Canine Immune-Mediated Polyarthritis

PART 1: PATHOPHYSIOLOGY

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ABSTRACT

Immune-mediated polyarthritis (IMPA) is a common disease process in the dog.[1] The immune-mediated polyarthropathies are divided into two major categories: erosive (or deforming) and nonerosive (or nondeforming). Understanding the pathophysiology of the immune attack on affected joints is paramount in choosing the most effective therapy for managing canine IMPA. This review article is the first of a two-part series and focuses on the pathophysiology of IMPA. The second article in this series, to be published in the March/April 2012 issue, concentrates on the diagnosis and treatment of immune-mediated polyarthritis. (*J Am Anim Hosp Assoc* 2012; 48:12–17. DOI 10.5326/JAAHA-MS-5744)

Introduction

Immune-mediated polyarthritis (IMPA) is an important disease process in the dog. Inflammation in multiple joints can lead to intense pain and may profoundly affect quality of life. This review article is the first of a two part series. Its aim is to discuss the pathophysiology of IMPA as well as associated syndromes and possible triggers of this immune-mediated disease process.

Pathophysiology

Immune-mediated nonerosive polyarthritis is believed to be driven by a type III hypersensitivity reaction where immune complexes comprised of antigen bound to antibody accumulate in the joint space. Implicated antigens are typically found in the systemic circulation, but can originate from within the joint space itself.[1–3] Systemic immune complexes can arise from a variety of chronic antigenic stimuli, including (but not limited to) viruses such as the distemper virus, other microbial agents, neoplasia, drug haptens, or even dietary elements. In addition, antibodies directed against self-antigens, such as heat shock proteins, immunoglobulins (rheumatoid factors), and nuclear elements (antinuclear antibodies) can also form complexes that accumulate in the joint space.[1–9] The presence of immune complexes in the joint space activates complement along the synovial membrane and within the synovial fluid. Complement fixation results in tissue damage and the release of cytokines, some of which attract neutrophils. These neutrophils also release cytokines and lysosomal enzymes that cause further tissue damage.[1–3,7] One study showed that there was an increase in CD4+ and CD8+ T cells in the synovial fluid (compared with the peripheral blood) in dogs afflicted with immune-mediated polyarthritis (IMPA). In addition, the frequency of major histocompatibility complex class II positive cells in the synovium was considerably higher in IMPA patients, suggesting local involvement in the development of inflammation. Proinflammatory cytokines produced by these cells, most notably tumor necrosis factor-α, were found in high concentrations in joint fluid from affected patients and are in fact a target for treatment in human patients with immune-mediated arthritis.[10]

In canine rheumatoid arthritis, a disease characterized by erosive joint damage, antibody directed against type II collagen has been found along the joint surface, as well as rheumatoid factors within the joint fluid.[4,11] In addition, chronic persistent synovitis

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CSF *cerebrospinal fluid;* HA *hyaluronic acid;* Ig *immunoglobulin;* IMPA *immune-mediated polyarthritis;* SLE *systemic lupus erythematosus;* SRMA *steroid responsive meningitis-arteritis*

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exists that is characterized by perivascular accumulation of mononuclear cells, indicating a possible type IV hypersensitivity component to this destructive disease. T lymphocytes, macrophages, and fibroblasts release matrix-degrading enzymes such as metalloproteinases, which cause cartilage degeneration and further inflammation.[3]

Erosive Polyarthritis

The erosive forms of immune-mediated polyarthritis are very rare compared with the nonerosive forms and represent only about 1% of all canine polyarthritis cases.[1] These forms are characterized by the presence of radiographic changes consistent with subchondral bone destruction. Radiographic changes may include: irregular joint surfaces; a narrowing or widening of the joint space; and "punched-out" lesions along the joint surface. It is important to note that radiographic changes can take up to 6 mo to appear.[2] Therefore, dogs with apparently nonerosive forms of polyarthritis in which clinical signs persist should be periodically re-evaluated for erosive changes.

Rheumatoid arthritis is the most notable form of immune-mediated erosive polyarthritis in dogs, but Felty's syndrome and an erosive polyarthritis of greyhounds have also been described. Felty's syndrome is a disease triad observed in humans that is characterized by rheumatoid arthritis, neutropenia, and splenomegaly described in humans.[3,12,13] Several dogs with a disease triad comparable to Felty's syndrome were described by Bennett in 1987.[12] Bennett analyzed 30 cases of canine rheumatoid arthritis. Although the majority of those dogs had normal circulating WBC counts, two dogs demonstrated concurrent leukopenia and splenomegaly and were cited as possible examples of Felty's syndrome.[12] Erosive polyarthritis of greyhounds has been reported most frequently in Australia and England, and *Mycoplasma spuman* has been isolated from at least one affected greyhound.[14]

Rheumatoid arthritis is typically diagnosed in small middle-aged dogs.[15] Diagnostic criteria for rheumatoid arthritis in the dog are adapted from those defined for humans, and are outlined and modified from Bennett and Kohn in **Table 1**.[7,12] The presence of 5 criteria is suggestive of rheumatoid arthritis, and the presence of at least 7/10 criteria is considered supportive of a definitive diagnosis of canine rheumatoid arthritis.

One study of 30 dogs diagnosed with rheumatoid arthritis reported that stifle and carpal joints were commonly affected, 7/30 dogs also had involvement of digital joints.[12] Antibodies directed against immunoglobulin (Ig) M, IgG, and IgA (i.e., rheumatoid factors) have been identified in the joint fluid and blood of dogs diagnosed with rheumatoid arthritis.[4,11] Bennett reported that 73% of 30 dogs diagnosed with rheumatoid arthritis had a positive agglutination test for serum rheumatoid factor directed against IgG.[12] Bell *et al.* reported that antibodies against both IgM and IgA were elevated in the sera and synovium of dogs with rheumatoid arthritis and that anti-IgA antibodies were the most helpful in distinguishing the presence of rheumatoid arthritis verses osteoarthritis in dogs.[4] The degree of elevation of anti-IgA antibodies can also be used as an indication of the disease severity and prognosis.[4]

Antibodies directed against canine distemper virus, heat shock proteins made by distressed cells, and type II collagen have also been found in the joint fluid of dogs with rheumatoid arthritis.[5,6,11] It has been hypothesized that the presence of distemper virus in synovial fluid leads to the development of antibodies that cross-react to heat shock proteins, causing sustained inflammation within the joints.[6] The presence of immune complexes and a direct antibody-mediated attack on collagen eventually leads to the erosive changes noted on joint radiographs.[5] Establishing a definitive diagnosis of rheumatoid arthritis is important because this disease has a more guarded prognosis compared with most of the more common nonerosive polyarthropathies.

Nonerosive Polyarthritis

Nonerosive forms of IMPA that lead to neutrophilic inflammation in multiple joints include: idiopathic polyarthritis; vaccine- and drug-induced polyarthritis; polyarthritis/polymyositis syndrome; steroid-responsive meningitis-arteritis; and breed specific polyarthropathies such as juvenile-onset polyarthritis of Akitas and familial Chinese shar pei fever. Systemic lupus erythematosus (SLE) also commonly involves the joints, but <20% of canine

TABLE 1

Diagnostic Criteria for Rheumatoid Arthritis in the Dog

1. Stiffness
2. Pain on manipulation of at least one joint
3. Signs of arthritis for at least 3 months
4. Periarticular soft tissue swelling
5. Typical radiographic changes such as subchondral bone destruction, indicated by irregularity of articular surface or 'punched out' erosions and loss of mineralization of epiphysis, calcification of soft tissue around joint, changes in joint space (increased or decreased width) or extensive bone destruction with gross joint deformity
6. Inflammatory synovial fluid
7. Characteristic, symmetrical deformations of distal joints
8. Detection of rheumatoid factors (anti-globulins) in serum
9. Three of the following histopathologic changes in synovial membrane: marked villous hypertrophy, synovial cell proliferation, fibrin deposits, foci of necrosis and lymphocytic-plasmacytic infiltration
10. Extra-articular symptoms such as lymphadenopathy

Criteria adapted from those used in people, as outlined by Bennett and Kohn.[7,12]

cases of polyarthritis can be attributed to SLE.[1,2] Idiopathic polyarthritis is by far the most common form of nonerosive IMPA in the dog.[2]

Idiopathic Polyarthritis

Idiopathic polyarthritis refers to all cases of immune-mediated arthropathy that cannot be classified into the other groups previously mentioned. Sporting dogs and large-breed dogs seem overrepresented, and the majority of affected patients are young adults with ages ranging from about 2.5 yr to 4.5 yr. Breeds that are commonly affected include the Labrador retriever, golden retriever, German shepherd dog, cocker spaniel and American Eskimo.[16–19] Although most retrospective studies have not revealed a sex predisposition, one study noted that females were more frequently affected than males at a ratio of 1.5:1.0.[16–19]

Idiopathic polyarthritis has been categorized into four subtypes: type I (no underlying disease), type II (reactive), type III (enteropathic), and type IV (neoplasia-related). Types II–IV are often grouped together and referred to as the reactive polyarthritides.[1–3,7,16,17,20] It should be noted that regardless of subtype, the pathophysiologic change that occurs in the joint space is the same. These subtypes merely point to the presence or absence of a concurrent disease process.

In type I (uncomplicated) polyarthritis, the cause is unknown, and no underlying disease can be detected. This is the most common form of the idiopathic polyarthritides, accounting for approximately 50–65% of all idiopathic polyarthritis cases.[7,19]

In type II (reactive) polyarthritis, an infectious or inflammatory disease distant from the joints is the underlying cause of the polyarthritis. These diseases produce antigens that combine with antibodies to form immune complexes that accumulate in the joints, activating complement, and leading to inflammation. Type II polyarthritis accounts for approximately 13–25% of all idiopathic polyarthritis cases.[1,3,7,19] The underlying infection can be bacterial, fungal, protozoal, or viral, and can be located anywhere in the body including: the heart valves; vertebral bodies or disc spaces; uterus, kidneys, or lower urinary tract, including the prostate; respiratory tract, including tonsils; oral cavity; skin; or even ears. Noninfectious inflammatory diseases such as pancreatitis have also been reported in association with immune-mediated arthritis.[17,21,22] With pancreatitis, increased fatty acids arise from lipase-induced lipolysis and have been found in the synovium of affected human patients at concentrations considered to be cytotoxic and proinflammatory.[22]

Type III (enteropathic) arthritis is associated with the presence of gastrointestinal or hepatic disease. In one retrospective study of dogs with suppurative nonseptic polyarthropathy, only 4% of 52 dogs were assigned to this category.[19] It has been theorized that disease of the gut leads to an increase in intestinal permeability to potential antigens, which then stimulate the production of immune complexes. In humans, there is a definite association between inflammatory joint disease and inflammatory bowel diseases, including ulcerative colitis and Crohn's disease.[8,20]

Type IV arthritis is associated with neoplasia that exists outside the joints. This is an uncommon manifestation of idiopathic polyarthritis, occurring in only 2% of 52 dogs with polyarthritis in one study.[19] It has been reported to occur in dogs with neoplasms such as pancreatic adenocarcinoma, renal carcinoma, tonsillar carcinoma, squamous cell carcinoma, mammary carcinoma, leiomyosarcoma, and lymphoma. Neoplasia may act as an antigenic stimulus against which antibodies are formed, leading to circulating immune complexes that deposit in the joint spaces.[3,7,20,22]

Vaccine-Induced Polyarthritis

Vaccine-induced polyarthritis can occur either after a first vaccination or after a booster vaccine. Clinical signs are evident within 30 days of receiving the vaccine.[23] Canine distemper virus has been implicated in some cases of rheumatoid arthritis. Increased concentrations of immune complexes containing distemper virus antigen have been found within the synovial fluid, and it is possible that a similar pathogenesis may occur in vaccine-induced nonerosive polyarthritis.[24] Some vaccine protocols recommend determining antibody titers to distemper virus prior to booster vaccination in all dogs at risk for vaccine reactions. If protective titers are detected, the distemper component of the vaccine is not given.[25] However, there is no evidence that this protocol prevents vaccine-associated polyarthritis.

In one case series, four young adult dogs were described with suspected vaccine-related polyarthritis occurring within 30 days of vaccinations.[23] All dogs experienced a sudden onset of lameness and several painful and swollen joints 3–15 days after polyvalent booster vaccination. Synovial fluid analysis in affected joints revealed WBC counts reaching 72,000/μL, with the majority of these cells being mature neutrophils. All dogs were treated with doxycycline and nonsteroidal anti-inflammatory drugs, and all recovered within 1–3 days.[23]

Vaccine-induced polyarthritis is usually transient, resolving within several days. However, some breeds such as the Akita appear to be predisposed to this condition and suffer a longer course of vaccine-associated polyarthritis.[25] Reports in Akitas describe profound joint pain and cyclic fevers lasting 24–48 hr, with initial signs occurring 3–29 days following vaccination.[25] In over 100 Akita puppies vaccinated with polyvalent modified live vaccines, approximately 10% were reported to experience adverse

reactions. These vaccine reactions may be related to the heritable juvenile-onset polyarthritis of Akitas described later in this report. Prognosis is guarded in affected dogs, which often do not respond to immunosuppressive therapy.[25]

Drug-Induced Polyarthritis

Drug-induced polyarthritis has been reported with multiple different drugs in many different breeds. The most widely reported manifestation occurs secondary to sulfonamide administration, particularly in Doberman pinschers.[9,26] Other drugs that have been implicated include phenobarbital, erythropoietin, penicillins, lincomycin, erythromycin, and cephalosporins.[1,20] Typically, the affected animal has either received the inciting drug in the past or has been on the medication long-term. Clinical signs usually resolve within 2–7 days of discontinuing the drug. Reactions associated with sulfonamide in dogs occur an average of 12 days after drug initiation (range, 5–36 days) or from 1 hr to 10 days after drug re-exposure.[9] The delay of ≥5 days from initial drug exposure to adverse reactions is suggestive of a delayed type IV hypersensitivity response, although the detection of marked complement activation when clinical signs are apparent may be more consistent with a type III sensitivity reaction.[9,27]

Polyarthritis/Polymyositis Syndrome

Polyarthritis/polymyositis syndrome is characterized by polyarthritis initially accompanied with focal or generalized muscle pain and swelling followed by eventual muscle atrophy and fibrosis. Most recorded cases of polyarthritis/polymyositis syndrome have been identified in spaniels. Bennett and Kelly described six cases occurring in two Cavalier King Charles spaniels, two springer spaniels, one cocker spaniel, and one whippet.[28] None of those dogs had a positive antinuclear antibody titer, making them less likely to have SLE.[28] Initially, polyarthritis/polymyositis syndrome causes muscle swelling and pain, but eventually leads to muscle atrophy and ultimately fibrosis and contracture, resulting in limited joint mobility. Animals present with fever and painful joints and muscles. Muscle enzymes, including creatine kinase, are often elevated, and diagnosis is based on the combination of electromyography, muscle biopsies, and joint taps.[2,28] Immunofluorescent studies of the synovium of affected dogs show IgG, IgM, and complement associated with macrophages and deposited within synovial vessels. In addition, IgG deposits on the sarcolemmal membranes were often demonstrated on muscle biopsy.[28]

Steroid-Responsive Meningitis-Arteritis

Steroid-responsive meningitis-arteritis (SRMA) is currently the most widely accepted term describing a disease syndrome that causes meningitis in medium- and large-breed dogs <2 yr of age.[29] The syndrome was first recognized in young laboratory beagles and was referred to as "beagle pain syndrome." Canine pain syndrome, canine juvenile polyartertis syndrome, canine meningeal polyarteritis, aseptic suppurative meningitis, and necrotizing vasculitis are also terms that have been used to describe essentially the same disease condition.[29] Other breeds that are predisposed to SRMA include the boxer, Bernese mountain dog, Nova Scotia Duck tolling retriever and German shorthaired pointer.[1,2,29] Typically, affected animals present with an acute onset of neck pain, fever, and lethargy.

Cerebrospinal fluid (CSF) analysis reveals inflammation and an increase in protein. More specifically, a high level of IgA is found both systemically and intrathecally. Paired measurements of IgA in the serum and CSF have proven useful for diagnosing SRMA[29,30] Histopathology of affected dogs shows migration of inflammatory cells into the meninges and inflammation of the meningeal arteries, which causes stenosis of the vessels.[31] Widespread arteritis in dogs with SRMA can affect any organ system. The coronary arteries are often involved in the beagle, and affected dogs commonly have a combination of myositis, meningitis, and polyarthritis.[31]

One recent study showed that the combination of IMPA and apparent SRMA is more common than previously suspected. Of 62 dogs diagnosed with IMPA, 18 (29%) had spinal pain. Of those 18 dogs, 11 had CSF collected, and 5/11 were diagnosed with probable concurrent SRMA. Spinal pain was most commonly demonstrated in the cervical region when the head was flexed or extended. Rarely did deep palpation of the dorsal processes of the cervical vertebrae reveal discomfort. Interestingly, no obvious lameness or joint swelling was present in affected dogs. All dogs with concurrent IMPA and SRMA were male and all had Type I idiopathic IMPA. It is recommended that a CSF tap be performed on all dogs suspected of having IMPA that have concurrent joint and spinal pain.[30]

Juvenile-Onset Polyarthritis of Akitas

Juvenile-onset polyarthritis occurs in affected Akitas between 9 wk and 8 mo of age. Affected dogs experience cycles of fever and severely painful and swollen joints that result in a reluctance to stand or walk. Neck and back pain can also be present, as well as mild to moderate lymphadenopathy. Episodes last about 24–48 hr before spontaneously resolving. Joint fluid analysis reveals neutrophilic inflammation. Occasionally, sterile suppurative meningitis is revealed via CSF analysis. Significant laboratory findings may include a mild to moderate nonregenerative anemia, neutrophilic leukocytosis, mild hypoalbuminemia, and mild hyperglobulinemia.[32]

Pedigree analysis of affected Akitas suggests that the disease is inherited.[32,33] Akitas that exhibit characteristic clinical signs should therefore not be breed.[32,33] Some clinicians believe that the development of this disease and its close association with immunization suggests that juvenile-onset polyarthritis in Akitas may be an immune-mediated response triggered by viral antigens or other components of vaccines.[25] Others believe the apparent association with vaccination is coincidental and that the disease naturally arises during the age when multiple booster vaccines are required.[33]

Familial Chinese Shar Pei Fever

Familial Chinese shar pei fever is an inherited autoinflammatory disease that occurs in 23% of shar pei dogs and is characterized by intermittent recurring attacks of inflammation and fever. The disease typically surfaces before 18 mo of age, although adult-onset attacks are not uncommon.[34–37] Recent research has uncovered a genetic mutation in shar pei dogs that leads to an increased production of hyaluronic acid (HA) by dermal fibroblasts.[38] HA accumulates in the skin causing the shar pei's characteristic thickened skin folds. Degradation of high molecular weight HA via trauma or oxidative damage creates smaller fragments that mimic microbial surface molecules. It is theorized that these fragments trigger the immune system to release interleukin-1β followed by interleukin-6, resulting in inflammation.[34,38] The sporadic 24–36 hr episodes of high fever that result are often accompanied by additional symptoms of inflammation that may include: a warm swollen muzzle; mild vomiting or diarrhea; abdominal pain; and signs of back, joint, or pleural pain.[34,36] Of those affected, approximately half have concurrent "swollen hock syndrome," which is characterized by periarticular swelling due to cellulitis with or without inflammation in the joint itself.[34,39,40] In some dogs, persistently elevated levels of acute phase proteins can lead to amyloid deposition in body organs, most notably the kidneys and liver, eventually leading to organ failure and death.[34,36,41]

SLE

SLE is a multisystemic immune-mediated disease reported infrequently in the dog.[42] Predisposition to SLE is thought to be inherited.[43] SLE in dogs does not have a sex predilection for females, unlike the disease in humans. Mixed-breed dogs as well as German shepherd dogs, Shetland sheepdogs, beagles, Afghan hounds, Irish setters, Old English sheepdogs, cocker spaniels, collies, and poodles are overrepresented.[42,44] Onset of disease typically occurs between 2–4 yr of age, although older dogs can be affected. Multiple concurrent immunologic reactions can be present in SLE patients, including type III (antigen-antibody complex mediated), type II (antibody directed against cellular self-antigens, including nuclear material, red blood cells, WBCs, and platelets) and, to a lesser degree, type IV (cell-mediated activity against self-antigen) hypersensitivities.[42,45] In general, a combination of abnormal immune activity, loss of self tolerance, and an antigenic trigger appear to be necessary for SLE to arise. Triggers are thought to be multifactorial and may include genetic predisposition and/or exposure to infectious agents, ultraviolet light, and certain drugs.[44] Interestingly, the prevalence of SLE among pet dogs owned by SLE human patients was estimated at >500/10,000 dogs (5%). The prevalence of SLE in the general dog population is only 0.03%, suggesting that a common environmental factor or zoonotic agent may be involved in the development of human and canine SLE.[42,44]

Clinical findings can be separated in two main categories (major signs and minor signs) based on their importance in contributing to the diagnosis of SLE. Major signs include polyarthritis, glomerulonephritis, hemolytic anemia, leukopenia, thrombocytopenia, characteristic skin lesions, and polymyositis. Minor signs include fever, central nervous signs, oral ulcerations, lymphadenopathy, pericarditis, and pleuritis. Nonerosive polyarthritis is the most frequent primary sign of SLE in dogs, and about 78% of canine SLE patients have polyarthritis. Consequently, the resultant shifting lameness is the most common finding on physical examination of dogs diagnosed with SLE.[42–44,46]

Conclusion

Neutrophilic inflammation in multiple joints can be associated with a wide variety of disease processes. Determining the underlying cause or complete disease syndrome is important when considering treatment and prognosis. In the second part of this series of review articles, the diagnostic approach to patients with suspected IMPA will be discussed, along with treatment options, monitoring parameters, and prognostic indicators.

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