Published in final edited form as:

J Am Vet Med Assoc. 2016 November 15; 249(10): 1156–1164. doi:10.2460/javma.249.10.1156.

Clinical features and pathological joint changes in dogs with erosive immune-mediated polyarthrititis: 13 cases (2004–2012)

Magen L. Shaughnessy, DVM, Dr. Susannah J. Sample, DVM, PhD, Carter Abicht, BA, Caitlin Heaton, BS, and Dr. Peter Muir, BVSc, MVetClinStud, PhD

UW Veterinary Care Hospital (Shaughnessy) and Comparative Orthopaedic Research Laboratory (Sample, Abicht, Heaton, Muir), School of Veterinary Medicine, University of Wisconsin, Madison, WI 53706

Abstract

OBJECTIVE—To evaluate the clinical features and pathological joint changes in dogs with erosive immune-mediated polyarthrititis (IMPA).

DESIGN—Retrospective case series.

ANIMALS—13 dogs with erosive IMPA and 66 dogs with nonerosive IMPA.

PROCEDURES—The medical record database of a veterinary teaching hospital was reviewed to identify dogs with IMPA that were examined between October 2004 and December 2012. For each IMPA-affected dog, information extracted from the medical record included signalment, diagnostic test results, radiographic findings, and treatments administered. Dogs were classified as having erosive IMPA if review of radiographs revealed the presence of bone lysis in multiple joints, and descriptive data were generated for those dogs. All available direct smears of synovial fluid samples underwent cytologic evaluation. The synovial fluid total nucleated cell count and WBC differential were estimated and compared between dogs with erosive IMPA and dogs with nonerosive IMPA.

RESULTS—13 of 79 (16%) dogs had erosive IMPA. Dogs with erosive IMPA had a mean $\pm$ SD age of 7.1 ± 2.4 years and bodyweight of 8.3 ± 3.4 kg (18.3 ± 7.5 lb). All 13 dogs had erosive lesions in their carpal joints. The estimated median synovial fluid lymphocyte count for dogs with erosive IMPA was significantly greater than that for dogs with nonerosive IMPA. All dogs received immunosuppressive therapy with leflunomide ($n = 9$), prednisone (3), or prednisone-azathioprine (1).

CONCLUSIONS AND CLINICAL RELEVANCE—Results indicated erosive IMPA most commonly affected the carpal joints of middle-aged small-breed dogs. Further genetic analyses and analysis of lymphocyte-subsets is warranted for dogs with erosive IMPA. Word count = 256

In dogs, IMPA is a common noninfectious idiopathic accumulation of inflammatory immune complexes within the synovial membrane of affected joints.^{1,2} Clinical signs are associated with pathological changes in the affected joints and frequently include signs of pain or

Address correspondence to Dr. Muir (peter.muir@wisc.edu).

Dr. Shaughnessy's present address is Department of Small Animal Clinical Science, College of Veterinary Medicine, Michigan State University, East Lansing, MI 48824.

stiffness, joint effusion, and lameness.^{3,4} Affected dogs may also be febrile with anorexia and lethargy.^{3,4} Up to 25% of dogs with IMPA do not have joint effusion or lameness, and instead are examined because of signs of vague systemic illness.^{3,4} The most commonly affected joints are the carpal, tarsal, stifle, and elbow joints.^{3,5–7} By definition, dogs with IMPA have multiple affected joints, although grossly evident clinical abnormalities may be limited to only 1 joint during initial physical examination of dogs in the early stages of the disease. A definitive diagnosis of IMPA is made on the basis of the detection of characteristic abnormalities during cytologic and radiographic evaluation of multiple joints.^{5,8–11}

Immune-mediated polyarthritis typically results in nonerosive lesions; IMPA-associated erosive lesions and bone destruction are rare. The term canine rheumatoid arthritis has been used to describe erosive IMPA,^{12,13} but the latter term will be used exclusively in the present report. Risk factors and the underlying mechanism for the development of erosive IMPA have yet to be elucidated. Dogs with erosive IMPA may develop joint instability subsequent to damage or destruction of the soft-tissue structures that support affected joints.^{12,13} Compared with dogs with nonerosive IMPA, dogs with erosive IMPA are less responsive to treatment, have a poorer prognosis, and often require lifelong treatment with high doses of immunosuppressive drugs with or without joint arthrodesis.^{12–15}

Immune-mediated polyarthritis is typically diagnosed on the basis of cytologic evaluation of synovial fluid samples obtained by arthrocentesis from multiple joints.¹⁶ Dogs with IMPA frequently have multiple joints in which the synovial fluid protein concentration is > 3.0 g/dL (reference range, 1.5 to 3.0 g/dL) and TNCC is > 3,000 cells/μL (reference range, 0 to 2,900 cells/μL).^{11,16} Synovial fluid samples with > 12% nondegenerate PMNLs are supportive of inflammatory arthritis.^{4,17} When an adequate volume of synovial fluid cannot be obtained for a complete analysis, evaluation of a direct smear can be used to estimate the TNCC.¹⁸ Evaluation of radiographic images of joints can be useful for determining which joints are affected and whether bone lysis is present in those joints.⁴ Additional diagnostic testing modalities such as bacterial culture may be indicated to rule out infectious causes of polyarthritis. Clinical information about erosive IMPA is limited. Therefore, the purpose of the study reported here was to evaluate the clinical features and pathological joint changes in dogs with erosive IMPA at initial examination and during subsequent immunosuppressive therapy.

Materials and Methods

Case selection

The medical records database of the University of Wisconsin Veterinary Care Hospital was searched to identify records of dogs that were examined between October 2004 and December 2012. Records of dogs with a clinical diagnosis of IMPA were reviewed. Immune-mediated polyarthritis was defined as an abnormally increased synovial fluid TNCC (> 3,000 cells/μL) or cytologic evidence of neutrophilic or mixed-inflammation without signs of sepsis in synovial fluid samples. Dogs were excluded from the study if radiographs of affected joints were unavailable for review. Dogs with radiographic evidence

of erosive joint changes were classified as having erosive IMPA, all other dogs were classified as having nonerosive IMPA.

The medical records of 84 dogs were reviewed. Four dogs were excluded from the study because radiographs of affected joints were unavailable for review. One dog was excluded from the study because the synovial fluid cytologic results did not support a diagnosis of IMPA. Of the remaining 79 dogs, 13 were classified as having erosive IMPA and 66 were classified as having nonerosive IMPA.

Medical records review

For each dog, information extracted from the medical record included signalment, bodyweight, history, previous medications administered, reason for examination, and results of physical and orthopedic examinations, CBC, serum biochemical analysis, urinalysis, infectious disease screening tests, and autoantibody (e.g., RF, ANA, and Coombs) tests (when available). Orthopedic examination findings were evaluated to determine how many joints were clinically affected in each dog. A joint was considered affected when there was evidence of effusion or signs of pain, crepitus, laxity, or a decrease in the range of motion during manipulation. Orthopedic examination findings associated with phalangeal joints were not assessed in this study.

Radiography

Survey radiographs of 4 to 10 joints, including both carpi, were obtained for each dog. Roentgen sign information obtained from the radiographic reports made at the time the radiographs were initially evaluated were reviewed. Radiographic evaluation included assessment for synovial effusion, osteophytosis, bone lysis, and periarticular swelling. Erosive IMPA was confirmed on the basis of radiographically apparent bone lysis within a joint. For each dog, the number of joints radiographed and the number of joints with radiographic evidence of erosive changes were recorded.

Cytologic analysis of synovial fluid

For most dogs, an insufficient amount of synovial fluid was obtained for an automated TNCC; therefore, the TNCC was estimated from evaluation of direct smears of synovial fluid samples that were stained with Wright-Giemsa stain. Direct smears were considered unsuitable for review when the synovial fluid was unevenly distributed, the base of the smear covered less than two thirds of the width of the slide, the smear lacked a complete feathered edge or contained >10% ruptured nucleated cells.¹⁸ Direct smears of synovial fluid samples that were unsuitable or unavailable for review were excluded from statistical analyses.

Suitable direct smears of synovial fluid samples were reviewed by use of a validated method for TNCC estimation¹⁸ by 1 investigator (MLS). Within each counting field, all nucleated cells were counted, including those with pyknotic and karyorrhectic nuclei, as well as cells within groups and naked nuclei. A cell was considered within the counting field if at least half the cell was visible within the field. Nucleated cells in fifteen 400X fields were counted and the mean number of nucleated cells/400X field was determined. After correction for the

dimensions of the 400X field area, the TNCC was estimated by use of the following regression formula: $y = 0.45x - 0.36$, where y is the estimated TNCC and x is the mean number of nucleated cells/400X field.¹⁸ The numbers of PMNLs, mononuclear cells, lymphocytes, and eosinophils were estimated on the basis of the differential for a count of 100 to 200 cells that was obtained from the medical record. When available, bacterial culture and antimicrobial sensitivity results for synovial fluid samples obtained at the time of IMPA diagnosis were reviewed and reported.

Statistical analysis

Descriptive data were generated for the dogs with erosive IMPA. For each variable assessed, the data distribution was assessed for normality by use of the Shapiro-Wilk test. Results for variables that were normally distributed (bodyweight and age) were reported as the mean $\pm$ SD, whereas those for variables that were not normally distributed (synovial fluid variables) were reported as the median (range). Synovial fluid cell counts were compared between dogs with nonerosive IMPA and dogs with erosive IMPA by use of the Mann-Whitney U test. For each group of dogs, the correlation between carpal synovial fluid cell counts and blood platelet count at IMPA diagnosis was assessed with the Spearman Rank test. For all analyses, values of $P \leq 0.05$ were considered significant.

Results

Clinical features of dogs with erosive IMPA

Thirteen of the 79 (16%) dogs evaluated were classified as having erosive IMPA. The dogs with erosive IMPA had a mean age of 7.08 ± 2.4 years and bodyweight of 8.3 ± 3.4 kg (18.3 ± 7.5 lb) and included 1 sexually intact male, 5 castrated males, and 7 spayed females. Breeds represented included Cavalier King Charles Spaniel ($n = 2$), Shi Tzu (2), and mixed breed, Chihuahua, Cocker Spaniel, Pembroke Welsh Corgi, Dachshund, Maltese, Papillon, Shetland Sheepdog, and Tibetan Terrier (1 each). Reasons for the initial examination included progressive lameness of 3- to 6-weeks duration ($n = 5$), progressive collapse of carpal or tarsal joints over the previous 3 months to 3 years (5), inappetence (3), intermittent pyrexia (3), previous diagnosis of IMPA (2), progressive weight loss (2), and intermittent right forelimb lameness (1); some dogs were examined because of multiple problems.

All dogs with erosive IMPA had instability ($n = 9$) or effusion (4) of multiple joints detected during orthopedic examination. Of the 9 dogs with joint instability, 6 had bilateral carpal joint instability, 2 had bilateral carpal and tarsal joint instability, and 1 had unilateral carpal joint instability. Of the 4 dogs with joint effusion, 2 had bilateral effusion of the carpal and stifle joints, 1 had bilateral effusion of the carpal joints, and 1 had bilateral effusion of the carpal, stifle, and tarsal joints.

Complete blood count results at the time of diagnosis were available for 12 of the 13 dogs with erosive IMPA. Three dogs had a mild nonregenerative anemia (mean $\pm$ SD PCV, $31\% \pm 1\%$; reference range, 39% to 51%). One dog had a regenerative anemia (PCV, 22%), which resolved with immunosuppressive therapy and was suspected to be immune-mediated. Five dogs had thrombocytosis (mean $\pm$ SD platelet count, $649,400 \pm 110,800$ platelets/ μ L;

reference range, 175,000 to 500,000 platelets/ μ L). One dog had a moderate thrombocytopenia (platelet count, 82,000 platelets/ μ L) despite the fact that all of the other CBC variables were within the respective reference ranges. Two dogs had a mild leukocytosis (mean $\pm$ SD WBC count, 21,000 $\pm$ 1,500 WBCs/ μ L; reference range, 5,000 to 14,000 WBCs/ μ L).

Serum biochemical analysis results at the time of diagnosis were available for all 13 dogs with erosive IMPA. Eight dogs had unremarkable serum biochemical results, whereas the remaining 5 dogs had hyperglobulinemia (mean $\pm$ SD globulin, 5.1 $\pm$ 0.3 g/dL; reference range, 1.7 to 3.8 g/dL). A urinalysis was performed at the time of diagnosis for 6 dogs, and the results were unremarkable. Bacterial culture of urine was performed for 2 dogs, and the results were negative for both dogs.

Ten of the 13 dogs with IMPA were screened for infectious agents that might be immunologic triggers for inflammatory arthritis. A serological panel for detection of antibodies against *Ehrlichia canis*, *Ehrlichia equi*, *Rickettsia rickettsia*, and *Borrelia burgdorferi* was performed on 9 dogs. Eight of those dogs were seronegative for antibodies against all of the pathogens, and 1 dog was seropositive for antibodies against *B burgdorferi*. A PCR assay for detection of vector-borne disease was performed on 1 dog, the results of which were negative. Four dogs were tested for RF; 3 dogs had negative results for RF and 1 dog had positive results for RF. The dog that had positive results for RF was also the dog that was seropositive for antibodies against *B burgdorferi*. An ANA test was performed on 2 dogs, and the results were negative for both dogs. A direct Coombs test was performed on 2 dogs, and the results were negative for both dogs.

Radiographic features of dogs with erosive IMPA

Radiographs of multiple joints, including both carpi, were obtained at the time of diagnosis for 10 of the 13 dogs with erosive IMPA. Nine of those dogs had erosions evident within the carpal joints. For the dog without erosive changes in the carpal joints at the time of IMPA diagnosis, radiographs of the carpal joints were obtained again at 6 and 15 months after diagnosis. The radiographs obtained at 15 months after diagnosis revealed erosive changes in both carpi.

Radiography was not performed at the time of IMPA diagnosis for 3 dogs. One dog was determined to have nonerosive IMPA and treated with prednisone by the referring veterinarian 22 months before it was examined at the veterinary teaching hospital, at which time erosive lesions were radiographically evident in both carpi. Another dog had endocarditis and secondary IMPA was suspected on the basis of the presence of severe effusion in multiple joints. After the dog was treated for endocarditis, it was started on immunosuppressive therapy, which reportedly improved the dog's comfort and mobility. Radiographs were obtained 4 years after IMPA was initially diagnosed, at which time erosive changes were bilaterally evident in the carpal and tarsal joints. Immune-mediated polyarthritis was diagnosed in the third dog by the referring veterinarian 8 months before it was examined at the veterinary teaching hospital. Radiographs obtained during the initial examination at the veterinary teaching hospital revealed erosive lesions in both carpal and tarsal joints as well as the vertebral column.

Radiographs were obtained of 4 to 8 joints for each dog. Within individual dogs, the joints radiographed included bilateral carpal, tarsal, and stifle joints (n = 8 dogs); bilateral carpal, elbow, tarsal, and stifle joints (2); bilateral carpal, elbow, and tarsal joints and unilateral stifle joint (1); bilateral carpal, tarsal, and elbow joints (1); and bilateral carpal and elbow joints (1). All 13 dogs had multiple joints with radiographic evidence of erosive changes detected either at the time IMPA was diagnosed or during subsequent treatment. Lytic lesions were ultimately detected in the carpi of all 13 dogs. Other joints in which erosive lesions were commonly observed included the tarsal, stifle, and elbow joints.

Radiographically, erosive lesions appeared as small punctate radiolucencies in the articular joint surfaces, mildly mottled opacities, or subchondral lytic lesions with indistinct or irregular margins frequently with bony proliferation in the articular surfaces (Figure 1). Radiographic evidence of carpal joint luxation or subluxation was observed in 3 dogs. The proximal interphalangeal joints were affected in dogs with severe disease. Bone lysis was identified in the tarsal joints of 8 of 11 dogs and in the stifle joints of 2 of 11 dogs. Stifle joint effusion was identified in 9 of 11 dogs. Fragmentation of the radiocarpal bone was observed in 1 dog. Angular deformity of the antebrachium was identified in 1 dog, and the medial coronoid process of the elbow was fragmented in another dog.

Cytologic evaluation of synovial fluid

Cytologic results of synovial fluid samples were reviewed for 11 of 13 dogs with erosive IMPA and 26 of 66 dogs with nonerosive IMPA. Direct smears of synovial fluid samples were either unsuitable or unavailable for review for the remaining 2 dogs with erosive IMPA and 40 dogs with nonerosive IMPA. For the dogs with erosive IMPA, cytologic results were reviewed for 1 joint in each of 4 dogs, 2 joints in each of 3 dogs, 3 joints in each of 2 dogs, and 4 joints in each of 2 dogs. Collectively, cytologic results were reviewed for synovial fluid samples obtained from 15 carpal joints, 4 stifle joints, and 3 tarsal joints among 11 dogs with erosive IMPA. For the dogs with nonerosive IMPA, cytologic results were reviewed for 1 joint in each of 11 dogs, 2 joints in each of 7 dogs, 3 joints in each of 6 dogs, and 4 joints in each of 2 dogs. Collectively, cytologic results were reviewed for synovial fluid samples obtained from 23 carpal joints, 13 stifle joints, 11 tarsal joints, and 4 elbow joints among 26 dogs with nonerosive IMPA. The synovial fluid TNCC was estimated from direct smears of samples obtained at the time of diagnosis for all 11 dogs with erosive IMPA and 26 dogs with nonerosive IMPA.

The overall estimated median synovial fluid TNCC for dogs with erosive IMPA (7,200 cells/ μ L; range, 400 to 51,000 cells/ μ L) did not differ significantly from that for dogs with nonerosive IMPA (8,800 cells/ μ L; range, 400 to 131,000 cells/ μ L; Figure 2). Similarly, the estimated median TNCC for specific joints (carpal, tarsal, or stifle joints) did not differ significantly between dogs with erosive IMPA and dogs with nonerosive IMPA. The overall median synovial fluid lymphocyte count for dogs with erosive IMPA (460 lymphocytes/ μ L; range, 0 to 491 lymphocytes/ μ L) was significantly ($P = 0.05$) greater than that for dogs with nonerosive IMPA (140 lymphocytes/ μ L; range, 0 to 393 lymphocytes/ μ L). Likewise, the estimated synovial fluid lymphocyte count for the carpal joints of dogs with erosive IMPA was significantly ($P < 0.005$) greater than that for dogs with nonerosive IMPA; however, the estimated median synovial fluid lymphocyte counts for the tarsal and stifle joints did not

differ between dogs with erosive IMPA and dogs with nonerosive IMPA. The estimated median synovial fluid PMNL, mononuclear cell, and eosinophil counts also did not differ significantly between dogs with erosive IMPA and dogs with nonerosive IMPA. At the time of IMPA diagnosis, the blood platelet count was not significantly correlated with the estimated carpal joint synovial fluid TNCC, and PMNL, lymphocyte, and mononuclear cell counts.

Aerobic bacterial cultures of synovial fluid were performed for 5 dogs at the time of IMPA diagnosis. All cultures yielded negative results.

Medical treatments

All 13 dogs with erosive IMPA were administered immunosuppressive therapy. Nine dogs were treated with leflunomide (2.6 to 4.5 mg/kg/day, PO), 3 dogs were treated with prednisone (2.0 to 2.7 mg/kg/day, PO), and 1 dog was treated with a combination of prednisone (2 mg/kg/day, PO) and azathioprine (1.6 mg/kg/day, PO). All dogs responded to immunosuppressive therapy. The time from initiation of immunosuppressive therapy to owner-perceived clinical response was not recorded for any of the dogs; however, clinical improvement was confirmed for 10 dogs during recheck examinations at the university hospital. Those recheck examinations occurred between 2 weeks and 8 months (mean $\pm$ SD, 10.6 ± 8.9 weeks) after initiation of immunosuppressive therapy.

Surgical treatments and CCLR

Among the 13 dogs with erosive IMPA, 1 was lost to follow-up after the disease was diagnosed, 1 underwent staged bilateral carpal arthrodesis for treatment of carpal joint hyperextension, 10 developed unilateral or bilateral CCLR (diagnosed on the basis of a positive drawer test for the affected joints) before, at the time of, or after diagnosis of erosive IMPA, and 1 did not develop CCLR or undergo any surgical treatments. Of the 10 dogs with CCLR, 2 developed the condition 9 and 10 months, respectively, before diagnosis of erosive IMPA and underwent unilateral and bilateral extracapsular stabilization of the stifle joint, respectively, at the time that CCLR was diagnosed. Four dogs had bilateral CCLR at the time of erosive IMPA diagnosis; 1 of those dogs underwent unilateral extracapsular stabilization of a stifle joint within 1 week after diagnosis of erosive IMPA. Four dogs had bilateral CCLR detected during a recheck examination at the veterinary teaching hospital after erosive IMPA was diagnosed. The recheck examinations for those dogs occurred between 4 months and 5 years (mean $\pm$ SD, 26.3 ± 23.8 months) after diagnosis of erosive IMPA. Two of those dogs were receiving prednisone and the other 2 were receiving leflunomide at the time CCLR was diagnosed; stifle stabilization was not pursued in these patients.

Discussion

In the present study, 13 of 79 (16%) dogs with IMPA that were examined at a veterinary teaching hospital between October 2004 and December 2014 were classified as having erosive IMPA, which was a much higher proportion than reported (1.9%) in a previous study.⁴ That fairly high prevalence of dogs with erosive IMPA allowed us to evaluate the

clinical and radiographic features and synovial fluid cytologic results associated with the disease.

The dogs with erosive IMPA in the present study had similar age and sex distributions as dogs with the condition evaluated in other studies.^{2,8–10,12,13,16} Dogs with either erosive or non-erosive IMPA typically develop the condition when they middle-aged.^{2,8–10,12,13,16} Erosive IMPA typically affects small-breed dogs, whereas nonerosive IMPA usually affects large-breed dogs.^{4,6} A cohort of 30 dogs with erosive IMPA included 3 (10%) Shetland Sheepdogs and 2 (7%) Cocker Spaniels; other breeds of Collies were also commonly represented in that cohort.^{12,13} The fact that certain small-breed dogs appear to have a predilection for the development of erosive IMPA suggests that genetic variation may be a contributing factor to the disease.¹⁹ Immune-mediated polyarthritis has an immunogenetic predisposition.²⁰ It is possible that differences in the immune system among breeds or individuals is an important factor in the pathogenesis of erosive IMPA. Environmental factors, such as the presence of canine distemper virus in synovial fluid resulting in sustained inflammation of the synovial membrane and joint erosions, have also been proposed to have a role in the development of erosive IMPA.²¹

Three of the 12 dogs with erosive IMPA in the present study that had a CBC performed at the time the disease was diagnosed had mild nonregenerative anemia. Anemia associated with chronic inflammatory disease, often referred to as anemia of chronic disease, is typically characterized as normochromic, normocytic, and nonregenerative, all of which result from cytokine-mediated inhibition of iron utilization and erythropoietin production and apoptosis of erythroid progenitors.²² Alternatively, the dogs of this study might have had autoimmune hemolytic anemia. In fact, the dog that had the most severe anemia was suspected of having autoimmune hemolytic anemia, and the anemia resolved with immunosuppressive therapy.

Five of the 12 dogs of this study that had a CBC performed at the time of erosive IMPA diagnosis had thrombocytosis. That was an unexpected finding because, to our knowledge, thrombocytosis had not previously been reported in dogs with erosive IMPA. Thrombocytosis is associated with rheumatoid arthritis in human patients, with a positive correlation between platelet counts and the extent of disease activity.²³ Platelets are important for hemostasis and are also potent immune cells that substantially influence synovial inflammation in human patients with autoimmune rheumatoid disease.²⁴ In the present study, we did not identify a significant correlation between the platelet count and the synovial fluid cell counts in carpal joints at the time of IMPA diagnosis. Further investigation of the relationship between thrombocytosis and IMPA in dogs is warranted.

The diagnostic testing protocol was not standardized for the dogs of the present study because of its retrospective nature. Therefore, the number of dogs that were evaluated for RF, ANAs, and antibodies against various pathogens and that had bacterial culture performed on synovial fluid samples varied. However, the fact that all 13 dogs in this study had radiographic evidence of erosive lesions in multiple joints and all 12 dogs for which follow-up information was available had a positive clinical response to immunosuppressive therapy supported the diagnosis of erosive IMPA. Although infectious causes of arthritis can cause erosions within affected joints, they rarely result in polyarthropathy,²⁵ and the

administration of immunosuppressive therapy to dogs with infectious arthritis should cause clinical signs to worsen instead of improve.^{8–10,12} Two of 13 dogs with erosive IMPA in the present study were evaluated for serum ANA titers, and both dogs were seronegative for ANAs. Currently, determination of the serum ANA titer is not considered a useful diagnostic test for the diagnosis of erosive IMPA in dogs unless the animal is suspected to have systemic lupus erythematosus.²⁶ Only 1 of the 4 dogs evaluated was seropositive for RF, which was consistent with results of another study²⁷ in which 6 of 22 (27.3%) dogs with erosive polyarthritis were seropositive for RF-specific IgM. Rheumatoid factor–specific IgM titers should be interpreted with caution in dogs with suspected erosive IMPA because, although the presence of RF-specific IgM is suggestive of a nonspecific inflammatory disease, the lack of RF-specific IgM does not rule out erosive IMPA.^{8–10} Results of a recent study²⁸ suggest that evaluation of biomarkers of synovial inflammation, such as C-reactive protein, in conjunction with cytologic evaluation of synovial fluid may be a reliable method for the diagnosis of IMPA in dogs.

In the present study, the carpal joint was the most commonly affected joint in dogs with erosive IMPA, which was consistent with information provided in a review² of the disease. This suggested that the carpal joints are the most important joints for radiographic evaluation and arthrocentesis during the diagnostic workup of dogs in which erosive IMPA is suspected. For dogs with confirmed erosive IMPA, the carpal joints might also be the ideal joints for serial monitoring to assess patients for response to treatment. Eleven of the 13 dogs with erosive IMPA evaluated in the present study had radiographic evidence of erosive lesions in one or both carpal joints at the time the disease was diagnosed. For the 2 remaining dogs, IMPA was diagnosed by the referring veterinarians 8 and 22 months, respectively, before examination at the veterinary teaching hospital. The referring veterinarians did not obtain radiographs of the carpal joints in those 2 dogs; therefore, it is unclear whether those dogs had erosive or nonerosive disease at the time of initial IMPA diagnosis.

Synovial fluid from multiple joints was not submitted for cytologic evaluation from all dogs at the time of erosive IMPA diagnosis. For most dogs, the reason that synovial fluid was not obtained from or evaluated for multiple joints was not recorded in the medical record. However, we suspect that the fairly small size of most dogs of the present study precluded the collection of a sufficient amount of synovial fluid for cytologic evaluation or contamination of some of the synovial fluid samples with blood prevented the attending clinicians from submitting those samples for evaluation.

In the present study, the estimated synovial fluid TNCC and PMNL count did not differ significantly between dogs with erosive IMPA and dogs with nonerosive IMPA. Results of other studies^{6,12,13} indicate that synovial fluid TNCC is not correlated with disease severity. However, the development of erosive IMPA might be positively associated with the synovial fluid lymphocyte count. In this study, the median synovial fluid lymphocyte count for dogs with erosive IMPA was approximately 4 times that for dogs with nonerosive IMPA. Although that finding was significant, we do not know whether it was biologically relevant given the small number of dogs evaluated and the overall small proportion of lymphocytes relative to the proportion of PNMLs within the synovial fluid samples. If lymphocyte

signaling is a key factor in the development of erosive IMPA, immunomodulatory drugs that target lymphocyte function such as leflunomide, which specifically inhibits T cell proliferation and B cell antibody production, might be particularly useful for treatment of dogs with erosive disease.^{1,16} Further research that involves the identification of lymphocyte subsets within the synovial fluid of dogs with erosive IMPA is warranted to elucidate the role of synovial lymphocytes in the pathogenesis of the disease. For example, type 17 helper T lymphocytes produce interleukin-17 and have a role in the development of neutrophilic inflammation as well as osteoclast activation, which results in bone loss in human patients with rheumatoid arthritis.²⁹ Despite the fact that PMNLs are often the predominate cell type found in the synovial fluid of dogs with IMPA, mononuclear cells and lymphocytes are more important than PMNLs in the regulation of the proinflammatory immune response and may have a key role in the pathogenesis of IMPA.¹

Although pancarpal arthrodesis has been used to successfully treat hyperextension of the carpal joints in dogs with erosive IMPA,¹⁵ only 1 of the 3 dogs with carpal luxation or subluxation in the present study underwent carpal arthrodesis. An interesting finding of the present study was that 9 of the 13 dogs with erosive IMPA developed bilateral CCLR. The pathogenesis of CCLR is complex; however, synovitis of the stifle joint is an early characteristic of the disease.^{30–32} It is possible there is a direct relationship between IMPA and the development of bilateral CR, and further investigation is warranted.

The present study had several limitations. Because of its retrospective nature, the diagnostic testing protocol and treatment varied among dogs and determination of a patient's response to treatment was made on the basis of clinician notes recorded in the medical record and cytologic findings (when available). Those limitations prevented us from performing a direct comparison between treatment response and the development of specific clinical features such as CCLR. A prospective study in which a standard protocol is used to manage dogs with IMPA should be performed so that the clinical outcomes for dogs with erosive IMPA and dogs with nonerosive IMPA can be compared. The treatment protocol we recommend for such a study is the administration of leflunomide as a disease-modifying agent until the estimated synovial fluid TNCC is < 3,000 cells/ μ L (as determined on the basis of cytologic evaluation of serially collected synovial fluid samples)^{1,16,18} and administration of an NSAID for analgesia as needed. The cytologic analyses for the dogs of the present study were limited because only direct smears of synovial fluid samples were available for review. Moreover, direct smears of synovial fluid samples were available for review for less than half of the dogs with nonerosive IMPA, which might have biased our comparisons between dogs with erosive IMPA and dogs with nonerosive IMPA, although use of a validated method¹⁸ to estimate the TNCC mitigated those concerns. Additionally, the chronicity of the disease process, which is difficult to determine clinically, could have affected the cytologic features of the synovial fluid samples.

Results of the present study suggested that erosive IMPA typically affects middle-aged small-breed dogs. Erosive lesions such as bone lysis were most frequently observed in the carpal joints of affected dogs, which suggested that the carpal joints were the most useful joints for radiographic and cytologic evaluation to diagnose erosive IMPA and for monitoring response to treatment. Many dogs with erosive IMPA were thrombocytopenic

and developed CCLR, and further research is necessary to elucidate the association between erosive IMPA and those 2 conditions. The estimated median synovial fluid lymphocyte count for dogs with erosive IMPA was significantly greater than that for dogs with nonerosive IMPA, which suggested that erosive disease was positively associated with lymphocytic inflammation in affected joints, but additional genetic analysis and evaluation of lymphocyte subsets in dogs with erosive IMPA is necessary to confirm that.

Acknowledgments

The authors thank Dr. Karen Young and Ms. Zhengling Hao for technical assistance.

ABBREVIATIONS

ANA	Antinuclear antibody
CCLR	Cranial cruciate ligament rupture
IMPA	Immune-mediated polyarthritis
PMNL	Polymorphonuclear leukocyte
RF	Rheumatoid factor
TNCC	Total nucleated cell count

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Figure 1.

Representative dorsopalmar radiographic images of carpal joints that depict the range of joint destruction observed in dogs with erosive IMPA that were examined at a veterinary teaching hospital between October 2004 and December 2014. A—Left carpus of a 7-year-old sexually intact male mixed-breed dog with subjectively mild subchondral bone lysis. B—Left carpus of an 8-year-old spayed female Cavalier King Charles Spaniel with subjectively moderate subchondral bone lysis accompanied by severe synovial swelling. C—Right carpus of an 8-year-old spayed female Chihuahua with severe erosive disease and antebrachiocarpal luxation. D—Right carpus of a 5-year-old spayed female Pembroke Welsh Corgi with severe erosive disease that has resulted in destruction of the metacarpal bones.

Figure 2.

Scatter plots of the TNCC (A) and PMNL (B), mononuclear cell (C), and lymphocyte (D) counts for 11 of 13 dogs with erosive IMPA and 26 of 66 dogs with nonerosive IMPA that were examined at a veterinary teaching hospital between October 2004 and December 2014. All cell counts are reported on a Power of 10 scale. More than 1 joint was evaluated for some dogs, and the cell counts for each joint evaluated are reported. For each group within each panel, the horizontal line represents the median. Significant ($P < 0.05$) differences between medians are indicated when present.