

CANINE POLYARTHRITIS/POLYMYOSITIS SYNDROME

In this form of non-erosive polyarthritis the radiographic and immunopathogenic features of the joint disease are similar to those of SLE. Clinical examination reveals swelling and pain on palpation of major limb joints (carpi, hocks, stifles, elbows) and there may be pyrexia and generalized lymphadenopathy (359). Analysis of synovial fluid reveals a white cell count of $20\text{--}80 \times 10^9/l$ ($20,000\text{--}80,000/\mu l$) dominated by neutrophils, and poor mucin clot formation.

Affected dogs also have muscle atrophy, pain and contracture, which is often generalized, involving muscles of the limbs, spine and skull. It may be difficult to distinguish between joint and muscle pain on clinical examination. Muscle biopsy reveals myofibre degeneration and infiltration of neutrophils, macrophages, lymphocytes and plasma cells. There may be leukocytosis and hypergammaglobulinaemia, but serum ANA is

negative. Concentrations of creatine kinase (CK), lactate dehydrogenase, aspartate aminotransferase and aldolase in the blood are often increased. Electromyography may show focal areas of spontaneous activity in affected muscles.

Aggressive immunosuppression is indicated for polyarthritis/polymyositis. Cytotoxic drugs are most often used, in combination with low dose corticosteroids. There may be remission of disease; however, some animals have residual lameness due to muscle fibrosis and contracture. In other cases, low grade muscle and joint inflammation persists, and low dose corticosteroids may be necessary to maintain quality of life.

POLYARTHRITIS/MENINGITIS SYNDROME

This syndrome is recognized in the Weimaraner, German Shorthaired Pointer, Boxer, Bernese Mountain Dog, Newfoundland and Japanese Akita, and is also reported in the cat. Affected animals present with stiffness and neck pain (360) and

sometimes nervous signs. They are negative for serum ANA. The arthritis is symmetrical and non-erosive, and is confirmed by synovial fluid analysis and synovial biopsy. Cerebrospinal fluid shows increased protein, white cells and CK levels, consistent with central nervous system (CNS) inflammation. The prognosis is usually good, as such cases respond to immunosuppressive doses of corticosteroids, but relapse can occur at any time. Some cases may be associated with polyarteritis, and the condition in the Japanese Akita is further discussed below because of the poor prognosis.

POLYARTHRITIS OF ADOLESCENT JAPANESE AKITAS

Affected Japanese Akitas are usually less than one year old and present with polyarthritis, peripheral lymphadenopathy and systemic illness (pyrexia, lethargy, inappetence) (361). Meningitis may also be present, as may other organ involvement, giving some resemblance to SLE. However, serum ANA is

not found. Anaemia and leukocytosis are common laboratory findings. These dogs have a poor prognosis, since response to anti-inflammatory and immunosuppressive drugs is generally poor. Use of these drugs in immature animals is more likely to have side-effects. Euthanasia is often necessary on humane grounds.

FAMILIAL RENAL AMYLOIDOSIS OF CHINESE SHAR PEIS

These dogs present with episodes of fever and swelling of one or both hocks and, occasionally, other joints, although seldom with a polyarthritis (362). The joints can be normal between attacks, which are often at 4–6 week intervals. The condition is often referred to as ‘Shar Pei fever’ or ‘Shar Pei hock’. There is synovitis of varying severity, and enthesiopathies are seen, most often as bony proliferation at the attachments of ligaments and tendons. The age of onset is variable; the condition may affect young puppies or adults.



359 Canine polyarthritis/polymyositis. A two-year-old Whippet with polyarthritis and polymyositis. This animal was unable to stand and walk. (From Bennett D. [1987] Immune-based nonerosive inflammatory joint disease of the dog. 1. Canine systemic lupus erythematosus. *Journal of Small Animal Practice* 28:871–889, with permission.)



360 Canine polyarthritis/meningitis. A one-year-old Weimaraner with polyarthritis and meningitis. In addition to joint pain, neck pain was an obvious feature.



361 Polyarthritis of the Japanese Akita. A seven-month-old Japanese Akita with polyarthritis. This dog also developed metaphyseal osteopathy. The prognosis for polyarthritis in juvenile Akitas is very poor. Euthanasia of this dog was necessary, since response to treatment was incomplete.

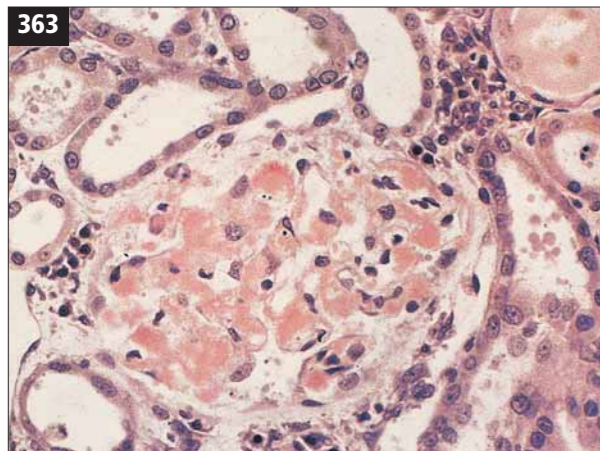


362 Familial renal amyloidosis of Shar Peis. A Chinese Shar Pei with amyloidosis. This dog suffered episodic attacks of arthritis for several years. It is now in renal failure, secondary to amyloidosis.

Amyloid deposition (amyloid A) occurs in several organs, but renal and hepatic amyloidosis is the most significant and eventually results in renal and/or hepatic failure (363), generally between 1.5–6 years of age, so the disease carries a poor prognosis. Some dogs have elevated levels of serum amyloid A and IL-6. Amyloid deposits can often be seen in renal and hepatic biopsies. The attacks of arthritis and pyrexia generally resolve within 24–48 hours without treatment; however, the use of non-steroidal anti-inflammatory drugs (NSAIDs) (e.g. meloxicam) helps control pain and pyrexia. Colchicine (0.03 mg/kg p/o q24h) on a continuous regime has been used in some cases. This drug does not prevent pyrexia/arthritis, but it does have anti-amyloid properties, although it is not clear whether it reduces the incidence or severity of amyloidosis. Amyloidosis is reported in other immune-mediated arthropathies, particularly RA, although it is a rare complication and seldom of clinical significance.

POLYARTERITIS NODOSA

This is most often a multisystemic disease (see below), but polyarthritis or pauciarthritis is a common feature. If polyarteritis is seen in a biopsy of synovium or other tissue, in the absence of serum ANA, a clinical diagnosis of polyarteritis nodosa is justified. Meningitis and myositis are often seen in combination with the arthritis, so there is overlap with the syndromes discussed above. Attacks of arthritis are often cyclical, although persistent signs can occur. Affected animals are often pyrexia, depressed and stiff. Meningitis produces extreme neck pain, which may



363 Familial renal amyloidosis of Shar Peis. A renal biopsy showing amyloid deposition within the glomerulus (Congo red stain).

be the only obvious symptom. In some young animals (e.g. Beagles) the prognosis is good, with spontaneous recovery as the animal matures. Treatment is by immunosuppression (high dose corticosteroids or cytotoxic drugs) and clinical remission can be achieved, although adult dogs may relapse at any time.

SJÖGREN'S-LIKE SYNDROME

In human rheumatology, both primary and secondary forms of Sjögren's syndrome are recognized. In the secondary form there is evidence of accompanying RA or other connective tissue disease. The clinical presentation of this autoimmune syndrome is of keratoconjunctivitis sicca (KCS) (see Chapter 11, p. 272) in combination with xerostomia (dry mouth), due to lymphocytic infiltration and destruction of the lacrimal and salivary glands. Although KCS is well-documented in the dog, true Sjögren's-like syndrome is rare. Only two dogs satisfying the criteria for diagnosis of this disease have been formally reported in the literature (with one further report as part of a case series). However, there may be some 'overlap syndromes' in which dogs presenting with apparently uncomplicated KCS have serological changes related to connective tissue disease (e.g. ANA and RF), or in which dogs with KCS have another concomitant autoimmune disease such as hypothyroidism, RA, diabetes mellitus, chronic active hepatitis or autoimmune skin disease. The two affected canine patients were part of an experimental breeding colony of dogs with SLE.

It has been suggested that canine primary Sjögren's-like syndrome may be underdiagnosed. Dogs presenting with primary KCS have been shown to have subclinical histopathological changes in salivary gland tissue, and some dogs with KCS that are evaluated for parotid duct transposition also have a degree of xerostomia. One study of 50 dogs with KCS identified ten animals as having evidence of xerostomia. All dogs presenting with polyarthritis should have their tear production regularly assessed using the Schirmer test in order to check for the complication of secondary Sjögren's-like disease.

A single case of Sjögren's-like syndrome has been reported in a two-year-old cat that presented with dysphagia, weight loss, ocular signs (blepharospasm and conjunctival hyperaemia), enlargement of salivary glands and 'tacky' oral mucous membranes with food debris within the mouth.

The treatment of KCS is discussed in Chapter 11. A combination of local ocular (e.g. ciclosporin) and systemic immunosuppressive/anti-inflammatory therapy can be used. Tear substitutes are also an important part of disease management.

IDIOPATHIC POLYARTHRITIS

Pathogenesis

Idiopathic polyarthritis is the most common presentation of immune-mediated arthritis in the dog and cat. Animals with idiopathic polyarthritis do not, at least initially, satisfy the diagnostic criteria for the entities described above. Affected animals most commonly have joint disease alone (type I) or joint disease in association with infectious disease of other body systems (type II; reactive arthritis), gastrointestinal disease (type III; enteropathic arthritis) or neoplastic disease of other body systems (type IV; arthritis of malignancy). The immunopathogenesis most likely involves synovial

immune complex deposition, and the complexes in types II, III and IV disease may involve microbial or tumour antigens. It has been suggested that type I disease may in some cases be triggered by vaccination, and the detection of distemper antigens in synovial immune complexes in some dogs adds support to this concept. In most cases there is synovial hyperplasia, which is occasionally villous. The inflammatory infiltrates consist of lymphocytes, plasma cells and neutrophils, and fibrin deposition and vasculitis are recorded.

Clinical signs

The presentation of idiopathic polyarthritis in dogs is similar to other forms of immune-mediated arthritis. The clinical features include overt lameness or stiffness after rest or exercise, joint pain, soft tissue thickening, synovial effusion, heat or crepitus (364–366). There may be periods of remission and relapse.

364–366 Idiopathic polyarthritis. (364) A four-year-old dog with an acute onset, non-erosive idiopathic type I polyarthritis. This dog has severe joint pain and was unable to stand or ambulate. (365) A Bearded Collie with ulcerative colitis and non-erosive polyarthritis, a probable example of type III idiopathic polyarthritis (enteropathic arthritis). (366) A young cat with polyarthritis and myeloproliferative disease confirmed by bone marrow biopsy. This is an example of an idiopathic type IV polyarthritis (the arthritis of malignancy).



Diagnosis

Radiographically the lesions are non-erosive, with soft tissue swelling and synovial effusion, and, sometimes, periosteal new bone formation may be seen (367, 368). Synovial fluid has poor mucin clot formation and neutrophil-dominated inflammation ($3\text{--}100 \times 10^9$ cells/l [$3,000\text{--}100,000$ cells/ μl]). Additionally, animals with idiopathic polyarthritis generally have signs of systemic illness. Both leukocytosis and leukopenia are recorded, and most dogs have elevated serum globulin. Serum ANA or RF are generally absent; however, occasional cases have low titred autoantibodies. Some cases of type I polyarthritis in the dog progress to erosive rheumatoid disease and require reclassification at a later stage.

Treatment and prognosis

The prognosis for type I polyarthritis is generally good. Most cases respond to immunosuppressive therapy; however, some fail to respond completely and may need continuous low dose corticosteroid

treatment to maintain quality of life. Other animals may go into remission, but relapse at any time.

The drug of choice for immunosuppressive therapy is prednisolone (2–4 mg/kg q24h for 2 weeks, then gradually tapered over 3–4 months). There is generally a marked response within a few days, but therapy must be maintained for several weeks in order to prevent relapse. Response to therapy can be judged by clinical examination or by repeating synovial fluid analysis (two weeks after commencing therapy) of one or more joints that were initially sampled for diagnosis. If the cell count has fallen below $4 \times 10^9/\text{l}$ (4,000/ μl), and most cells are mononuclear, the prognosis is reasonably good. If relapse occurs after finishing prednisolone therapy, the treatment regime can be repeated.

Cytotoxic drugs are indicated if the animal relapses while receiving corticosteroid treatment, if there is poor response to corticosteroid therapy alone, or if there are repeated relapses after cessation of therapy. Cytotoxic drugs are SAARDs;

they are combined with low dose (anti-inflammatory) prednisolone (0.25–0.5 mg/kg q24h), which reduces joint inflammation and pain and improves the animals' quality of life while the cytotoxic drugs take effect. The cytotoxic drug of choice for immune-mediated arthritis is cyclophosphamide (1.5 mg/kg for dogs <30 kg; 2.0 mg/kg for dogs 15–30 kg; and 2.5 mg/kg for animals less than 15 kg [including cats]). The drug is given on four consecutive days of each week, although it can be used on alternate days or every third or fourth day depending on the dosage. Cyclophosphamide is usually given for 3–4 months, but prolonged therapy is not recommended as bladder toxicity may develop. Urine samples should be regularly tested for blood. The presence of significant haematuria is an indication for cessation of therapy. Haematology should also be monitored every 7–14 days and, if the white cell count falls below $6 \times 10^9/\text{l}$ (6,000/ μl) or platelets below $125 \times 10^9/\text{l}$ (125,000/ μl), the dose should be reduced by a quarter. If the white cell count falls below $4 \times 10^9/\text{l}$ (4,000/ μl) or platelets below $100 \times 10^9/\text{l}$ (100,000/ μl), the drug is discontinued for two weeks and then recommenced at half the original dose. There is substantial anecdotal evidence that the use of levamisole (3–7 mg/kg p/o every other day) in addition to cyclophosphamide and low dose corticosteroids can improve the possibility of successful remission. Levamisole should not be used for longer than four months.

If cyclophosphamide therapy is unsuccessful, or if immunosuppressive treatment is needed for more than four months, azathioprine is generally used (2 mg/kg every other day, alternating with low dose prednisolone also used every other day). Bone marrow suppression is more likely with thiopurines and may occur within 4–6 weeks of therapy (cyclophosphamide takes several months). There has been limited experience with the use of ciclosporin in the treatment of type I polyarthritis, but when used as monotherapy this agent has not proven efficacious.

If remission is achieved with cytotoxic drugs but relapse occurs subsequently, the previously successful regime can be repeated as often as necessary. If remission is not achieved, or relapses become common or occur shortly after finishing immunosuppressive therapy, the latter should not be repeated and low dose corticosteroid treatment should be used to maintain quality of life. Because of the associations between immune-mediated

polyarthritis and CDV antigens referred to above, all dogs that have suffered immune-mediated polyarthritis should not receive distemper booster inoculations unless antibody titres are significantly low. Booster vaccinations should never be given if the dog is on immunosuppressive therapy.

Some cases of mild, type I polyarthritis will have spontaneous remission within a day or two, without treatment. NSAIDs may be used to relieve joint pain and pyrexia while the diagnosis of immune-mediated polyarthritis is being confirmed. Immunosuppressive treatment should not be instigated until other diagnoses (e.g. bacterial endocarditis) have been ruled out.

Treatment of type II idiopathic polyarthritis is directed towards controlling the infection and if this is successful, the arthritis should resolve spontaneously. Occasionally, low dose corticosteroids are used in combination with antimicrobial therapy to help resolve the arthritis.

Treatment of type III idiopathic arthritis concentrates on controlling the gastrointestinal disease. Low dose corticosteroids may provide relief from arthritis while the gastrointestinal problem is being treated, but corticosteroids may sometimes be appropriate for both the intestinal and joint disease.

The prognosis for type IV idiopathic arthritis depends on the prognosis for the tumour. In cats, myeloproliferative disease is the most common association, and the bone marrow of cats with non-erosive polyarthritis should be examined if there is no response to treatment.

DRUG INDUCED ARTHRITIS

Drug-induced vasculitides (see Chapter 5, p. 145) are increasingly recognized in dogs and are reported in the cat. Polyarthritis is one feature of such reactions, which may also involve fever, lymphadenopathy or cutaneous lesions. Antibiotics are most commonly incriminated, particularly sulphonamides, lincomycin, erythromycin, cephalosporins and penicillins. The most prevalent syndrome occurs in Dobermanns given sulphadiazine-trimethoprim; they may develop polyarthritis, glomerulonephritis, focal retinitis, polymyositis, skin lesions, fever, anaemia, leukopenia and thrombocytopenia. Diagnosis is made on the basis of worsening clinical signs while on therapy and rapid improvement after drug withdrawal. Occasionally, low dose corticosteroid therapy aids recovery.



367, 368 Idiopathic polyarthritis. (367) Lateral radiograph of right stifle joint showing loss of intrapatellar fat pads and distension of the caudal joint capsule, consistent with marked synovial effusion. No bony changes are present. (368) Lateral radiograph of hock joint showing increased soft tissue density around the tarsocrural joints, consistent with synovial effusion. No bony changes are present. The lack of bony change is typical of all non-erosive immune-mediated polyarthropathies. Soft tissue changes are usually the only feature and these may not be easily seen in certain joints or with mild cases.

ARTHRITIS ASSOCIATED WITH VACCINATION

Immune-mediated polyarthritis can follow vaccination, most commonly 5–7 days after primary vaccination of kittens (369). The calicivirus component is incriminated and calicivirus antigens have been identified within synovial macrophages in affected joints. The lameness is generally transient, lasting 24–48 hours, and further episodes after subsequent inoculations are unlikely. There is evidence that calicivirus is a feline joint pathogen and a cause of viral arthritis characterized by joint pain, stiffness, overt lameness and pyrexia. Some field strains of calicivirus may also produce an immune-mediated arthritis, similar to that produced by vaccine strains.

Polyarthritis following primary vaccination is also reported in puppies that develop transient lameness. Treatment of transient, vaccine-associated polyarthropathy is seldom required, although NSAIDs can be given. Some cases of rheumatoid and idiopathic polyarthritis become apparent within three weeks of vaccination (see above), although this does not necessarily imply an aetiological association.

LYMPHOPLASMACYTIC ARTHRITIS OF STIFLE JOINTS

This form of canine arthritis affects both stifles and is characterized by intense lymphoplasmacytic synovitis and synovial hyperplasia, which may be villous. There is no clear evidence that this disease is primary immune-mediated in nature.



369 Vaccine-associated arthritis. This kitten developed lameness five days after its first vaccination. This is an example of polyarthritis associated with vaccination.

ARTHRITIS FOLLOWING MICROBIAL JOINT INFECTIONS

Immune-mediated arthritis as a sequela to bacterial arthritis, and the possibility of such disease following *Borrelia* or calicivirus infection, has been discussed above. Bacterial endocarditis is an important condition to consider when dealing with a suspected case of immune-based polyarthritis. It can lead to both a true infective polyarthritis and/or an immune-mediated polyarthritis, and affected dogs can have high levels of circulating ANA and RF. Such dogs usually have a cardiac murmur and ultrasonography will generally reveal the vegetative endocarditis lesion. Ophthalmological examination may reveal retinitis and/or retinal haemorrhages.

RELAPSING POLYCHONDritis

This is a rare disease reported in the cat (see also Chapter 5, p. 169) and yet another term taken from human rheumatology. Relapsing polychondritis is characterized by episodic attacks of inflammation of hyaline and elastic cartilaginous structures including the ears, nose and laryngotracheal and articular cartilage, as well as the organs of special sense. It is thought to be an autoimmune response against cartilage, based on these cardinal features, the observed association with other conditions such as vasculitis, the presence of cartilage inflammation on biopsy, the demonstration of anti-collagen antibodies and a therapeutic response to corticosteroid therapy. It is reported mainly in middle-aged cats and auricular chondritis is the single most common manifestation. This may show as erythema, swelling, alopecia, crusting and pruritus of the pinnae, with curling of the ear margins. Involvement of articular cartilage leads to non-erosive inflammatory polyarthritis and lameness. Involvement of the laryngeal and tracheal/bronchial cartilages causes respiratory signs and inflammation of the heart valves can lead to valvular incompetency. Corneal opacification has also been reported in the cat. Dapsone has been used as a treatment (1 mg/kg p/o q24h).

MYOSITIS

Primary myositis is uncommon in the dog and rare in the cat. Four forms of immune-mediated myositis are documented in dogs: masticatory muscle myositis (MMM), extraocular myositis (EOM), dermatomyositis (DM) and polymyositis (PM).

MASTICATORY MUSCLE MYOSITIS

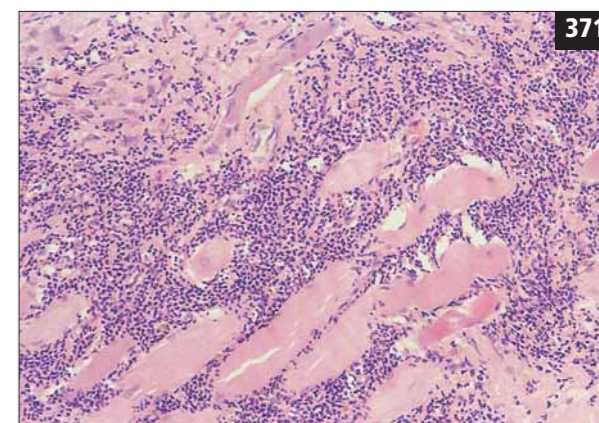
MMM is the most prevalent form of myositis in the dog. It involves the temporal, masseter and pterygoid muscles of the head, and presents clinically with symmetrical wasting of these muscle groups, pain on opening the mouth, restricted jaw movement and difficulty in eating (370). There may be mild elevation in serum CK and electromyographic abnormalities may be detected.

Canine masticatory muscles have a unique type 2M myofibre composition, which may explain their

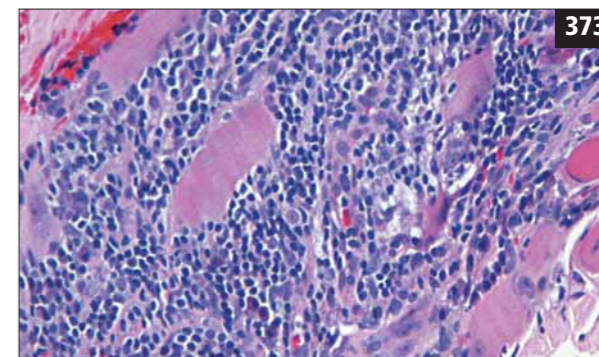
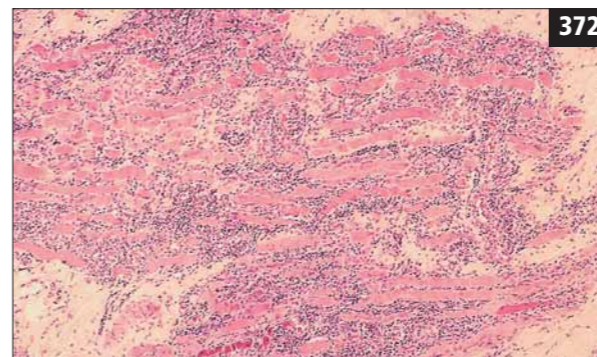
apparently selective involvement in these disorders. Autoantibodies specific for these 2M myofibres may be demonstrated in affected dogs. Biopsy reveals degenerative change in muscle fibre bundles, with fibrosis and inflammation. The infiltrate may be predominantly eosinophilic during the acute phase of disease (371) or during periods of relapse, whereas in chronic stages or periods of remission the lesions are dominated by lymphocytes and plasma cells (372, 373). This spectrum of histological change was once considered to



370 Canine masticatory myositis. A dog with atrophic myositis. Initially the temporal muscles become swollen and painful with the acute inflammatory phase. Very soon the muscles atrophy and fibrous contracture can result. This case shows obvious temporal muscle atrophy.



371 Canine masticatory myositis. Muscle biopsy from a three-year-old GSD with swelling of the temporal muscle. There is an intense infiltration of eosinophils, with focal lymphoplasmacytic aggregates associated with degeneration of muscle fibre bundles.



372, 373 Canine masticatory myositis. (372) Biopsy of temporal muscle from a three-year-old Golden Retriever with atrophy of masticatory muscles. There is myofibre degeneration, with an infiltrate of lymphocytes and plasma cells. (373) Biopsy of temporal muscle from a 14-year-old, neutered female crossbred dog with a six-week history of wasting of the temporal muscles. The dog has elevated serum creatinine kinase and abnormalities on EMG examination. This high power view shows intense infiltration of lymphocytes and plasma cells, with loss of myofibres.