breeds) 400 UI (medium breeds) and 600 UI (large breeds) every 12 hours [4]. Romero, et al. [38] described the case report of an animal affected by dermatomyositis in which there was marked growth of hair and improvement in the quality of the skin after eight weeks of combination therapy using pentoxifylline (25 mg/Kg a every 12 hours), doxycycline (100 mg/Kg every 12 hours), niacinamide (500 mg every 24 hours) and oclacitinib (0,4 mg/Kg every 24 hours [39].

Considerations

More studies are need to best evaluate the classification of dogs with dermatomyositis based on racial, clinical and histological characteristics in conjunction with molecular studies for a better characterization of their pathogenesis. Thus, new molecular targets can be identified for the use of targeted therapies against the disease.

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