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What’s New in Inflammatory Myopathies and Muscular Dystrophies

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Inflammatory Myopathies — The most common inflammatory myopathies (IMs) in humans are immune-mediated and fall into three major subsets: polymyositis (PM), dermatomyositis (DM), and inclusion body myositis (IBM). Other less common forms include focal myositis, infectious myositis, macrophagic myofasciitis and IM with abundant macrophages. A similar spectrum of focal and generalized inflammatory myopathies has been described in dogs, with immune-mediated and infectious causes most common. Of the immune-mediated diseases, masticatory muscle myositis and polymyositis occur most frequently and are the most completely studied. A canine equivalent of human IBM has not yet been identified. This presentation will focus on the immune-mediated causes of IM.

Masticatory muscle myositis — Masticatory muscle myositis (MMM) is a focal, immune-mediated inflammatory myopathy that affects only the muscles of mastication (temporalis, masseter, medial and lateral pterygoid, and rostral portions of the digastricus muscles) and spares the extracocular, esophageal, and limb muscles. In the acute phase of the disease, there is swelling of the masticatory muscles with restricted jaw movement (trismus). A clinical characteristic of this phase of MMM is the inability to open the jaw, even under general anesthesia. In the chronic phase, there is progressive atrophy of the masticatory muscle group, and trismus may or may not occur. Variable degrees of cellular infiltration are present in the acute phase but fibrosis is not usually observed. In the chronic phase, myofiber loss and fibrosis may be extensive.

The masticatory muscle group contains type 2M fibers, a unique fiber type that is not present in limb muscle. While the ATPase reactions in frozen muscle sections are similar to those of type 2C fibers (acid stable following preincubation in acid media at pH 4.5 and 4.3), type 2M fibers contain a unique native myosin isoform, heavy chain and light chains. Muscle fiber type specific autoantibodies against masticatory muscle myosin heavy chain and light chains are routinely found in dogs with MMM and an ELISA assay is used as a diagnostic test for this disease. Most recently, autoantibodies against a previously unidentified protein have been characterized and the autoantigen identified as a masticatory muscle variant of the myosin binding protein C family. In addition to the expected intracellular location, autoantibodies partially co-localize with dystrophin, suggesting this protein is also located at or near the cell surface. A sarcolemmal localization would expose it to the immune system and perhaps even be a trigger for an autoimmune reaction.

Cellular infiltrates in MMM have been characterized, and there are distinct differences from other canine inflammatory myopathies, such as polymyositis. In MMM there is prominent B-cell infiltration, dendritic cells and macrophages in greater numbers than T cells, CD4+ T cells in greater numbers than CD8+ T cells, and numerous T cells with TCRγδ. Major histocompatibility complex class I (MHC class I) and class II (MHC class II) antigens are expressed on muscle fiber membranes in the presence or absence of cellular infiltrations. Results of gene expression profiling were consistent with the immunophenotypic studies and showed that several genes involved with innate and adaptive immunity were highly upregulated including those that participate in macrophage and dendritic cell activation and migration, antigen processing and presentation, and B cell and immunoglobulin genes. The complement pathway was also highly active in MMM.

Polymyositis — Polymyositis (PM) in humans is considered a rare disease with an incidence of only 5-10 cases per million per year. Since the total number of dogs in the population is not known, an exact incidence of PM cannot be given for direct comparison. However, of 527 cases with limb and masticatory muscle biopsy specimens submitted for analysis to the Comparative Neuromuscular Laboratory at the University of California, San Diego in 2006, 58 (11%) were confirmed with polymyositis based on clinical signs, histopathological changes in multiple muscles, and the absence of a known infectious cause. In humans, symptoms may evolve over weeks to months, and may be difficult to recognize, so if the same is true for dogs, the actual incidence may be higher than suspected. In dogs with PM, common clinical signs include generalized weakness, a stiff-stilted gait, generalized and progressive muscle atrophy including the muscles of mastication, and esophageal (regurgitation from megaesophagus) and pharyngeal (dysphagia) weakness. Similar to humans, clinical signs in dogs may mimic other neuromuscular disorders such as autoimmune myasthenia gravis. Results of acetylcholine receptor antibody testing and the examination of muscle biopsies usually resolve this diagnostic dilemma.
Myositis-specific autoantibodies are found in approximately 20-30% of human patients with idiopathic IM and include autoantibodies against ribonucleoproteins involved in protein synthesis (anti-synthetase), against components of translational transport (anti-signal-recognition particle), or against components of the nucleosome remodeling complex (anti-Mi2). Myositis-associated autoantibodies, such as anti-RNP, have an association with myositis, but are often found in other conditions. While these autoantibodies are myositis-specific or associated, they are not specific for muscle tissue. Information is not available regarding the occurrence of similar autoantibodies in canine PM. However, sarcolemma-specific autoantibodies have been identified in a population of dogs with PM, particularly in the Boxer and Newfoundland breeds. These IgG autoantibodies are specific to striated muscle and do not react with other tissues such as liver, spleen, lung, or stomach. The autoantibodies are not species specific, suggesting they are directed against conserved antigens present also in humans. Since there is a high incidence of these autoantibodies in Boxers and Newfoundland breeds, this may define a specific form of PM that may be genetic in origin. Antibodies against masticatory muscle type 2M fibers have not been detected in these dogs except in very rare cases with an overlap syndrome of MMM and PM.

Populations of infiltrating cells in canine PM are similar to those described for human PM; CD8+ T cells are present in greater numbers than CD4+ cells. T cells and macrophages are most numerous in the endomysium and surround and invade non-necrotic fibers. The αβ T cell receptor is the most common. Neither B cells or γδ T cells are present in canine PM. Similar to MMM, there is upregulation of both MHC class I and class II antigens, both in areas with cellular infiltration and in areas without. With the exception of the increased expression of genes associated with the complement pathway and Igs including IgA, expression of genes for innate and adaptive immunity were similar between MMM and PM.

The clinical presentations, histopathological changes in muscle biopsy specimens, and phenotypes of infiltrating cells are strikingly similar between canine and human PM, and thus, canine PM should be a valuable animal model for preclinical therapeutic trials in human PM. Also, similar to human inflammatory myopathies, other organs and systems may be involved in canine PM including the heart (myocarditis), gastrointestinal tract (inflammatory bowel disease), thyroid (thyroiditis), and skin.

Cancer may be associated with canine PM. In a study of 200 dogs with inflammatory myopathy (Evans 2006), 88 dogs were diagnosed with immune-mediated PM, and of these dogs, 12 developed neoplasia within 1 year of the diagnosis of PM. Of the 12 dogs, 8 were Boxers with lymphoma, anaplastic round cell tumor (1) or plasmacytoma (1). Although mitotic figures were observed in muscle biopsies at the time of diagnosis of neoplasia in the Boxers with lymphoma, there was no evidence of neoplastic cells in the muscle biopsies at the time of original diagnosis of PM. An association between inflammatory muscle disease and cancer in humans was first described in 1935, and many studies have been published since that time. The meaning and significance of this association is still not completely understood. Paraneoplastic PM has also been described in dogs with thymoma.

Dermatomyositis — Dermatomyositis is an inflammatory disease of striated muscle, skin and vasculature; and in humans, adult and juvenile forms have been described. Perivascular accumulations of inflammatory cells are early changes. Angiopathy is characteristic of this disease, particularly in the childhood form, and a perifascicular pattern of muscle fiber atrophy is characteristic. Microvascular deposits of the C5b-9 complement membrane attack complex and foci of capillary depletion support this diagnosis. A familial form of dermatomyositis, with similarities to the human juvenile form, has been described in Collies, Shetland Sheepdogs, and occasionally in Collie-mixes or other breeds of dogs. In dogs, the skin lesions are most problematic, and the muscle lesions usually mild. In contrast, in humans, the muscle lesions are most problematic. While the conditions are not identical, vascular lesions are present in both conditions. Although perivascular accumulations of lymphocytes are described, perifascicular atrophy has not yet been identified. In this author’s laboratory, muscle biopsies from only very few cases of canine dermatomyositis have been evaluated. This may be because dogs, including the Collie and Shetland sheepdogs, with clinically and histologically pathognomonic skin changes rarely undergo more extensive evaluation including muscle biopsy. This is unfortunate, as increased knowledge of dermatomyositis in dogs, and its potential similarity to the human condition, will be hampered until more in-depth studies can be performed.

Extraocular muscle myositis — Extraocular muscle myositis (EOM) is a focal inflammatory myopathy with cellular infiltration limited to the extraocular muscles and sparing of the masticatory muscles, limb muscles, and other specialized muscle groups. The clinical course is similar to that of MMM with muscle swelling in the acute phase and clinical signs of bilateral exophthalmos and cellular infiltrates present in a biopsies of extraocular muscles. Fibrosis resulting in restrictive strabismus and enophthalmos occurs in the chronic phase. Although fiber types in canine extraocular muscles have not been completely characterized, there is evidence in other species that extraocular muscles...
have fundamentally distinct properties that make them selectively vulnerable to certain disorders. For example, extraocular muscles express the entire array of striated muscle myosins, including a specialized myosin heavy chain MYH13. Similar to MMM, specialized proteins in this muscle group that are not present in other muscle groups may, in part, explain the selective involvement of the extraocular muscles in this focal canine inflammatory myopathy.

**Muscular Dystrophies** — Of the over 30 different types of muscular dystrophy now described in humans, only a handful have been characterized in dogs and cats. Identification of the dystrophic phenotype in muscle biopsy specimens is critical. The serum CK activity is usually, but not always, markedly and persistently elevated.

**Dystrophin deficiency** — Dystrophin deficiency has been reported in several breeds of dogs including the Golden Retriever, Rottweiler, German Short-haired Pointer, Irish Terrier, Groenendaeler Shepherd, Samoyed, Miniature Schnauzer, Brittany Spaniel, Rat Terrier, Pembroke Welsh Corgi and Labrador Retriever. Specific mutations have been identified for the Golden Retriever, Rottweiler, and German Short-haired Pointer. A hypertrophic muscular dystrophy has been described in domestic short-haired cats. As the dystrophin gene is located on the X-chromosome, males are most commonly affected. However, affected females have been reported. A truncated dystrophin has been described in Japanese Spitz dogs.

**Laminin α2 deficiency** — Congenital muscular dystrophies in human beings are a heterogeneous group of autosomal recessive diseases manifesting at birth or during infancy with muscle atrophy, hypotonia, weakness, and contractures. Approximately 50% of these patients have a deficiency of merosin (laminin α2) expression in muscle. Laminin α2 is the major component of the basal lamina that surrounds each muscle fiber. Laminin α2 is one of the extracellular ligands for the dystrophin-associated glycoprotein complex that links dystrophin to the extracellular matrix and contributes to the stability of the muscle basement membrane. Deficiency of laminin α2 has now been reported in cats and dogs.

**Sarcoglycan deficiency** — The sarcoglycans are part of the dystrophin glycoprotein complex which stabilizes myofiber membranes during contraction. Sarcoglycan mutations are responsible for a subset of the human autosomal recessive muscular dystrophies known as the limb girdle muscular dystrophies. Recently, sarcoglycan deficiency has been documented in a 5-month-old female Chihuahua, an 11-month-old female Cocker Spaniel, and in young male Boston terriers.

**α-Dystroglycan deficiency** — Deficiency of α-dystroglycan (α-DG) has recently been identified in Sphynx and Devon Rex cats (Martin 2008, in press). In human dystroglycanopathies, clinical and pathological findings correlate with the extent of loss of native α-DG expression resulting from its under-glycosylation and loss of laminin binding in affected tissues. However, studies in the Sphynx and Devon Rex cats suggest that this dystrophic myopathy results from underexpression of the α-DG protein rather than from abnormal glycosylation. A specific mutation has not yet been identified.

**Selected References**


