Medical Neurology for Advanced Practitioners Mini Series

Session Three: Inflammation and the CNS - How to Approach When Tests Don't Help

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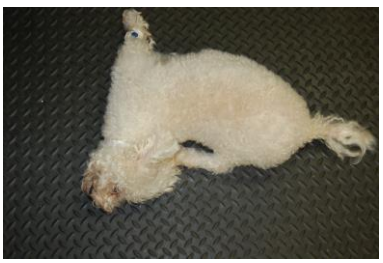

INFLAMMATORY DISEASE OF CNS IN DOGS AND CATS
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The hallmark of CNS inflammation is infiltration of peripheral blood leukocytes into the neuroparenchyma and its coverings, resulting in various types of encephalitis and/or meningitis, and sometimes associated with altered vascular integrity that leads to edema. The etiologies of inflammatory disease of the CNS are very diverse. Simplistically, they can be classed as pathogenic and non-pathogenic, with the latter being potentially related to immune-system dysfunction and comprising about 80% of cases in Europe and the USA. Infectious causes may be viral, protozoal, bacterial, rickettsial, or fungal.

GRANULOMATOUS MENINGOENCEPHALOMYELITIS

Granulomatous meningoencephalomyelitis (GME) is a sporadic, idiopathic, inflammatory disease of the CNS of dogs. This disease appears to have a worldwide distribution, with recent reports coming from the USA, Australia, New Zealand, and Europe. The cause of GME is unknown.

Most cases of GME occur in small breed dogs, and commonly in terrier and toy breeds and Poodles, although any breed may be affected. The majority of confirmed cases occur in young to middle-aged dogs, with a mean age around 5 years (ranging from 6 months to 12 years). GME occurs in both sexes; however, there appears to be a higher prevalence in females. A lack of obvious correlation between clinical signs and the course of the disease has been reported. Clinical signs usually reflect several (i.e. multifocal) syndromes, e.g., cerebral, brain stem, and spinal cord syndromes, as a result of the scattered distribution of lesions. However, focal signs have been reported in up to 50% of cases. Common signs include incoordination, ataxia and falling, cervical hyperesthesia, head tilt, nystagmus, facial and/or trigeminal nerve paralysis, circling, visual deficits, seizures, depression, and tetanic spasms. Occasionally, fever, peripheral neutrophilia, and excess non-segmented neutrophils will accompany the clinical neurological signs. An infrequently reported ocular form of GME appears to be related to lesions localized in optic nerves and optic chiasm resulting in visual impairment and abnormal pupillary reflexes.

A tentative diagnosis of GME may be suggested by signalment data, the clinical course of the disease, and clinical signs. Haematology, serum chemistry, and urinalysis studies are usually normal and electroencephalographic recordings are frequently non-specific. Rarely, an intrathecal filling-defect may be detected myelographically in dogs possibly due to focal cord swelling or subarachnoid granulomas. The most useful diagnostic aid is CSF analysis. In most dogs, CSF is abnormal with mild to pronounced pleocytosis, ranging from 50 to 900 WBCs/ul. Cells are predominantly mononuclear, including lymphocytes (60 - 90%), monocytes (10 - 20%), and variable numbers of large anaplastic mononuclear cells with abundant lacy cytoplasm. While neutrophils typically comprise from 1 - 20% of the cell type differential, they may be the predominant cell type on rare occasions. Occasionally, protein is elevated without pleocytosis. In one retrospective study of dogs with GME, lumbar-derived CSF contained fewer cells and less protein than CSF derived from cisternal puncture. CSF protein and cellularity is not necessarily influenced by the degree of meningeal involvement or the extent of necrosis within the granulomatous lesions. A combination of CSF and MRI findings may also be useful, the latter being characterized by isointense lesions on T1-weighted images. Pial/dural meningeal enhancement may be found with MRI. Although infrequently performed, brain biopsy can be a very useful diagnostic test in animals with focal lesions.

Prognosis for permanent recovery is gaurded. Some dogs die from inhalation pneumonia secondary to megaesophagus. Shortest survival periods, ranging from several days to weeks, are seen with the disseminated and ocular forms. Longer survival periods of from 3 to 6 months, or longer, are more suggestive of a focal lesion. In one retrospective study of 42 dogs with GME , median survival time for dogs with focal versus disseminated disease was 114 and 14 days, respectively, and dogs with focal forebrain signs (e.g., seizures) had significantly longer survival times (>395 days) than did dogs with focal signs in other areas of the CNS (59 days).

Long-term therapy is generally unsatisfactory, although temporary remission of signs is often achieved with corticosteroid administration, such as oral prednisone, 1 to 2 mg/kg/day initially for several days, then reducing the dosage to 2.5 - 5 mg on alternate days. Most dogs will require continued therapy to prevent recurrences of signs. Improvement may last for several days, weeks or months, although most will eventually succumb to the disease. Part of the temporary improvement may be related to a reduction of mast cell function in dogs receiving glucocorticoid medication. Cessation of glucocorticoid therapy is invariably associated with rapid and dramatic clinical deterioration. Results of a recent retrospective study suggested that radiation therapy (e.g., total doses ranging from 40 to 49.5 Gy, divided in 2.4- to 4.0-Gy fractions) may be an effective treatment for dogs with GME, particularly those with clinical signs suggesting focal involvement. Meningoencephalomyelitis (MEM) is defined as inflammation of the meninges (dura, arachnoid, and pia mater) and the neuroparenchyma (e.g, forebrain, brainstem, cerebellum and/or spinal cord). MEM may be focal, multifocal, or disseminated and typically cases are presented for asymmetric neurological signs. Idiopathic MEM occurs commonly in the dog, but seems to be extremely rare in the cat. Clinical signs reflect the location of the lesions, and GME typically is fatal if not treated aggressively with immunosuppression.

The primary therapy for idiopathic MEM is immunosuppression with corticosteroids and secondary immunosuppressive agents. Once an infectious etiology has been ruled out, and a presumptive or definitive diagnosis of idiopathic MEM is reached, treatment should be instituted as soon as possible. The patient first should be stabilized initially if neurological derangements have produced respiratory or cardiovascular abnormalities (e.g., seizures or brainstem lesions causing secondary autonomic changes). Supplemental oxygen should be given for hypoxemia and crystalloid/colloid support for perfusion and hypotension, as/if needed. Once systemic parameters are stabilized, therapy should be instituted to: 1) prevent neurological deterioration, 2) halt the immune response with immunosuppressive therapy, and 3) provide support for a recumbent patient if needed.

At present, immunosuppression is the mainstay of therapy for idiopathic MEM. Many immunosuppressive and cytotoxic protocols have been investigated for the treatment of idiopathic MEM. Glucocorticoids, cytarabine, azathioprine, lomustine, leflunomide, procarbazine, mycophenolate mofetil (MMF) and cyclosporine have all been used to treat idiopathic MEM.

Most clinicians treat idiopathic MEM with corticosteroids (prednisone or dexamethasone). In a large study of dogs with GME, radiation therapy appeared to be the only independent predictor of patient survival. However, these results may be biased as patient inclusion was based on only necropsied GME dogs. Depending on the severity of signs and the index of suspicion for infectious disease, some clinicians will initiate therapy with anti-inflammatory steroids (prednisone 0.5 – 1.0 mg/kg q 24 hrs PO) and await serology and PCR results for screening of regional infectious diseases. If the index of suspicion is *extremely* high for idiopathic inflammatory disease (e.g., Pug with MRI lesions consistent with inflammatory disease), the author directly initiates immunosuppressive therapy. Response to corticosteroids is variable and may be temporary, but dogs often have a favorable, initial response to steroid monotherapy. Additional immunosuppression is considered on a case by case basis, but the author typically utilizes secondary immunomodulatory agents upon review of negative serology and PCR results.

In a clinical setting, steroid monotherapy may resolve signs associated with idiopathic MEM in some dogs, but insufficiently or only transiently provides resolution in others. Moreover, long-term, high-dose corticosteroid therapy often causes adverse effects including polyuria-polydipsia, polyphagia, weight gain, hepatotoxicity, gastrointestinal ulceration, pancreatitis and iatrogenic hyperadrenocorticism. These combined factors have led to a recent focus on additional immunomodulatory drugs to treat idiopathic MEM such as cytosine arabinoside (CA) at 50 mg/m² q 12 hrs SC for 2 days, procarbazine at 25-50 mg/m² q 24 hrs PO, cyclosporine at 5-10 mg/kg q 12 hrs PO, azathioprine at 2 mg/kg q 24 hrs PO, mycophenolate 10-20 mg/kg q 12 hours PO, and leflunomide at 2-4 mg/kg q 24 hrs PO. In a recent study, patient survival times and adverse affects were compared between a prednisone/vincristine/cyclophosphamide (COP) protocol and a prednisone/CA protocol. There was no significant difference between survival times between the two groups.

Intravenous rescue cytosine arabinoside (CA) protocols (IV CRI at 200mg/m^2 over 48 hours) have been described for the initial treatment of severe idiopathic MEM. Recent evidence indicates that the IV route has a better pharmacokinetic profile than when administered via the SC route. The authors have also used a higher IV dose regimen (600 mg/m^2 over 48 hours), which seem to be useful for severe relapses. It is recommended to use I.V. rescue CA protocols with severely affected dogs with idiopathic MEM.

Recently mycophenolate mofetil (MMF) has been evaluated as a potentially affordable, safe, effective and practical alternative to the other aforementioned immunomodulators. MMF is the pro-drug of mycophenolic acid, an inhibitor of the enzyme inosine 5'-monophosphate dehydrogenase (IMPDH). Lymphocytes require IMPDH in the *de novo* synthesis of guanosine monophosphate for purines. Anticipated advantages of MMF over other immunosuppressive medications include the availability of oral and parenteral forms, rapid onset of action, and lack of myelosuppression or hepatotoxicity

Treatment with any immunomodulator is monitored by clinical response and regression of neurological deficits and occasionally repeated CSF analysis and MRI. Side effects have been minimal and dogs with MUE have a fair long-term prognosis with any of the immunomodulation therapies.

STEROID RESPONSIVE MENINGITIS-ARTERITIS

A severe form of steroid responsive meningitis-arteritis (SRMA) has been reported in Beagles, Bernese Mountain Dogs, Boxers, German Short-Haired Pointers, and sporadically in other breeds. This condition has a worldwide distribution and represents one of the most important inflammatory diseases of the canine CNS. Beagles, especially but not exclusively those in laboratory-bred colonies, appear at risk. In the Beagles, the condition has been termed Beagle pain syndrome, necrotizing vasculitis, polyarteritis, panarteritis, juvenile polyarteritis syndrome, and primary periarteritis. In other breeds, this condition previously appears under the terms necrotizing vasculitis, corticosteroid-responsive meningitis, aseptic suppurative meningitis, and corticosteroid-responsive meningomyelitis. This plethora of terminology reflects not only the dearth of knowledge about this condition but also highlights important clinical signs such as pain, improvement following corticosteroid medication, and histologic involvement of the meninges and blood vessels.
Affected animals usually are most commonly young adults between 8 and 18 months of age, although the age range may extend from 4 months to 7 years. The clinical course is typically acute with recurrences. A more protracted form of the disease may be seen following relapses and inadequate treatment. Signs include recurring fever, hyperesthesia, cervical rigidity, and anorexia. There may be a creeping gait, arching of the back with head held down, and crouched posture. Some dogs with protracted disease may show clinical signs of parenchymal involvement such as ataxia, paresis, tetraparesis or paraplegia. Hematological studies often reveal a peripheral neutrophilia with a left shift, increased erythrocyte sedimentation rate, and in some cases, an elevated a-2-globulin fraction. CSF studies indicate increased protein and neutrophilic pleocytosis.
The cause of SRMA remains unknown. To date, no bacterial or viral infectious agents have been identified, although activated T cells have been found in some dogs indicating these cells have had contact with some unidentified antigen.
The prognosis is guarded to favorable, especially in dogs with acute disease that are treated promptly using immunosuppressive doses of corticosteroids. Untreated dogs tend to have a remitting and relapsing course. Tipold recommends the following long-term therapy (e.g., for at least 6 months), especially in any dog that has had a relapse: prednisolone at 4 mg/kg/day, PO or IV initially. After 2 days, the dose is reduced to 2 mg/kg daily for 1 to 2 weeks, followed by 1 mg/kg daily. Dogs are re-examined, including CSF analysis and hematology, every 4 to 6 weeks. When signs and CSF are normal, the dose can be reduced to half of the previous dosage until a dosage of 0.5 mg/kg every 48 to 72 hours is attained. Treatment is stopped 6 months after clinical examination, CSF, and blood profiles are normal. In refractory cases, other immunosuppressive drugs such as azathioprine (at 1.5 mg/kg PO every 48 hours) may be used in combination with steroids (e.g., alternating each drug every other day). Antibiotics are ineffective.

Results of a long-term treatment protocol (up to 20 months) involving 10 dogs with SRMA have been recently published. Eight of the 10 dogs were without clinical signs up to 29 months after the treatment was terminated. Long-term glucocorticosteroid treatment resulted only in mild clinical side effects, such as polyuria/polydipsia, polyphagia and weight gain, which were reversible after the therapy was discontinued. It was noted that elevated serum and CSF IgA levels did not decrease to normal values during prednisolone treatment and were still slightly increased after the therapy was discontinued.

BACTERIAL ENCEPHALITIS / MENINGITIS

Bacterial meningitis is a rarely reported condition in dogs and cats. Animals of any age may be affected, although most affected dogs are adult, with a mean age around 5 years. Bacterial infections of the CNS most often occur via haematogenous spread from distant foci within the body (e.g., lung or splenic abscess, vegetative endocarditis, pleuritis, and urinary tract infections), by direct extension from sinuses, ears and eyes, as a result of trauma (e.g., bite wound), meningeal spread with entry along nerve roots, or from contaminated surgical instruments (e.g., spinal needle). Organisms usually disseminate via CSF pathways and produce cerebrospinal meningitis, often associated with microabscess formation of brain and spinal cord. A plethora of organisms have been cultured from dogs with bacterial meningitis including *Pasteurella* sp (e.g., *P. multocida*), *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus albus*, *Actinomyces* sp, *Nocardia* sp, *Escherichia coli*, *Streptococcus* sp (e.g., *S. pneumoniae*) and *Klebsiella* sp.
Irrespective of the etiologic agent, bacterial meningitis usually is acute in onset and tends to be characterized by a group of clinical signs that include hyperesthesia, fever, cervical pain, and frequently, cervical rigidity. In addition, vomiting, bradycardia, anorexia, occasional cranial nerve deficits, and seizures may be observed. Seizures may be caused by high fever, hypoglycemia, brain edema, or inflammation, while vomiting may result from increased intracranial pressure or from direct effects on the vomiting center. In some animals, clinical signs may develop that suggest parenchymal involvement. The clinical diagnosis of bacterial meningitis is supported by the finding of highly pleocytic CSF (500 to 1000+ WBCs/ul) with a high proportion of neutrophil cells. The protein content of the CSF is usually increased as well (100 to 1000+ mg/dl). Low CSF glucose, relative to plasma glucose values, are typical. Organisms may be seen on CSF cytology. Neutrophilia may be present in blood samples and there may be evidence of shock, hypotension, and disseminated intravascular coagulation Thrombocytopenia, abnormal liver enzymes, electrolyte imbalance, abnormal anion gap, and uremia have been reported in some cases. Electroencephalographic traces may demonstrate high voltage (30 - 70□v), fast (20 - 35 Hz) or slow (5 - 10 Hz) wave activity. Definitive diagnosis is made by bacterial culture of CSF (both aerobic and anaerobic). Blood and urine cultures may incriminate a pathogenic organism when CSF cultures are negative (which is usually the case in our experience). Meningeal inflammation, ventriculitis, and possibly brain edema can be detected using MRI or CT scans.
Prognosis is guarded since death is common even if appropriate therapy is administered, and relapses are frequently encountered. Appropriate use of antibiotics, according to the culture results, is basic to successful therapy of bacterial meningitis (encephalomyelitis). Antibiotic therapy should be maintained for several weeks after clinical signs have resolved. Chloramphenicol (up to 50 mg/kg, IV, IM, or SC, bid), metronidazole (10 - 15 mg/kg, PO, tid), trimethoprim-sulfonamide (from 30 to 60 mg/kg, PO, daily; note that complications may include sulfonamide urolithiasis in dogs and nephrotoxicity in cats) penetrate the CNS in therapeutic concentration. Ampicillin and penicillin enter the CNS only with meningeal irritation. Aminoglycosides and cephalosporins reportedly do not adequately penetrate the CNS, even when inflammation exists. Intrathecal administration of antibiotics should only be considered in refractory cases. Corticosteroids, in general, are contraindicated in the treatment of bacterial meningitis . It has been suggested that *Staphylococcus* sp. should be assumed when the organism involved is not known. Ampicillin, 5 - 10 mg/kg, IV, every 6 hours is recommended. Diazepam or other anticonvulsants can be used for seizures if they occur. Osmotic diuretics may be useful for treating increased intracranial pressure secondary to brain oedema.

Note that it may be very difficult to differentiate between bacterial meningitis and steroid responsive meningitis-arteritis (SRMA).
The latter is more common and probably should be at the top of the differential list. Analysis of CSF for elevated levels of IgA should be diagnostic for SRMA.

MYCOTIC DISEASES OF THE CNS

Mycotic agents sporadically produce a granulomatous meningoencephalomyelitis in dogs and cats. The more common mycotic infections of the CNS are caused by *Cryptococcus neoformans*, *Blastomyces dermatitidis*, *Histoplasma capsulatum* and *Coccidioides immitis*. Each agent has a particular geographic distribution in the USA. The pathogenesis is similar for blastomycosis, histoplasmosis and coccidioidomycosis. The organism is present in the soil, producing mycelia and airborne spores. The coccidia of spores are probably inhaled, deposited in the alveoli, phagocytosed and converted into the spherical parasitic, yeast form. This form is disseminated via lymphatics producing local hilar lymphadenopathy and there is hematogenous spread to other organs. The fate of the infected host is believed to be dependent upon time and ability to develop cellular immunity to fungal antigens. Unlike other mycotic diseases, *C. neoformans* exists only in the yeast form and has a worldwide distribution. Endemic areas have not been identified. Infection is probably acquired from the environment rather than from animals. Cryptococcosis infection often occurs in mature dogs and cats that are immunodepressed (e.g., cats with feline leukemia virus or feline immunodeficiency virus, or dogs with ehrlichiosis), and infection may be accelerated or worsened by glucocorticoid therapy. Cats contract the disease more frequently than dogs. The natural route of infection is generally believed to be the respiratory tract, with subsequent hematogenous and lymphogenous dissemination to other areas of the body. As with bacteria, mycotic infections also may reach brain and spinal cord by direct spread from an adjacent infection, e.g., from the nasal chambers, tooth alveolus and sinuses, outer ear, eustachian tube, middle/inner ear, petrous temporal bone, and basilar bone. Pyogranulomatous encephalitis has been reported occasionally in dogs and cats in association with blastomycosis. Neurological disease associated with histoplasmosis and coccidioidomycosis is rare or quite uncommon, although granulomatous meningitis attributable to *C. immitis* was diagnosed on postmortem examination in a 4 year old Border Collie by demonstration of coccidioides endospores in brain tissue. There are a few reports of CNS infection in dogs and cats associated with uncommon opportunistic fungi, such as phaeohyphomycoses, in which the agents involved are almost always Cladosporidium species, and usually *C. bantianum* . CNS disease is usually due to localized brain abscess or to multiple large pyogranulomatous lesions in the cerebrum and meninges, sometimes with multifocal malacic foci, and is invariably fatal.
Diagnosis of mycotic infection is based on demonstration of the organisms in tissue sections using immunofluorescent procedures or in material taken from aspirates or impression smears, culture, and serology. A commercial latex agglutination test is available for detecting cryptococcal capsular antigen in serum, urine, or cerebrospinal fluid. Inflammatory mycotic lesions may be detected using MRI.
Prognosis of mycotic infection is always guarded, especially in the disseminated form and with CNS involvement. Most of the organisms are sensitive to treatment with amphotericin B (AMB), e.g., using a dosage of 0.1 to 0.5 mg/kg body weight, IV, three times weekly, in dogs and cats. The treatment of choice for cryptococcosis still appears to be AMB and flucytosine (FCY), although toxic epidermal necrolysis may sometimes be seen as a side-effect. A recommended dosage for FCY is 120 mg/kg body weight, divided into 4 equal doses daily. Due to the inability of AMB and FCY to cross the blood-CNS barrier, it is recommended that these drugs be used in combination with other antifungal agents such as itraconazole (ITZ, at 5 - 10 mg/kg, PO, bid) or fluconazole (FCZ, at 5 - 15 mg/kg, PO, bid) in animals with CNS disease. It would seem that the same recommendation would apply to other fungal diseases having CNS involvement, e.g., itraconazole at 10 mg/kg, PO, daily is suggested for dogs with blastomycosis/brain involvement. In a recent report of cryptococcosis in 19 cats, treatment with ketoconazole (KTZ), was unrewarding in cases with CNS involvement, although KTZ and ITZ (both at 10 mg/kg, PO, daily) successfully treated a small number of experimentally-infected cats, including some with CNS disease.

PROTOZOAN ENCEPHALITIS-ENCEPHALOMYELITIS

Toxoplasmosis is an infectious condition caused by the protozoal parasite *Toxoplasma gondii* and occurs in acquired and congenital forms in man and animals. Cats are the definitive host for this parasite. TX-NS in dogs resulting in a systemic infection will typically affect most organs, and the CNS, in particular. Neurological signs associated with TX-NS encephalomyelitis are variable and may reflect a focal or multifocal disease process. In dogs, signs include hyperexcitability, depression, intention tremor, paresis, paralysis, head tilt, and seizures.

In the diagnosis of TX-NS neurological disease, abnormal hematological parameters may include non-regenerative anemia, neutrophilic leukocytosis, lymphocyosis, and eosinophilia. Serum alanine aminotransferase and aspartate aminotransferase levels may be increased, especially in dogs with acute hepatic and muscle necrosis. Results of CSF may be abnormal, with elevated protein content and a mixed monocytic-polymorphonuclear pleocytosis. An eosinophilic pleocytosis was found in 2 dogs with a granulomatous encephalomyelitis due to protozoan infection. Xanthochromia will be present if hemorrhage has occurred. Electromyographic testing may reveal fibrillation potentials, positive sharp waves, bizarre high-frequency potentials, and myotonic-like discharges. Nerve conduction velocities may be decreased. Serum creatine kinase levels are often increased. Protozoan meningoencephalitis has been detected using MRI scans. The close resemblance between *T. gondii* and *N. caninum* tachyzoites and tissue cysts prevents definitive diagnosis by histopathology, and the clinical syndromes appear to be identical. Differentiation between the two protozoan organisms can be made using assays for circulating antibodies, by tissue immunocytochemistry, and ultrastructural studies. Sensitive polymerase chain reaction assays have been reported for the detection of both *Neospora caninum* DNA and *Toxoplasma gondii* DNA in biological samples. Muscle biopsy of appropriate muscles (as suggested by the clinical signs) may also provide the possibility of a definitive premortem diagnosis using the aforementioned techniques.

Prognosis is poor when signs of pelvic limb spasticity are observed and is guarded in any animal with signs of CNS disease. In one study involving 27 cases of neosporosis, recovery was less likely in peracute cases with severe clinical signs, and when treatment was delayed. Many animals with myositis-polyradiculoneuritis have concomitant lesions in the CNS. A 4 to 8 week regimen of trimethoprim-sulfonamide (at 15 - 20 mg/kg combined dose, PO, bid) and pyrimethamine (at 1 mg/kg, PO, daily) has successfully treated animals with TX-NS-induced encephalomyelitis and myositis-polyradiculoneuritis. Clindamycin is considered to be the drug of choice for treating canine and feline toxoplasmosis, at a dose of 10 to 40 mg/kg/day, PO or IM, divided bid to tid. This dose can also be used for treating dogs with neosporosis. Clindamycin crosses the blood-brain barrier. Oral and parenteral dosages are similar because of the good intestinal absorption of clindamycin. Oral clindamycin can cause anorexia, vomiting, or diarrhoea in dogs and cats.