

Immune-mediated polyarthritis: pathophysiology and classification

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ABSTRACT

Immune-mediated polyarthritis (IMPA) is a form of inflammatory joint disease of non-infectious aetiology characterised by synovitis and often accompanied by systemic signs of illness. The incidence of IMPA is probably underestimated because of a lack of clinical awareness and understanding. IMPA occurs as a primary disorder, usually of idiopathic origin, or secondary to systemic infectious, neoplastic or parasitic disease. The classification of various types of IMPA is driven by the presence or absence of extra-articular disease in addition to polyarthritis, radiographically observed erosive changes in affected joints, and any identifiable primary initiating disease process. While the process can be complex as well as costly and labour-intensive, attempts to classify the type of IMPA present are important where possible, as it is only this that provides a definitive diagnosis. The type of IMPA present can impact significantly on the appropriate treatment options and also the prognosis and it is important to make owners aware of both of these before commencing therapy.

Immune-mediated polyarthritis (IMPA) is a form of inflammatory joint disease of non-infectious aetiology. It is characterised by a synovitis accompanied by systemic signs of illness, usually lethargy, arthralgia and fever.

IMPA occurs as a primary disorder, usually of idiopathic origin or secondary to systemic infectious, neoplastic or parasitic disease aetiology. It is much more commonly polyarticular than monoarticular (Davidson, 2003). IMPA can further be classified as erosive, in which a progressive destruction of the joints occurs, or non-erosive, which is non-deforming and sometimes proliferative (Magne, 2000).

Pathophysiology

The incidence of polyarthritis (PA) is probably underestimated because of the lack of clinical awareness and understanding. The incidence in one hospital was reported to be 0.37% (Jacques et al, 2002), with 31% of dogs, in which arthrocentesis was performed, being diagnosed with PA in a two-year period. This study provided evidence PA may be more common than initially suspected. Other studies have reported incidences varying between 0.35% (Stull et al, 2008) and 1.09% (Ohno et al, 2006).

Non-erosive PA is considered a type three hypersensitivity reaction in which an immunologic stimulus triggers creation and deposition of immune complexes in the basement membrane of the synovium. Through activation of the complement cascade, inflammatory cells, including neutrophils and macrophages, are recruited to the site of inflammation. The end result, after phagocytosis of the immune complexes, is the release of nitric oxide, free radicals and proteases that cause tissue destruction (Gorman and Werner, 1986; Jacques et al, 2002).

Although findings in some retrospective studies suggest susceptibility of certain dog breeds or sex to IMPA, agreement among these reports does not exist. In some forms of IMPA, the inciting antigen can be identified (for example, IMPA associated with infection distant from the joints or drug induced IMPA).

Non-erosive IMPA has been associated with concurrent systemic disorders such as bacterial endocarditis, discospondylitis, immune-mediated bowel disease, myeloproliferative disease, other neoplasia and chronic hepatitis (Lipowitz, 1985; Pedersen et al, 2000). Vaccinations, Lyme disease, seasonality and genetics could also play roles in the development of the condition; however, most cases of IMPA remain idiopathic (Dawson et al, 1994; Kornblatt et al, 1985; Stull et al, 2008; Ollier et al, 2001; Innes, 2012).

Occasionally, IMPA may appear in the period after vaccination, leading to speculation that vaccination may initiate it. Certainly, in kittens this has been associated with the calicivirus component of a vaccine (Dawson et al, 1994) although this appears to be of historic interest now, presumably because of the reformulation of vaccines. One study of type one IMPA in dogs found no association between time of vaccination and onset of disease (Clements et al, 2004). Thus, at present, there is a lack of evidence to implicate vaccination associated with the onset of IMPA (Innes, 2012).

Many dogs in the retrospective studies of IMPA were seropositive for antibodies against *Borrelia burgdorferi*, the causative agent for Lyme disease. In endemic areas, Lyme disease is a common initial differential diagnosis in dogs presenting with inflammatory joint disease. Young dogs that are experimentally infected with Lyme disease through the bite of an infected tick develop a suppurative polyarthritis that manifests as recurring fever and lameness, which is most severe in the limb closest to the bite (Appel et al, 1993).

Similar findings have been reported in naturally infected dogs in the clinical setting (Kornblatt et al, 1985). However, in some Lyme-endemic areas, more than 80% of clinically normal dogs may have antibodies against *B burgdorferi* (Magnarelli et al, 1990) and it is thought as few as 5% of dogs with antibody ever develop clinical disease (Levy and Magnarelli, 1992). In one study, a significantly greater percentage of dogs with suppurative PA were Lyme seropositive when compared to the general hospital population (Rondeau et al, 2005). Based on the fact more study dogs were Lyme positive than the general hospital population, the author suggested Lyme disease was a significant cause of polyarthropathy and that initial treatment with anti-borrelial antibiotics is appropriate in dogs presenting with signs of polyarthropathy in Lyme-endemic areas, but to conduct further diagnostics to rule out other causes of polyarthrititis (Rondeau et al, 2005).

When IMPA cases in one study were divided into categories, a significant seasonal pattern to systemic lupus erythematosus (SLE) admissions was noted (Stull et al, 2008), with SLE cases being more likely to be seen during the summer and autumn. Classically, seasonal patterns are associated with infectious or allergic-based disease. The greatest canine tick infestation also occurs during summer and late autumn in the central northern United States (Raghavan et al, 2007) with onset of tick-borne disease occurring in the autumn (Greig et al, 1996). The seasonality was consistent with that found in association with SLE in this study, suggesting an undiagnosed aetiologic agent could, theoretically, be responsible (Stull et al, 2008). To the author's knowledge, further work to support this supposition has not been performed to date.

In human beings, and more recently in dogs, significant genetic predispositions to IMPA syndromes have been documented. It is estimated major histocompatibility complex genes confer 30% to 50% of the genetic component of susceptibility to human rheumatoid arthritis (Innes 2012). In dogs, specific dog leukocyte antigen (DLA) haplotypes appear to predispose to canine IMPA (Innes, 2012; Ollier et al, 2001). Recent studies have also demonstrated genetic predispositions to a canine SLE-related complex (Wilbe et al, 2009; Wilbe et al, 2010) in the Nova Scotia duck tolling retriever.



Figure 1. Dorsopalmar view of the left carpus from a six-year old corgi suffering from bilateral forelimb lameness secondary to erosive polyarthritis. The soft tissues circumferential to the carpus are thick. Multiple rounded lucencies are noted within the carpal bones, distal radius and proximal metacarpals. A mild amount of irregular proliferation is noted along the medial malleolus. Additional more indistinct proliferation is seen on the distomedial radius.

Erosive forms of PA are characterised by cellular and humoral immunopathogenic factors and the intra-articular release of chondrodestructive collagenases and proteases, resulting in articular cartilage destruction. The pathogenesis of erosive IMPA is better understood than its fundamental cause. As a consequence of either defective immunoregulation (failure of self-tolerance) or production of an immunogenic IgG antigen molecule, the pathogenic autoantibody rheumatoid factor (RF) is formed.

Plasma cells and activated B lymphocytes produce RF, which circulates and settles in synovial fluid. The synovium functions as a phagocytic tissue and, as a consequence, immune-complex ingestion occurs, triggering the activation and proliferation of synoviocytes. Activated synoviocytes release inflammatory mediators and enzymes (interleukin-1, collagenases, peptidases, and prostaglandin E2). Osteoclasts are activated and resorb subchondral bone. Subchondral bone cysts form as a consequence of this osteolysis (**Figure 1**).

Intra-articular formation of granulation tissue arising from the inflamed synovium forms a pannus. Lymphocytes, plasma cells, neutrophils and proliferating activated synoviocytes compose the pannus. Fibroblast proliferation promotes fibrosis with scarring, contracture and joint deformation (Lewis, 1994). Systemic infectious diseases, such as with staphylococci, mycoplasmas, corynebacteria, bacterial L-forms and viruses (feline leukaemia virus, syncytia-forming virus) have been implicated as triggering factors for erosive PA (Lipowitz, 1985; Pedersen et al, 2000).

Classification

The classification of various types of IMPA is driven by the presence or absence of:

- extra-articular disease in addition to PA
- radiographically observed erosive changes in affected joints
- any identifiable primary initiating disease process (for example, remote infection, neoplasia)

Although the classification system can help with case management and prognosis, it can often be difficult to accurately classify an individual case, particularly in the initial stages. The clinician should remain focused on tests that will influence clinical decision making rather than serve merely as an academic exercise in classification (Innes, 2012).

Non-infectious inflammatory arthropathies have been classified as erosive or non-erosive on the basis of radiographic signs. Non-erosive polyarthropathies have been broadly classified into types one to four (see later), but also include SLE and SLE-related disorders, polyarthritis/polymyositis syndrome (Bennett and Kelly, 1987) polyarthritis/polymeningitis syndrome (Webb et al, 2002), breed-specific polyarthropathies (Dougherty et al, 1991; May et al, 1992; DiBartola et al, 1990) and drug-induced polyarthropathy (Giger et al, 1985; Trepanier et al, 2003; Trepanier et al, 2004).

As mentioned earlier, tick-borne infectious diseases, especially ehrlichiosis, Rocky Mountain spotted fever and Lyme disease have also been implicated – either as direct pathogens or by causing a reactive polyarthritis (Pedersen et al, 2000; Cowell et al, 1988; Goodman et al, 2003; Goodman et al, 1998; Kornblatt et al, 1985; Appel et al, 1993).

Erosive arthropathies include canine rheumatoid arthritis (Bennett, 1987) idiopathic erosive arthritis (Ralphs and Beale, 2000; Ralphs et al, 2000) and a breed-specific polyarthritis recognised in greyhounds (Woodard et al, 1991; Huxtable and Davis, 1976). The term idiopathic erosive arthritis has recently come into favour because there are several differences between what has been called canine rheumatoid arthritis and the human disease of the same name. In fact, RF has been detected in less than 30% of dogs with rheumatoid arthritis in some studies (Pedersen et al 1976; Chabanne et al, 1993).

Idiopathic (type one) IMPA

Idiopathic (type one) is the most common non-erosive IMPA. This category is applied to IMPA when an underlying cause cannot be identified and it is not associated with extra-articular disease. Necessarily, this is a diagnosis of exclusion.

In a retrospective study, all dogs with type one IMPA presented with stiffness as a clinical sign (Clements et al, 2004) – 22 out of 39 dogs had pyrexia and 20 of 39 had lymphadenopathy. The

carpal and tarsal joints were most commonly affected by pain and swelling and the stifle and elbow joints showed the same effects later in the disease process.

Haematologic abnormalities were noted in more than half of the dogs, with neutrophilic leukocytosis being the most common. Serum biochemical abnormalities were noted in 26 dogs with moderately raised liver enzymes being the most common. Overall, clinical signs and initial laboratory and clinical investigative findings were frequently abnormal, but non-specific, and were not associated with the likelihood of recovery (Clements et al, 2004).

IMPA associated with infection remote from the joint (type two IMPA)

Type two cases have been reported to account for approximately 25% of cases of non-erosive IMPA without multisystem involvement in dogs (Bennett, 1987b). Sites of infection that have been associated with IMPA include endocarditis, respiratory infection, genitourinary tract infection, pyoderma and abscessation (Innes, 2012). It is thought the chronic infection acts as a persistent source of antigens that drive the chronic immune complex disease. Comparisons have been drawn between this category of IMPA and reactive arthritis (Reiter's syndrome) in humans. In dogs with type two IMPA, treatment of the initiating infection can bring about resolution of the condition; however, this is not necessarily the case and chronic or recurrent IMPA can persist (Innes, 2012).

IMPA associated with gastrointestinal disease (type three IMPA)

IMPA associated with some form of gastrointestinal (GI) disease was reported to account for approximately 15% of cases of non-erosive IMPA without multisystemic involvement in dogs (Bennett, 1987b). The most common GI signs were vomiting and diarrhoea. However, it must be recognised this study was uncontrolled and the background incidence of vomiting and diarrhoea in dogs is relatively high – this could lead to overestimation of this category of IMPA. However, clearly the GI tract is a potential source of bacterial and food antigens that could trigger an immune complex disease (Innes, 2012).

IMPA associated with neoplasia (type four IMPA), paraneoplastic arthritis

Tumour cells may serve as a source of persistent antigens that can trigger a secondary IMPA. Paraneoplastic syndromes are defined by clinical, radiologic, or biologic manifestations associated with malignant disease, but without direct invasion of the tumour.

In humans, such syndromes most commonly occur in patients with solid or haematologic tumours and the clinical course of the paraneoplastic rheumatic disorder generally parallels that of the cancer with surgical removal of the tumour, or its medical treatment usually resulting in marked regression of the clinical manifestations of the rheumatic disorder.

In humans, this type of arthritis is typically asymmetric and seronegative for RF (Racanelli et al,

2008). Only a few reports have described paraneoplastic IMPA in dogs. In a small series of six dogs (Bennett, 1987b) all had solid tumours of various types (seminoma, mammary carcinoma, renal carcinoma, tonsillar carcinoma, Sertoli cell tumour or leiomyoma), but some had more than one tumour type diagnosed at postmortem.

SLE and SLE-related disorders

SLE is a multisystem immune-mediated disorder traditionally associated with the appearance of anti-nuclear antibody (ANA). The exact definition of SLE in the veterinary literature, however, is unclear. No single clinical sign or disease syndrome is pathognomonic for SLE and various criteria have been used to establish a diagnosis. The diagnosis should be based on the presence of major supporting clinical signs and a positive serum ANA titer (Innes, 2012).

Most dogs and cats with SLE present with pyrexia and a symmetric non-erosive IMPA along with a combination of skin disease, mucocutaneous ulceration, immune complex glomerulonephropathy, haemolytic anaemia, leukopenia or lymphopaenia, thrombocytopaenia, aseptic meningitis, polymyositis, serositis, keratoconjunctivitis sicca, retinopathy and uveitis.

A diagnosis of definitive SLE is based on the appearance of at least two major signs (skin lesions, polyarthritis, haemolytic anaemia, glomerulonephritis or substantial haematuria, polymyositis, leukopenia and thrombocytopaenia) or is made if the dog has an ANA titer more than 160, one major sign and at least two minor signs (pyrexia of unknown origin with CNS signs including seizures, oral ulceration, lymphadenopathy, pericarditis and pleuritis; Smee et al 2007).

Polyarthritis/polymyositis syndrome





Figure 2. A four-year-old Akita with polyarthritis/polymyositis syndrome. Note the pronounced muscle atrophy particularly affecting the temporalis muscle group.

Criteria for the diagnosis of polyarthritis/polymyositis syndrome include the following.

- The presence of a non-erosive symmetrical inflammatory polyarthropathy determined by clinical examination and confirmed by radiography, examination of synovial fluid samples and a synovial membrane biopsy from at least one joint.
- Clinical features consistent with inflammatory polymyopathy, which include bilaterally symmetrical muscle atrophy, myalgia and muscle contracture (**Figure 2**). The myositis must be confirmed in at least two of several muscle biopsies.
- Other clinically similar conditions, such as rheumatoid arthritis, SLE and subacute bacterial endocarditis, must be excluded. In one study, six dogs were diagnosed with polyarthritis/polymyositis syndrome. In these dogs, synoviocentesis showed characteristics consistent with an inflammatory polyarthropathy, and synovial biopsy confirmed chronic active inflammation within the synovium and an inflammatory response affecting at least two muscle groups based on histopathology.

A syndrome of polyarthritis and polymyositis can also occur as part of SLE, but all the dogs in this study were negative for ANA. The cause of the polyarthritis/polymyositis was unknown. It has been classified as an immune-based connective tissue disease. The histological characteristics of the synovium and muscle, in the absence of recognisable infection, suggests the immune system was involved, as does the response to immunosuppressive therapy (Bennett and Kelly, 1987).

Polyarthritis/polymeningitis syndrome

Spinal pain is commonly noted in cases with IMPA, with up to 29% of cases demonstrating this (Webb et al, 2002). Spinal pain in dogs with IMPA was initially speculated to arise from arthritis of the vertebral articular facets (Bennett, 1987b). However, in up to 46% of dogs with IMPA and

concomitant spinal pain, this spinal pain may be the result of steroid-responsive meningitis-arteritis (SRMA), which can occur concomitantly (Webb et al, 2002). Spinal pain in dogs with SRMA arises from meningeal inflammation and irritation (Meric, 1986). In some dogs with SRMA, the joint disease can be difficult to appreciate; in one study, dogs with concomitant SRMA and IMPA did not have obviously swollen joints or signs of lameness (Webb et al, 2002). IMPA is easier to monitor during long-term therapy than is meningitis, and it is also possible (although as yet unknown) that dogs with SRMA and IMPA may have a different prognosis to those with either condition alone. It could be argued that any dog with SRMA should be routinely evaluated for subclinical polyarthritis through synovial fluid analysis (Webb et al, 2002).

Breed-associated non-erosive IMPA syndromes

Specific forms of IMPA associated with certain breeds have been reported. These include the Akita (Dougherty et al, 1991), boxer, Weimaraner, Bernese mountain dog (Meric et al, 1986), German shorthaired pointer, spaniel and beagle breeds (Taylor, 1998; Bennett, 1995). The Shar-Pei syndrome is a familial amyloidosis colloquially named Shar Pei fever, which presents as recurring inflammatory disease of the distal limb joints, especially the tarsi.

Over the longer term, affected individuals develop renal amyloidosis. The prognosis for Shar Peis with renal amyloidosis appears to be poor because of amyloid-induced renal failure (Innes, 2012).

IMPA in the Japanese Akita usually commences in adolescence and may be associated with aseptic meningitis. The Akita breed is affected by a number of distinct immune-mediated diseases including, but not limited to, thyroiditis, sebaceous adenitis, pemphigus foliaceus, uveitis, myasthenia gravis and uveodermatologic syndrome.

A proposed genetic association exists for uveodermatologic syndrome (Angles et al, 2005) and while there are no reported genetic associations with immune-mediated polyarthritis/meningitis in this breed, it seems a genetic mutation probably exists (Innes, 2012).

Drug-induced IMPA

Rarely, IMPA is seen as a side-effect of drug therapy, notably some antibiotics, especially sulfonamides, penicillin-derivatives, erythromycin, lincomycin and cephalosporins.

It is hypothesised immune complex hypersensitivity reactions occur as a result of drug antibody interactions. Reactions to sulfonamides represent the most common drug-associated IMPA. In reported cases, the time from drug initiation to onset of lameness ranged from seven to 21 days (Trepanier, 2004). Synovial fluid analysis in affected cases revealed a predominance of neutrophils without toxic change or visible organisms. Typically, withdrawal of the drug leads to improvement in lameness in one to three days.

Large breed dogs appear to be predisposed to sulfonamide arthropathy with Dobermann pinschers over-represented. Among Dobermann pinschers, signs of multisystemic disease may be apparent including lymphadenopathy, retinitis, protein-losing nephropathy, leukopenia and modest thrombocytopenia (Giger et al, 1985).

Rheumatoid arthritis

Rheumatoid arthritis is characterised by a deforming symmetric polyarthritis, associated with synovitis of joints and tendon sheaths, articular cartilage loss, erosion of juxta-articular bone and, in most patients, the presence of IgM RF (**Figure 3**). The disease process often leads to the destruction of articular cartilage and subchondral bone associated with an invasive tissue in joints called pannus.



Figure 3. Three pictures of an eight-year-old domestic shorthaired cat suffering from erosive polyarthritis affecting both carpi. Note the laxity and deformation associated bilaterally.

Canine and feline rheumatoid arthritis are distinguished from other immune-mediated polyarthritis syndromes by virtue of radiographically diagnosed erosive changes in joints and the appearance of RF in serum. Diagnostic criteria have been defined for canine rheumatoid arthritis (Bennett, 1987) based on those used for diagnosis of rheumatoid arthritis in humans. Depending on the number of criteria satisfied and the duration of these criteria, “classical” (seven criteria), “definite” (five criteria), “possible” and “probable” rheumatoid arthritis can be diagnosed (Bennett 1987; Bennett and Nash, 1988).

In a series of 30 cases of rheumatoid arthritis (Bennett, 1987), on haematology, only three cases had a leukocytosis and, of the remainder, six had a lowered white blood cell count. The erythrocyte sedimentation rate was elevated in 24 dogs and the platelet count slightly lowered in two dogs.

Blood alkaline phosphatase, aspartate aminotransferase and alanine aminotransferase levels were increased in approximately one third of cases. Twenty-two of the dogs (73%) had an RF titer of one in 40 or greater in at least one of the serum samples taken. In addition, three dogs gave a positive

titer for ANA. This is a recognised confounding factor in the diagnosis of rheumatoid arthritis – the presence of other antibodies in the circulation as a result of polyclonal activation of B-lymphocytes.

Polyclonal activation is the non-specific reactivation of memory B-lymphocytes with consequent production of multiple antibodies. As a result, affected patients may show increased circulating levels of many antibodies, including some that are important in the diagnosis of other IMPA syndromes, such as ANA. This can confuse attempts at definitive diagnosis and attempts to unravel the etiopathogenesis of IMPA. The clinician should consider this phenomenon when interpreting the results of other antibody tests (Innes, 2012).

Breed-specific polyarthritis recognised in greyhounds

A semiosive polyarthritis of greyhounds has been reported generally affecting dogs between three to 30 months of age. The condition is characterised by mild to severe fluctuating swelling of the limb joints distal to, and including, the elbows and stifles. This condition leads to excessive joint fluid, thickened synovial membranes and ulcerative erosions of the articular cartilage.

In many dogs, the tendon sheaths in the carpal and tarsal regions are also affected. Histological features include hyperplasia of the synovial membrane with a variable inflammatory reaction, mild pannus formation at the margins of joints, severe cartilage degeneration in the absence of pannus formation over most of the articular surface and highly reactive draining lymph nodes.

The pathological changes can be classified essentially as a subacute non-suppurative synovitis with evidence of florid destructive fibrinous exacerbations. In these cases, rheumatoid factor and ANA antibodies were negative and there were no significant abnormalities in haemograms or electrophoretograms. Tests for antibodies to *Erysipelothrix*, *Brucella* and *Chlamydia* species were all negative (Huxtable and Davis, 1976).

This article demonstrates the complexity of IMPA and the classification thereof. However complex, attempts to classify the type of IMPA present are important, as it is only this that provides a definitive diagnosis. The type of IMPA present can impact significantly on the appropriate treatment options and also the prognosis.

- More information on both treatment options and the prognosis associated with IMPA can be found in part two of this article, covering clinical signs, diagnostic tests, treatment and prognosis.

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