Skipping Into the Unknown

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Introduction:

Inflammatory brain disease is divided into two broad categories: infectious and non-infectious. Infectious causes of inflammatory brain disease range from protozoal, viral, and rickettsia infections with bacterial causes occurring less frequently. Non-infectious causes are generally thought to be immune-mediated in etiology and recently have been given the umbrella term of meningoencephalomyelitis of unknown origin/etiology, or MUO/MUE.

MUO is broken down into two categories: necrotizing encephalitis (NE) and granulomatous meningoencephalomyelitis (GME).[1,2,4,9] NE has been further subcategorized into necrotizing meningoencephalitis (NME) and necrotizing leukoencephalitis (NLE). All three forms of MUO have a similar clinical presentation and differentiation between the categories can only be made via histopathology. Breed predilections exist for some of the subtypes with pugs and Maltese dogs being over-represented for NME and Yorkshire Terries for NLE. [1,2,9] GME is thought to be the more common presentation of MUO and will be the main focus of this paper.

Although the true prevalence of MUO is unknown, some studies have reported the incidence of MUO anywhere from 5% to 25% of all central nervous system (CNS) disorders in dogs.[9] While MUO can affect any breed, the classical presentation is seen in young to middle-aged small or toy breed dogs presenting with focal or multifocal neurological deficits.[1,2,4,6] Clinical signs may include seizures, altered mentation, vestibular dysfunction, paresis, ataxia, and/or spinal hyperpathia.

A definitive diagnosis of MUO generally cannot be confirmed antemortem as brain biopsies are not commonly performed in veterinary medicine and is a diagnosis of exclusion based on the clinical picture, advanced imaging findings, cerebrospinal fluid (CSF) analysis, and

negative infectious disease testing. Proposed guidelines for diagnosing MUO include: dogs older than 6 months of age with evidence of multifocal neurolocalization and magnetic resonance imaging (MRI) T2 images showing hyperintensity lesions. Additionally, CSF analysis should demonstrate >50% mononuclear cells, and all infectious diseases should be ruled-out. [3] The gold standard and definitive diagnosis of MUO can only be made with histopathology of the brain, most commonly performed at necropsy. [1,2,4]

Because MUO is an auto-immune disease, immunosuppression is the treatment of choice with prednisone considered the mainstay of therapy with extreme variance in median survival times when used as a monotherapy. Recent advancements in therapy with additional immunosuppressants such as cytosine arabinoside have been shown to extend the median survival time. [1,5] Additional immunosuppressive medications used include cyclosporine, azathioprine, procarbazine, and lomustic.

History and Presentation:

A 5-year-old male neutered chihuahua presented to Mississippi State College of Veterinary Medicine emergency service on June 16th, 2021 for further evaluation of a month-long history of progressive neurologic dysfunction. The patient was initially evaluated by his primary care veterinarian for a recent onset of aggressive behavior, trembling, and suspected spinal pain. At that time, the patient was prescribed an unknown pain medication and unknown muscle relaxer. Two weeks after the initial visit, the patient re-presented to his primary veterinarian for follow up because his neurologic symptoms had not improved. The patient was subsequently prescribed a two week tapering dose of prednisone, which initially resulted in improvement in his clinical signs. However, upon cessation of the prednisone, his clinical signs returned.

Upon presentation to MSU-CVM, the patient weighed 4.5 kg with a body condition score of 5/9. The patient had normal vitals with a temperature of 100.9 F, pulse heart rate of 112 beats per minute, and a respiration rate of 40 breaths per minute. His hydration status and perfusion appeared normal indicated by pink, moist mucous membranes and a capillary refill time of less than 2 seconds. Cardiothoracic auscultation was unremarkable. His eyes were clear bilaterally of any discharge, but corneal scarring was noted OS as well as a lens abnormality OS. His abdomen was soft and non-painful while all peripheral lymph nodes were soft and symmetrical. No free fluid was detected on AFAST or TFAST and his remaining point-of-care diagnostics, were unremarkable.

On neurologic exam the patient was dull and frequently squinting his eyes and holding them shut. He was ambulatory with a vestibular ataxia, and would fall to the right but no true circling was present. A moderate right sided head tilt was also appreciated. Cranial nerve examination showed a vertical nystagmus and ventromedial strabismus OS. Direct and indirect pupillary light reaction (PLR) OS was could not be assessed due to the corneal abnormalities previously described in his physical exam, but his direct PLR OD was intact. Proprioceptive placement was absent in the left thoracic and pelvic limbs, but normal in the right limbs. His flexor withdrawal reflexes and segmental spinal reflexes were intact in all limbs. No pain was elicited upon spinal palpation.

The patient was admitted to the hospital for stabilization, evaluation by the Neurology/Neurosurgery Service and further diagnostic work-up. He was started on maintenance fluids, maropitant citrate, and pantoprazole. Once stabilized, the patient was transferred to the Neurology/Neurosurgery Service on June 17th, 2021.

Diagnostic Approach:

The emergency service diagnostics consisted of a complete blood count (CBC) and chemistry panel. CBC revealed a mild leukocytosis (WBC 18.08/ul [reference range: 5.0 – 14.2]), characterized by a mature neutrophilia (Neut % 97.1 [reference range: 42.0 – 84.0]); (Neu# 17.54/ul [reference range: 3.1 – 11.8]) and lymphopenia (Lymph % 1.8 [reference range: 10.1 - 48.0]); (Lymph# 0.32/ul [reference range: 1.1 – 4.8]). These findings were consistent with a stress response – not a systemic infection or inflammatory response. No clinically significant abnormalities were present on the chemistry panel.

Upon transferring to the neurology department, a brain MRI with contrast and cerebrospinal fluid analysis were performed. MRI findings showed an ill-defined T2 hyperintense, T1 FLAIR hypointense region within the mid to caudal aspect of the pons that extended into the cranial aspect of the medulla oblongata. Similar intensity was also seen in the C1-C2 section of the spinal canal. Dilation of the lateral and third ventricles was present and mild herniation of the cerebellum into the foramen magnum was noted. Based on the hyperintensity findings within the pons and medulla, a primary consideration was given to an infectious or inflammatory process, with further testing needed to rule-out an infectious cause. Neoplasia also could not be ruled-out at this time. The findings within the spinal canal were likely due to the same etiology as found in the pons and medulla, but syrinx formation could was also considered.

Following his MRI, a cerebromedullary cistern (the atlanto-occipital space) CSF tap was performed under general anesthesia. Results from the CSF revealed a severe lymphocytic pleocytosis. The cell differential count showed 92% lymphocytes and 8% large mononuclear cells. Nucleated cell count was severely elevated at 4221/ul (reference range: < 5cells/ul) and

protein levels were also elevated at 119/ul (reference range: <25 mg/dl)[11]. No infectious agents or neoplastic cells were detected.

Given the clinical picture as well as the MRI and CSF findings, inflammatory brain disease was the top differential; however, infectious vs non-infectious could not be completely eliminated without additional testing. Possible differentials for a severe lymphocytic pleocytosis include toxoplasmosis, rabies, distemper and MUO.

Pathophysiology:

MUO is classified as an idiopathic inflammatory CNS disease that is characterized by infiltration of mononuclear cells (lymphocytes and macrophages).[1,2,4,6] While the exact underlying pathophysiology remains unknown, recent studies show evidence that MUO is a Type-IV delayed hypersensitivity reaction.[1,6,8] Previously, it was thought the CNS immune system was isolated from the peripheral immune system, but recent studies have shown there is communication between the two as peripheral immune cells have been found to cross the blood brain barrier. This can stimulate the resident microglia (macrophages of the CNS) to become active, resulting in an immune response with subsequent neurodegeneration.[9] Thus, this triggers the inflammatory cascade, activating the T cells and microglia, which play a major role in the inflammatory process within the CNS. Microglia express major histocompatibility complex class two (MHC II), which allows them to become antigen presenting cells. Cytokines such as IL-4 and IFN-y activate the innate immune system within the CNS, causing the microglia to express MHC and activate pro-inflammatory cytokines such as IL-1b and TNF-a.[4,7,8] T-cells within the CNS are also known to express the CD3 antigen, which has commonly been found in brain histopathology of dogs with MUO.[4,8] Histopathologic studies comparing canine brains with MUO and normal canine brains using immunohistochemistry have demonstrated that majority of

dogs with MUO had marked CD3 antigen present on T-cells, while macrophages near lesions were all found to express MHC II antigen compared to the normal brains that demonstrated no T cells or B-cells.[7] The same study found that B-cells were not highly present in any of the MUO brains, further suggesting that T-cells and a delayed hypersensitivity is the cause. Human CNS diseases such as Creutz-feldt-Jakob disease and multiple sclerosis have been known to express T-cells and MHC class II antigen as well, further supporting an immune mediated cause of inflammation in canine MUO. [7,8]

Treatment:

Given the clinical picture, blood work, MRI findings, CSF analysis and previous response to steroids, the patient met the diagnosis criteria of MUO. In an ideal world, immunosuppression would not be initiated until negative infectious disease test results were obtained; however, given the patient's rapid decline, severity of clinical signs, and previous response to steroids, the owner elected to move forward with immediate immunosuppression. The patient was started on a 12 hour constant rate infusion of cytosine arabinoside (Cytosar) at 200 mg/m2 and an immunosuppressive dose of dexamethasone SP (0.2 mg/kg IV q 24 hr).

Cytosar is an intercalating chemotherapeutic agent used treat CNS lymphoma that is also (at a lower dose) an adjunctive immunosuppressive medication for patients with MUO[5,6] The previous recommendation for Cytosar administration is to give 200 mg/m2 (divided into 4 doses) subcutaneously every three weeks then every four to six weeks based on the patient's tolerance and response to therapy. Recent studies have shown the possibility that giving Cytosar in a constant rate infusion for the first dose may increase survival rate. The study compared groups given the standard subcutaneous dose to a CRI group. 44% of patients in the subcutaneous group survived to the 3-month interval compared to 90% of the CRI group. It was then noted that all

dogs, regardless of which group, who survived to 3 months were still alive at the 12-month interval.[9] Thus, administering Cytosar as a CRI may improve short term survival time based on achieving higher plasma levels when given intravenously compared to subcutaneously.

In addition to Cytosar and dexamethasone SP, the patient was started on pantoprazole (1 mg/kg IV q 12) to protect from potential gastrointestinal ulceration and anti-nausea medications including maropitant citrate and ondansetron. The patient's Cytosar infusion ended on June 19th and the patient was monitored the following day for any adverse effects of the chemotherapy and response to treatment.

Case Outcome:

The diagnosis of MUO was made based on signalment, multifocal neurolocalization, the T2 hyperintense lesions detected on MRI, and severe mononuclear pleocytosis. Within 24 hours of receiving Cytosar, the patient become more alert, his vestibular ataxia improved, and his nystagmus and proprioceptive deficits resolved.

The patient was discharged on June 21st with oral prednisone (2 mg/kg PO q 24 hr) and omeprazole(1 mg/kg PO q 12 hr). The client was instructed to monitor for worsening of neurologic signs such as altered mentation, ataxia, paresis, and/or seizures. They were instructed to have a CBC checked with their primary veterinarian to monitor for any bone marrow suppression that can occur with Cytosar therapy. Interaction with other dogs, dog parks or kennels, were discouraged for risk of secondary infection. Additionally, the owner and primary care veterinarian were cautioned against administration of vaccinations apart from rabies as this could result in a relapse of his disease. The patient returned on July 16th and August 3rd for

rechecks and additional Cytosar therapy. At each recheck, the patient's neurologic signs had resolved and was doing well at home.

Discussion:

Based on the patient's presenting signs of vestibular ataxia, altered mentation, proprioceptive deficits, and ventral nystagmus, a neurolocalization to the brainstem was considered most likely. Differential diagnoses for such this presentation should consist of infectious or inflammatory etiology, toxins, or neoplasia. A gold-standard diagnostic work-up should include minimum database, infectious disease panels (*Toxoplasma gondii* /*Neospora caninum,* Rickettsial diseases, canine distemper virus, various fungal organisms), brain MRI, and CSF analysis. Based on results and rule outs, a diagnosis of MUO can be made.

Criteria for diagnosing MUO typically consists of young to middle aged small breed dogs present that present with focal or multifocal CNS deficits, T2 hyperintense lesions on MRI with variable patterns of contrast enhancement, >50% mononuclear pleocytosis on CSF analysis and absence of antibodies for *Toxoplasmosa gondii/Neospora caninum*, and other infectious agents depending on index of suspicion and geographic location.[8]

As previously mentioned, this patient did not undergo complete infectious disease testing as previous steroid administration was previously performed and would have likely caused a drastic decline in the patient's status had infectious disease been the cause. He was also severely affected and the risk of not immediately initiating immunosuppressive therapy greatly outweighed the risk of an underlying infectious disease.

Generally, MUO has a poor prognosis and if left untreated is invariably fatal. Certain factors such as younger age at diagnosis, focal lesions compared to multifocal, and shorter time

from clinical onset to treatment have been associated with a better prognosis. [6,9] Multi focal lesions and seizures have been associated with worse prognosis and the response to treatment is highly variable. [1,2,6] Most dogs diagnosed with MUO will succumb to the disease within the first three months, and multiple studies have showed that anywhere from 15% to 56% of patients die within the first week. [3,5,9,10] Thus, the need for rapid and aggressive immunosuppression therapy is required.

When a patient is diagnosed with MUO, lifelong immunosuppressive therapy is required. The prednisone is gradually tapered over many month (usually 6-8 months) and an additional immunosuppressive medication, such as Cytosar, cyclosporine, or procarbazine will be required for the remainder of their life. While the goal is to ultimately eliminate corticosteroids completely and maintain the animal on an alternative immunosuppressant alone, many dogs will require very low doses of steroids in order to stay in remission, The increased chance of secondary infection can significantly alter the patient's and owner's lifestyle and is an important consideration; they should not be around new dogs, visit the park or be boarded. Additionally, extreme caution should be exercised when administering as these have been known to trigger a immune response and relapse of disease. Thus only necessary vaccines (e.g. rabies virus) should be administered.

In conclusion, MUO is a severe immune-mediated brain disease commonly seen in dogs that is fatal if left untreated. An extensive diagnostic work-up is needed for proper diagnosis and life-long immunosuppressive therapy is often required in order to maintain remission of the disease. Prompt diagnosis and treatment is essential for survival, but prognosis is still variable despite rapid intervention.

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