Granulomatous Meningoencephalomyelitis in Dogs

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ABSTRACT: Granulomatous meningoencephalomyelitis (GME) is a nonsuppurative inflammatory disease of unknown origin that affects the central nervous system of dogs. GME is characterized histologically by large perivascular cuffs of mononuclear cells in the parenchyma and meninges of the brain and spinal cord. If left untreated, it is usually fatal. Immunosuppressive doses of glucocorticosteroids have been the mainstay of treatment for GME; however, new and more effective therapies have recently been proposed. This article reviews the pathology, origin, clinical signs, therapeutic response, and outcome of GME in dogs.

Granulomatous meningoencephalomyelitis (GME) is a nonsuppurative inflammatory disease of the canine central nervous system (CNS).1-7 Its cause is unknown. This devastating disease was first called reticulosis by Koestner and Zeman in 1962.8 The term GME was proposed by Braund and colleagues in 1978.9 GME has a worldwide distribution and accounts for 5% to 25% of all CNS disorders in dogs.1,10

PATHOLOGY

GME is thought to account for most lesions previously described as reticulosis.5,11,12 The term reticulosis refers to an abnormal increase in cells derived from, or related to, monocyte macrophages (i.e., histiocytes).1 Because GME lesions contain histiocytes, GME may, by definition, represent a form of reticulosis.1 In 1972, reticulosis was divided into three categories: inflammatory (granulomatous) reticulosis, neoplastic reticulosis, and microgliomatosis.13 More recently,9 the inflammatory form has been referred to as GME,2,4-6,9,10,14,15 and neoplastic reticulosis has been reclassified as lymphoma or malignant histiocytosis.11

At necropsy, gross lesions of GME are evident if the angiocentric inflammatory reaction is sufficient to produce changes of the normal brain symmetry (i.e., falk deviation or compression of surrounding structures).3 Lesions are seen as areas of swelling and yellow to gray discoloration and are predominantly found in white matter; however, gray matter and leptomeninges also may be affected.4,5 Meninges may appear thickened and cloudy. In some cases, optic nerves are grossly enlarged.2
Microscopically, lesions of GME are characterized by perivascular cuffs of lymphocytes, varying numbers of macrophages, and plasma cells in the parenchyma and meninges of the brain and spinal cord. The lesions consist of single or clustered aggregates of perivascular inflammatory cell accumulation. The presumed vessels are occluded by eosinophilic amorphous material, with scarce spindle cells (fibroblasts). Original magnification ×10.

Figure 1. Histopathology section of a canine brain with disseminated GME. (Courtesy of Dr. A. Armien)

Hematoxylin and eosin stain shows tightly aggregated whorls of lymphocytes, spindle-shaped phagocytes, and collagen deposition around demonstrated (arrow) or presumed vascular structures (asterisks). The lesions consist of single or clustered aggregates of perivascular inflammatory cell accumulation. The presumed vessels are occluded by eosinophilic amorphous material, with scarce spindle cells (fibroblasts). Original magnification ×10.

Reticulin stain shows that the spindle cells are rich in extracellular reticular fibrin deposition. Original magnification ×20.

OCCURRENCE

Microscopically, lesions of GME are characterized by perivascular cuffs of lymphocytes, varying numbers of macrophages, and plasma cells in the parenchyma and meninges of the brain and spinal cord. The lesions consist of single or clustered aggregates of perivascular inflammatory cell accumulation. The presumed vessels are occluded by eosinophilic amorphous material, with scarce spindle cells (fibroblasts). Original magnification ×10.

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Reticulin stain shows that the spindle cells are rich in extracellular reticular fibrin deposition. Original magnification ×20.

ORIGIN

The cause of GME is unknown. Autoimmune, infectious, and neoplastic causes have been theorized; an autoimmune cause is considered most likely. Recent data indicate that the inflammatory lesions in GME consist of a T-cell–mediated delayed-type hypersensitivity reaction with organ-specific autoimmune disease. Lesions of the optic nerve also support this hypothesis. An antiastrogliocyte
autoantibody was recently identified in the cerebrospinal fluid (CSF) of dogs with GME or necrotizing meningoencephalitis (NME), indicating a possible relationship between these two diseases and the autoantibody. However, it remains unclear whether the autoantibody is the cause or the consequence of the inflammation.

Pathologic features and lesion distribution distinguish GME from idiopathic encephalitides of small-breed dogs, such as NME of young pugs and Maltese terriers and the necrotizing leukoencephalitis of Yorkshire terriers and Chihuahuas. NME of pugs and Maltese terriers is histopathologically characterized by inflammatory changes with lymphocytic, plasmacytic, and histiocytic infiltration and extensive parenchymal necrosis restricted to the cerebral hemispheres. Necrotizing leukoencephalitis of Yorkshire terriers has similar necrotic lesions on histopathologic evaluation, but brainstem lesions occur in addition to cerebral lesions.

INCIDENCE AND PREDISPOSITION

The disease has been described more commonly in small-breed dogs, especially in toy breeds and terriers; however, other breeds have been affected. The disease frequently affects young to middle-aged dogs, with a mean age around 5 years (range: 6 months to 12 years). A female predisposition has been observed, with a female:male ratio ranging from 1:8:1 to 3:1. One study (21 dogs) reported a higher incidence in males, with a male:female ratio of 1.5:1.

CLINICAL SIGNS

GME usually has an abrupt onset and an inexorably progressive course. If left untreated, it is usually fatal in a few days or weeks. Clinical signs are variable and reflect the morphologic type of GME and the site of the lesion in the neuraxis.

Disseminated (Multifocal) Form

In dogs with disseminated GME, several areas of the CNS are damaged and any combination of clinical signs reflecting lesions in multiple CNS areas is likely. Dogs are determined to have multifocal involvement if they display signs referable to at least two of the following structures of the nervous system: optic nerve, forebrain, cerebellum, brainstem, spinal cord, or meninges (Figure 2). Occasionally, fever may accompany neurologic signs.

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Focal Form

The focal form of GME causes clinical signs suggestive of a single, space-occupying lesion. If the lesion is in the forebrain, the clinical signs are usually seizures, behavior and mental status change, ataxia, circling, pacing, head pressing, and central visual impairment with normal pupillary reflexes. If the lesion involves the midbrain, mental depression and mydriasis unresponsive to light with normal vision are typical clinical signs. If the lesion involves the pons or medulla oblongata, clinical signs may include hemiparesis ranging to tetraplegia; multiple cranial nerve deficits, such as depressed palpebral, corneal, and gag reflexes; facial and trigeminal nerve paralysis; and central vestibular syndrome. If the lesion involves the cerebellum, spas-
ticity, goose-stepping gait, and intention tremor are common clinical signs.14

**Ocular Form**

Ocular GME is the least commonly reported form of GME.14 It is characterized by acute onset of visual impairment, with unilateral or bilateral dilated pupils that are unresponsive to light stimulation as a result of optic neuritis.14 Funduscopic examination may reveal a hyperemic, edematous disk (Figure 3). Vessels may be dilated, and focal hemorrhage may be present.14

**DIAGNOSTIC APPROACH**

Signalment, history, neurologic and ophthalmic examinations, and progression of the neurologic signs may be typical, but definitive diagnosis of GME requires brain biopsy or necropsy.29-32 A presumptive diagnosis of GME is usually made on the basis of compatible findings on CSF analysis and magnetic resonance imaging (MRI) or computed tomography (CT) in a dog with a characteristic signalment and suggestive clinical signs.

**Minimum Database**

A minimum database for a dog with clinical signs of CNS dysfunction should include a hemogram, serum chemistry panel, and urinalysis to help differentiate GME from metabolic encephalopathies. Survey radiographs of the thorax and abdominal ultrasonography can help diagnose malignant neoplasia.33,34 An ante-

mortem presumptive diagnosis of GME may be obtained via CSF analysis, CT or MRI, and elimination of other encephalitides, such as those produced by protozoal infections (e.g., neosporosis, toxoplasmosis) and fungal infections (e.g., blastomycosis, histoplasmosis, coccidiomycosis, cryptococcosis, aspergillosis), using serologic testing.3,35 Canine distemper viral encephalitis may be ruled out by negative results of CSF neutralizing antibody titer and urine reverse transcriptase-polymerase chain reaction assay; however, in some cases, definitive diagnosis of canine distemper encephalitis requires necropsy.

Based on the site and distribution of lesions, GME is classified as one of three morphologic forms: disseminated, focal, or ocular.

Cerebrospinal Fluid Analysis

Analysis of CSF collected from the cerebellomedullary cistern usually reveals a high protein concentration and an elevated total nucleated cell count (pleocytosis).3,4,21 A total nucleated cell count less than 3 cells/μl and a protein concentration less than 25 mg/dl are usually considered normal CSF values.6,37 In dogs with GME, the total nucleated cell count usually ranges from 50 to 900 cells/μl; however, there is marked variability (from 0 to 11,840 cells/μl), and in one study, about 10% of dogs had a normal value.

Cytology

In pleocytosis associated with GME, the cells are predominantly mononuclear, including small lymphocytes (60% to 90%), monocytes (10% to 20%), and large macrophages2 (Figure 4). Neutrophils usually make up 1% to 20% of the cell population; occasionally, they are the predominant cell type, accounting for 50% to 60%
of the cell type differential.\textsuperscript{2,21,28} Fewer lymphocytes than monocytes are reported in some cases.\textsuperscript{38} Mononuclear pleocytosis is more common in the disseminated form of GME, although in one report,\textsuperscript{21} 17\% of dogs had a predominantly neutrophilic inflammation, emphasizing the variability in CSF findings that can be encountered with GME. CSF pleocytosis can develop in dogs with focal disease if lesions are close to the ventricular system or meninges.\textsuperscript{3,21}

**Protein**

The protein concentration in the CSF may increase because of the breakdown of the blood–brain barrier with subsequent extravasation of serum protein and intrathecal antibody production.\textsuperscript{4,9} Protein levels are variable in dogs with GME, usually ranging from 40 to 400 mg/dL.\textsuperscript{2}

**Imaging**

**Magnetic Resonance Imaging**

Magnetic resonance features of GME consist of singular or multiple lesions that are hyperintense on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images and mildly to moderately hypointense on T1-weighted images, relative to adjacent brain tissue.\textsuperscript{40} (Figure 5). Meningeal enhancement may also be evident.\textsuperscript{41} If affected, optic nerves and the optic chiasm may be more identifiable than usual (Figure 6).

**Computed Tomography**

Although not as sensitive as MRI in imaging brain and meningeal lesions, CT can provide evidence of GME. Both focal and disseminated forms of GME show contrast enhancement, and the mass effect may be indirectly observed by displacement of surrounding brain tissue.\textsuperscript{42–45} Meningeal and optic nerve contrast enhancement may also be seen on high-quality images. GME lesions in the forebrain may show contrast enhancement\textsuperscript{42,43} (Figure 7), but brainstem lesions are more difficult to see due to beam-hardening artifacts from the petrous temporal bones.\textsuperscript{44,46}

**Brain Biopsy**

Although infrequently performed, brain biopsy can be a very useful diagnostic test in an animal with GME.\textsuperscript{21}
Figure 6. T1-weighted, contrast-enhanced MRI images of a 9-year-old spayed dachshund that presented with acute blindness and absent pupillary reflexes in both eyes.

CSF analysis showed increased protein concentration and lymphocytic pleocytosis. On this dorsal view, both optic disks are enlarged and hyperintense (arrows) and extend into the vitreous.

Brain biopsy can be performed via stereotactic CT-guided technique (Figure 8) or by open surgical resection.

TREATMENT PROTOCOLS AND PROGNOSIS

Various treatment protocols have been suggested for GME, including glucocorticosteroids, radiation therapy, cytosine arabinoside, procarbazine, leflunomide, and cyclosporine. Common adverse effects, median survival time, and approximate cost of therapy are summarized in Table 1.

Glucocorticosteroids

Administration of immunosuppressive doses of glucocorticosteroids, particularly prednisone (2 mg/kg/day PO) tapered with response over the following months to achieve the lowest dose possible to control signs, is the traditional primary treatment. Response is variable; clinical signs often recur quickly with tapering doses; and the prognosis for permanent recovery is poor, causing overall results to be unsatisfactory. Long-term, high-dose corticosteroid treatments predispose patients to gastrointestinal ulceration, pancreatitis, and iatrogenic hyperadrenocorticism. A median survival time for 15 dogs with focal clinical signs treated with corticosteroids alone was 41 days in one report (range: 3 to \( >1,215 \) days). In this report, a difference in survival was noticed on the basis of clinical signs: dogs with multifocal signs had a median survival time of 8 days.
Radiation Therapy

Radiation has been proposed as an alternative treatment for focal GME on the basis of the assumption that the focal form may actually be primary B-cell lymphoma of the CNS.\textsuperscript{21, 49} Although this assumption remains unproven, in one study,\textsuperscript{21} six dogs treated with radiation therapy for focal forebrain signs had significantly longer survival times (median: \textgtr 404 days) than 15 dogs with the focal form treated with steroids only (median: 41 days). In the same study, 12 of 21 dogs with multifocal signs died before any therapy could be initiated, and eight of the remaining nine dogs had such debilitating neurologic signs that they were not considered suitable candidates for radiotherapy.

Acute radiation reactions of incidentally irradiated normal tissue are self-limiting and generally well tolerated. Such reactions include epilation, otitis, and (when the eyes are included in the treatment field) conjunctivitis, keratoconjunctivitis, and corneal ulcers. Acute radiation side effects subside within 3 to 5 weeks after completion of therapy.\textsuperscript{50} An important consideration in the use of radiation therapy is delayed adverse radiation effects. Early delayed effects can occur from 2 weeks to 3 months after treatment and may be due to transient demyelination. Animals with early delayed effects may present with signs similar to those of the initial presentation, or they may be generally stuporous. These effects are infrequently encountered, are usually transient, and respond to systemic corticosteroids.\textsuperscript{50} Late delayed effects can occur 6 months to years after treatment; the most serious is brain necrosis.\textsuperscript{50, 51} The risk for late delayed effects increases with the size of each radiation fraction and with a higher total dose.

Cytosine Arabinoside

Cytosine arabinoside (cytarabine) is an antineoplastic drug with immunosuppressive effects. In conjunction with prednisone or as a sole agent, it has been reported to be effective in some dogs with GME.\textsuperscript{35, 52} Cytarabine acts on mitotically active cells by inserting itself into DNA molecules, causing premature chain termination. Due to the ability of the drug to cross the blood–brain barrier and its effect on immunosuppression, it has been theorized that cytarabine may be useful in treating GME in dogs.\textsuperscript{35} The drug is administered as a subcutaneous injection of 50 mg/m\textsuperscript{2} twice a day for 2 consecutive days.\textsuperscript{35, 53} This regimen is initially repeated every 3 weeks.\textsuperscript{15, 53} Gloves should be worn during the administra-
<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Dogs</th>
<th>Therapy</th>
<th>Side Effects</th>
<th>Median Survival Time (days)</th>
<th>Survival Range (days)</th>
<th>Dose</th>
<th>Cost of Therapy(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coates et al(^4)</td>
<td>11</td>
<td>No treatment</td>
<td>—</td>
<td>18</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Coates et al(^4,6)</td>
<td>20</td>
<td>Procarbazine ± prednisone</td>
<td>Myelosuppression, hemorrhagic gastroenteritis</td>
<td>450</td>
<td>NA</td>
<td>25–50 mg/m(^2)/day PO</td>
<td>$60–$120/mo(^c)</td>
</tr>
<tr>
<td>Munana and Lutgen(^2)</td>
<td>15</td>
<td>Prednisone</td>
<td>Gastrointestinal ulceration, pancreatitis, iatrogenic Cushing’s syndrome</td>
<td>41(^d)</td>
<td>3–1,215</td>
<td>0.25–2 mg/kg PO bid</td>
<td>$3–$7/mo</td>
</tr>
<tr>
<td>Munana and Lutgen(^2)</td>
<td>7</td>
<td>Radiation therapy + prednisone</td>
<td>Demyelination (early delayed); brain necrosis (late delayed)</td>
<td>404(^d)</td>
<td>NA</td>
<td>Total 40–49.5 Gy, divided in 2.4– to 4.0-Gy fractions</td>
<td>$4,000 for full cycle</td>
</tr>
<tr>
<td>Zarfoss et al(^3,)</td>
<td>10</td>
<td>Cytarabine ± prednisone</td>
<td>Myelosuppression</td>
<td>531</td>
<td>45–1,025</td>
<td>50 mg/m(^3)/bid SC for 2 consecutive days, repeated initially q3wk, then once q2–3mo</td>
<td>$10 for each drug per cycle/ + professional fee for the two injections per cycle</td>
</tr>
<tr>
<td>Adamo et al(^3,)</td>
<td>10</td>
<td>Cyclosporine ± corticosteroids</td>
<td>Gingival hyperplasia, hypertrichosis, excessive shedding, vomiting, diarrhea</td>
<td>930(^d)</td>
<td>60–1,290</td>
<td>Starting dose: 6 mg/kg PO bid; adjust to obtain blood trough cyclosporine level of 200–400 ng/ml</td>
<td>$60/mo(^b) + serial CSF and cyclosporine blood level</td>
</tr>
<tr>
<td>Adamo et al(^3,)</td>
<td>10</td>
<td>Cyclosporine + ketoconazole</td>
<td>Gingival hyperplasia, hypertrichosis, excessive shedding, vomiting, diarrhea</td>
<td>930(^d)</td>
<td>60–1,290</td>
<td>Cyclosporine (5 mg/kg) + ketoconazole (8 mg/kg) sid</td>
<td>$28/mo(^b) + serial CSF and cyclosporine blood level</td>
</tr>
</tbody>
</table>

NA: not available.
\(^a\)Cost of therapy is approximated for a 13.2-lb (6-kg) dog.
\(^b\)In this study, the prednisone dose was reduced or discontinued in 17 dogs.
\(^c\)Procarbazine is available as 10–80-mg capsules; the approximate price is $2 for a 10- or 20-mg capsule and $3 for a 30-mg capsule; the price increases progressively to $8 for an 80-mg capsule. The drug is also available as an aqueous solution or oil-based suspension (Diamondback Drugs, Scottsdale, AZ); the price for these formulations is the same as for the capsules.
\(^d\)As calculated by Kaplan-Meier analysis.
\(^e\)Initially in combination with prednisone (1 mg/kg q12h); after the second round of cytosine injections, prednisone therapy is reduced and, in some cases, discontinued. In this study, 8 dogs received long-term prednisone (0–1.7 mg/kg bid) treatment, and 2 dogs received tertiary immunosuppressive chemotherapeutics (procarbazine and leflunomide) in addition to the prednisone–cytarabine regimen.
\(^f\)Cytarabine is supplied as a 20 mg/ml injectable solution in 5–ml (100–mg) vials ($10/vial).
\(^g\)In this study, 7 dogs were treated with cyclosporine alone or in combination with ketoconazole, and 3 dogs were treated with cyclosporine and corticosteroids. Because of the small total number of cases in the study, all data were grouped together.
\(^h\)Cyclosporine is available in 10-, 25-, 50-, and 100-mg capsules; it may also be reformulated in capsules from oral solution (Neoral; Novartis). The approximate price is $1 for a 25-mg capsule and $6 for a 100-mg capsule. A generic formulation could cost approximately one-third to one-half of the wholesale price.
tion of this agent because it can be absorbed through the skin.\textsuperscript{35} A complete blood count (CBC) is conducted 10 to 14 days after the first course of cytarabine therapy and periodically throughout the course of treatment (usually once every 2 to 3 months).\textsuperscript{35} To increase treatment efficacy, cytarabine is usually used initially in combination with prednisone (1 mg/kg bid); after the second round of cytarabine injection, prednisone therapy is reduced.\textsuperscript{35} The most significant side effect is myelosuppression. Other side effects include vomiting, diarrhea, and hair loss.\textsuperscript{35} In one study,\textsuperscript{53} the use of cytarabine was investigated in 10 dogs with suspected GME. Eight dogs received long-term prednisone (0 to 1.7 mg/kg bid) treatment, and tertiary immunosuppressive chemotherapeutics (procarbazine and leflunomide) were added to the prednisone–cytarabine regimen in two dogs (Table 1).\textsuperscript{51} In this study, the median survival time was 531 days (range: 46 to 1,025 days), and five of the 10 dogs were alive at the time of the study’s conclusion.

**Procarbazine**

Procarbazine, an antineoplastic drug with multiple sites of action, has been used as an adjunct therapy to prednisone or as a single agent.\textsuperscript{35,54} It inhibits incorporation of small DNA precursors as well as RNA and protein synthesis. Procarbazine can also directly damage DNA through an alkylation reaction.\textsuperscript{35,55} Procarbazine is lipid soluble and crosses the blood–brain barrier.\textsuperscript{35,55} In one study,\textsuperscript{54} procarbazine and prednisone were investigated in 20 dogs with suspected GME, and the results were compared with those of an untreated control group (11 dogs) with histopathologically confirmed GME (Table 1). In this study, the prednisone dose was reduced or discontinued in 17 dogs, and the median survival time was 15 months.\textsuperscript{54} Procarbazine has been used orally at a dose of 25 to 50 mg/m\textsuperscript{2}/day.\textsuperscript{35,54} The main side effect associated with procarbazine therapy (usually associated with the higher dose) is myelosuppression (30% in one study).\textsuperscript{54} The CBC should be monitored...
once weekly for the first month, then monthly thereafter. Other side effects include hemorrhagic gastroenteritis (15% in one study), nausea, vomiting, and hepatic dysfunction.\textsuperscript{35,34} Cyclosporine

The rationale for using cyclosporine in GME arose from recent data suggesting that GME is a T-cell–mediated, organ-specific, autoimmune disease.\textsuperscript{35} Cyclosporine has profound immunosuppressive properties and suppresses T-cell–mediated immune responses through inhibition of synthesis of interleukin (IL)-2 and other cytokines.\textsuperscript{56,57} Cyclosporine also suppresses activation of macrophages and monocytes and the production of other cytokines (IL-3, IL-4, IL-5, tumor necrosis factor-\(\alpha\), and \(\gamma\) interferon), thus indirectly inhibiting antigen presentation by class I and II major histocompatibility complex, mononuclear cell function, mast cell and eosinophil production, and growth and differentiation of B cells.\textsuperscript{58} The blood–brain barrier permeability of cyclosporine is poor; however, because GME is a perivascular disease and the blood–brain barrier is disrupted during inflammation, therapeutic high blood concentrations (>3,000 ng/ml) are maintained.\textsuperscript{51,52}

In a retrospective study\textsuperscript{63} of 10 dogs with presumptive GME treated with cyclosporine alone or in combination with corticosteroids and/or ketoconazole, cyclosporine either alone or in combination with ketoconazole was found to be effective (Table 1). In this study, no significant abnormalities were detected on serial CBC and serum chemistry panel in any dog. Serial CSF analysis showed a marked improvement in inflammation in all dogs (Figure 9). Side effects of cyclosporine therapy at the therapeutic dose included excessive shedding, gingival hyperplasia, and hypertrichosis (Figure 10); signs of overdose included gas-
trointestinal signs (e.g., vomiting, diarrhea, anorexia). The overall median survival time for all dogs in the study was 930 days (range: 60 to >1,290 days), and five dogs were still alive at the time of the study’s conclusion. Based on the results of this study, we recommend cyclosporine as monotherapy at a starting dose of 6 mg/kg PO q12h, with a blood cyclosporine trough level target of 200 to 400 ng/ml. The blood cyclosporine trough level should be tested after 5 to 7 days and reevaluated together with CSF after 1 month and every 4 or 6 months thereafter, or any time the patient neurologically deteriorates.

**Cyclosporine and Ketoconazole**

If cyclosporine monotherapy is cost prohibitive, coadministration of cyclosporine and ketoconazole has been suggested. Ketoconazole has been shown to decrease the systemic clearance of cyclosporine in dogs through inhibition of hepatic cytochrome P450 3A microsomal enzymes. We found the coadministration of ketoconazole and cyclosporine clinically effective using a starting dose of 5 mg/kg PO q24h of cyclosporine and 8 mg/kg of ketoconazole. The target trough blood cyclosporine level and serial monitoring are similar to the protocol described for cyclosporine used as monotherapy. This combined treatment has the advantage of being given only once daily. No significant side effects from ketoconazole were observed after 2 years in one dog and 14 months in two other dogs after receiving this combined therapy. This combination protocol is not recommended if liver enzyme levels are elevated or any other medical condition that might exacerbate liver insufficiency is present at the time of diagnosis or during treatment.

**Leflunomide**

Leflunomide is an immunomodulator used in a preliminary clinical study in three dogs with inflammatory or malacic brain lesions of unknown cause. In this study, leflunomide replaced an effective treatment with immunosuppressive doses of glucocorticosteroids, which had to be discontinued due to the onset of iatrogenic Cushing’s syndrome. This study indicated a favorable response in all three dogs that survived more than 12 months after starting leflunomide therapy.

**Surgery**

Surgical removal of brain GME lesions has also been reported. Surgical intervention is not a typical treatment modality for inflammatory or infectious brain disorders; however, it is suggested that the mass removal and the decrease in intracranial pressure afforded by craniotomy may benefit the patient. Surgical removal may also enable histologic confirmation of GME, which then may be followed by the most appropriate medical treatment.

**CONCLUSION**

Untreated GME is invariably fatal, and the disseminated form carries the worst prognosis. Radiation therapy combined with corticosteroids has been shown to significantly increase survival time in dogs with the focal form presenting with forebrain signs. Leflunomide therapy is promising; however, prospective evaluations of a larger treatment group with a longer follow-up to substantiate these initial findings is warranted. Cytarabine, procarbazine, and cyclosporine treatment for GME may result in better long-term outcomes than those previously reported with glucocorticosteroid treatment alone.

**ACKNOWLEDGMENTS**

The authors thank Drs. R. Carter, A. Armien, and R. Dickinson for providing the images of the fundus of the eye, the histopathology of brain section, and the cytology of CSF, respectively.

**REFERENCES**

5. **Definitive diagnosis of GME requires**
   a. viral isolation.
   b. detection of a histopathologic lesion on brain biopsy or necropsy.
   c. detection of inclusion bodies in lymphocytes in the CSF.
   d. detection of unidentified protozoa in macrophages in the CSF.

6. **CSF analysis in dogs with GME is characterized by**
   a. high total protein concentration and elevated total nucleated cell count with a predominance of
      a. macrophages.  c. small lymphocytes.
      b. neutrophils.  d. eosinophils.

7. **Characteristic MRI features of GME consist of**
   a. single or multiple lesions, primarily involving the white matter, that are hyperintense on T2-weighted and FLAIR images and hypointense on T1-weighted images.
   b. single or multiple lesions, primarily involving the white matter, that are hypointense on T2-weighted and FLAIR images and hypointense on T1-weighted images.
   c. single or multiple lesions, primarily involving the white matter, that are hyperintense on T2-weighted and FLAIR images and hyperintense on T1-weighted images.
   d. No characteristic MRI features have been described for GME.

8. **The following new alternative therapies have been proposed for GME:**
   a. cytarabine, procarbazine, radiation therapy, leflunomide, and cyclosporine.
   b. cytarabine, amphotericin B, radiation therapy, and cyclosporine.
   c. cytarabine, cyclophosphamide, procarbazine, and radiation therapy.
   d. cytarabine, itraconazole, radiation therapy, and cyclosporine.

9. ________ is the most significant side effect of cytarabine when used in the treatment of GME.
   a. Myelosuppression  c. Renal failure
   b. Papillomatosis  d. Hepatic failure

10. **The most common side effects of cyclosporine in the treatment of GME are**
    a. gingival hyperplasia and hypertrichosis.
    b. lymphopenia and anemia.
    c. hepatic and renal failure.
    d. gingival hyperplasia and hepatic failure.