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Diffuse Leptomeningeal Malignant Histiocytosis in the Brain and Spinal Cord of a Tibetan Terrier

K. UCHIDA, M. MOROZUMI, R. YAMAGUCHI, AND S. TATEYAMA

Abstract. An 8-year-old male Tibetan Terrier showed prolonged astasia, complete paralysis, ticlike signs, and seizure and died 2 months after the onset of symptoms. Histopathologically, there was moderate to severe infiltration of pleomorphic histiocytic mononuclear cells bilaterally in the basiarachnoidal and ventricular areas of the brain. The spinal dura mater, arachnoidal space, and leptomeninges were also affected by infiltrative proliferation of these mononuclear cells. The infiltrating cells had the morphologic characteristics of histiocytes but exhibited moderate pleomorphism and atypia, with abundant mitotic figures. With immunohistochemistry and lectin histochemistry, most of the infiltrating cells were positive for lysozyme and lectin RCA-1 and negative for glial fibrillary acid protein, suggesting that they were of monocytic/histiocytic-origin. Positive proliferating cell nuclear antigen immunostaining demonstrated that most nuclei of the histiocytic cells were in the S phase of the cell cycle, consistent with a proliferating population of cells. Based on these findings, the case was diagnosed as diffuse leptomeningeal malignant histiocytosis.

Key words: Brain; dogs; histiocytosis.

Malignant histiocytosis is a well-documented neoplastic disorder characterized by proliferation or infiltration of atypical histiocytes in multiple organs, especially the lungs, subcutaneous tissues, spleen, and lymph nodes. In dogs, malignant histiocytosis has been primarily recognized in Bernese Mountain Dogs[10,11] but also has been confirmed in several other breeds.[1,3,7] Involvement of the central nervous system (CNS) is considered to be one of the systemic lesions associated with this disorder. Malignant histiocytosis with multiple organ involvement, including the lumber epidural space, was reported in a golden retriever[3]. Although there have been a few reports of primary histiocytosis in the human CNS,[13] the condition is considered to be extremely unusual. Recently, primary malignant histiocytosis in the brain of a Miniature Schnauzer was reported.[1] The right parieto occipital lobe had a poorly demarcated mass formed from a proliferation of neoplastic histiocytes. The meningeal infiltrates of the histiocytes were described as limited to areas adjacent to the intraparenchymal tumor mass.[1] Here, we describe the morphologic features of widely disseminated leptomeningeal histiocytosis within the brain and spinal cord of a Tibetan Terrier and discuss the possible differential diagnoses.

On 5 August 1998, an 8-year-old male Tibetan Terrier was admitted to a private animal hospital with incomplete hind limb paralysis. Clinical examination revealed cerebrospinal fluid (CSF) abnormalities, 152 cells/μl, composed of mononuclear cells and neutrophils (1 : 1), and a total protein of 95 mg/dl, suggesting meningitis or myelitis. At that time, no atypical cells were seen in the CSF. The antibody titer against canine distemper was ×20. Corticosteroid and antibiotic treatment was given, but the clinical signs progressed. On 25 August, the dog developed astasia and complete paralysis of the fore- and hind-limbs. On 7 October, the dog exhibited ticlike signs and seizures and developed keratitis in the right eye. The dog died on 8 October and was necropsied by the veterinary clinician. The brain, spinal cord (C1 to T10), lung, liver, spleen, kidney, small intestines, and pancreas and the CSF samples, which had been stored at 4 C, were given to the Department of Veterinary Pathology, Miyazaki University. Gross examination performed on tissue samples fixed in 10% formalin revealed severe diffuse discoloration of the spinal white matter (C1 to T10, Fig. 1). The CSF sample was submitted for microbacterial examination, although no bacteria were cultured.

Paraffin-embedded sections (4–6 μm thick) were stained with hematoxylin and eosin (HE). Selected brain and spinal cord sections were also stained with Grocott's methenamine silver impregnation, Luxol fast blue, periodic acid–Schiff (PAS), Gram's stain, and acid-fast stain. Immunohistochemistry was performed by the Envision polymer method (Dako Japan, Kyoto, Japan). The primary antibodies used were rabbit antibodies against glial fibrillary acidic protein (GFAP, prediluted; Dako Japan), CD3 (1 : 40, Dako Japan), lysozyme (prediluted, Dako Japan), and alpha-1-antitrypsin (1 : 200, Dako Japan) and mouse monoclonal antibodies against the N-protein of canine distemper virus (CDV; VMRD, Pullman, WA) and proliferating cell nuclear antigen (PCNA, prediluted; Dako Japan). Lectin histochemistry using *Ricinus communis* agglutinin-1 (RCA-1, 1 : 400; E-Y Laboratories, San Mateo, CA) and immunohistochemistry for canine IgG using a biotin-labeled sheep antiserum against canine IgG (1 : 100, American Qualex, San Clemente, CA) were performed using the avidin–biotin peroxidase complex method (Vector Laboratories, Burlingame, CA). The reaction products were visualized with 3,3′-diaminobenzidine (Sigma, San Ramon, CA).

The histologic lesions were characterized by marked infiltration of pleomorphic histiocytic cells. These changes were distributed bilaterally within the basiarachnoidal and ventricular areas of the brain. Thalamus and hippocampus were the most severely affected regions of the brain. A large number of cells had accumulated in the adjacent leptomeninges around the tunica adventitia and sometimes within the tunica media of the lesional arterioles. In the hippocampus, there was a large focus of histiocytic mononuclear cells with massive central necrosis and hemorrhage bilaterally. Most of the cells had abundant eosinophilic to clear cyto-

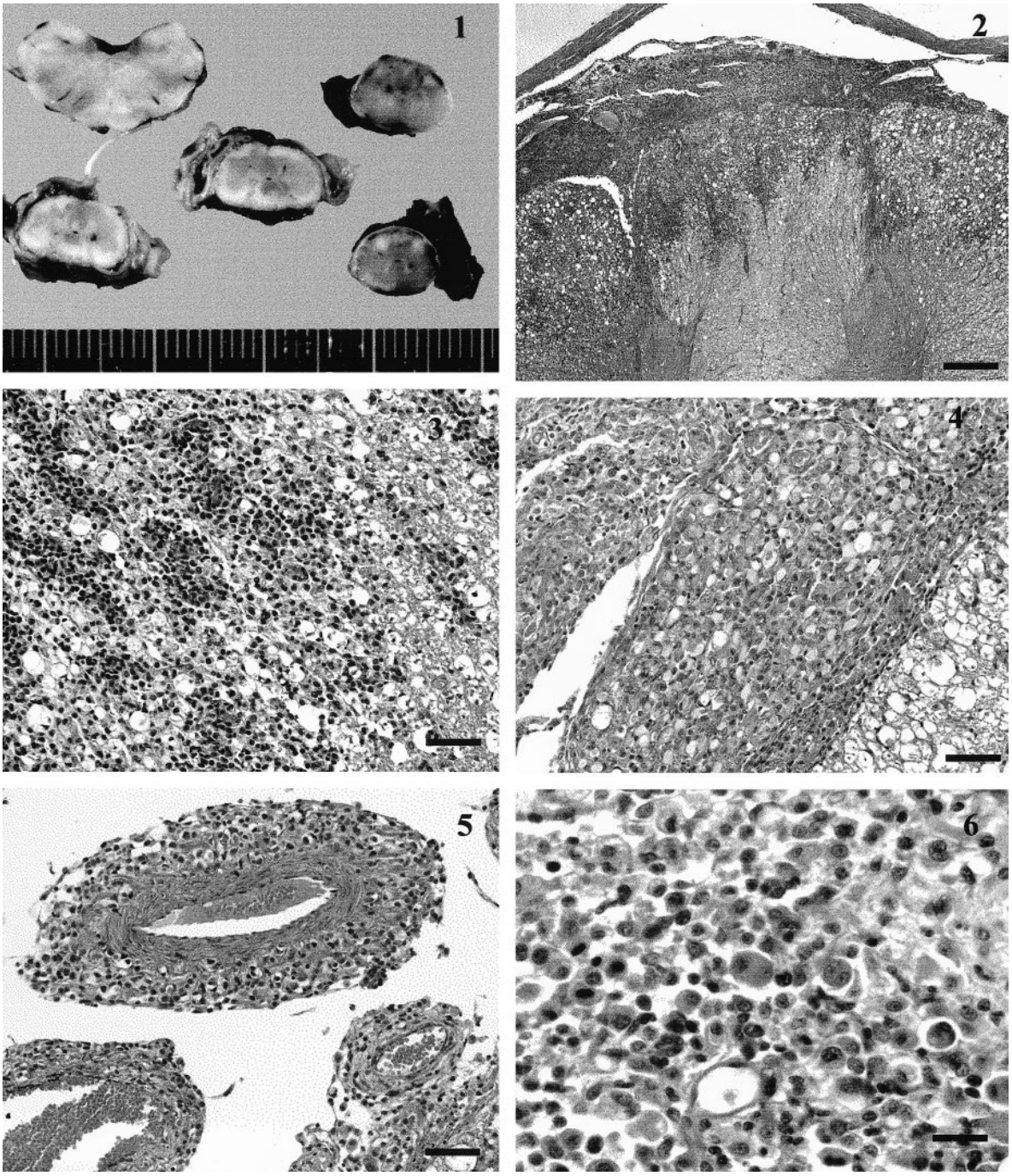

Fig. 1. Medulla oblongata, segmental sections of spinal cord (cervical and thoracic regions); dog. Note diffuse discoloration of the spinal white matter and moderate to mild thickening of the spinal meninges.

Fig. 2. Spinal cord (cervical region); dog. Note severe thickening of the arachnoidal space and leptomeninges and marked cellular infiltration in these areas and in the spinal white matter. HE. Bar = 200 μm.

Fig. 3. Spinal cord (cervical region); dog. Note diffuse cellular infiltration in the spinal white matter. HE. Bar = 100 μm.

Fig. 4. Spinal cord (cervical region); dog. Note diffuse cellular infiltration in the spinal nerve root. HE. Bar = 100 μm.

Fig. 5. Spinal cord (cervical region); dog. There is accumulation of histiocytic cells around the blood vessel in the spinal leptomeninges. HE. Bar = 100 μm.

plasm and showed obvious phagocytosis. Cellular atypia was mild, and mitotic figures were commonly observed (1–3 mitoses/high-power field). In the pyramidal layer of the hippocampus, there were many shrunken ischemic neurons accompanied by vacuolar changes in the surrounding neuropil. Except for the frontal lobe, almost all parts of the cerebral and cerebellar cortex were intact. In the spinal cord (C1 to T10), more severe lesions were observed. The dura mater, arachnoidal space, and leptomeninges were heavily infiltrated with mononuclear cells (Fig. 2). In the spinal white matter, the cells exhibited the characteristic morphology of foamy macrophages, containing abundant degenerating myelin sheaths or lipid granules in their cytoplasm (Fig. 3). The histiocytic cells diffusely infiltrated the adjacent spinal nerve roots (Fig. 4). Furthermore, these cells were commonly accumulated around the tunica adventitia of the leptomeningial arterioles (Fig. 5) and sometimes invaded the tunica media. These infiltrating cells displayed moderate pleomorphism and atypia with abundant mitotic figures (3–5 mitoses/high-power field). Although the cells exhibited morphologic variations, most were typical mononuclear histiocytes with clear to eosinophilic cytoplasm; some mimicked epithelioid cells characterized as polygonal binucleated or polynucleated giant cells with abundant eosinophilic cytoplasm (Fig. 6). Staining with Grocott's methenamine silver, PAS, and Gram's or acid-fast stain revealed no bacteria or fungi in the lesions. Antigens for CDV were not detected within the CNS. Immunohistochemically, most of the proliferating mononuclear cells in the CNS were positive for lysozyme. There were a very small number of canine IgG- or CD3-positive cells, suggesting that cells of the lymphocyte lineage were also in the lesions. Lectin histochemistry for RCA-1 demonstrated that almost all of the infiltrating and microglial cells within the CNS lesions showed a positive reaction. The results of immunohistochemistry and lectin staining suggested that the predominant cells were of monocytic/histiocytic origin. Positive PCNA immunostaining showed that most of the nuclei of the histiocytes were in the S phase of the cell cycle, consistent with a proliferating population of cells. In the visceral organs apart from the CNS, apparent proliferation or infiltration of histiocytes was not confirmed, and moderate lymphoid follicular hyperplasia was seen in the spleen.

Based on all these findings, the diagnosis for this case was diffuse leptomeningeal malignant histiocytosis involving the brain, spinal cord, and spinal nerve roots. Proliferation of histiocytes was considered to be a neoplastic change rather than an inflammatory reaction because of the remarkable mitotic activity, common PCNA nuclear staining, mild to moderate cellular atypia, and pleomorphism of the infiltrating cells. In addition, negative results for the detection of infectious agents by CSF culture, special stains for bacteria, and antibody titer and immunohistochemistry against CDV support this diagnosis. Although the neoplastic proliferation of histiocytes is termed malignant histiocytosis or histiocytic sarcoma in humans and animals, leptomeningeal neoplastic histiocytosis seems to be a better histologic diagnosis for this dog. It was uncertain whether the diagnostic term ''malignant histiocytosis'' was adequate, because the distribution pattern of the lesions was quite different from that seen in the previous canine CNS malignant histiocytosis.[1] In this dog, tumor mass formation was not found (unlike in a previous case), and the proliferation of histiocytes was widespread within the spinal meninges and basiarachnoidal spaces of the brain. If the term malignant histiocytosis simply means the neoplastic proliferation of histiocytes regardless of the distribution or mass formation, we should use this diagnostic term for this case. In humans, primary or secondary malignant histiocytosis in the brain commonly spreads diffusely within the meningeal or ventricular areas.[5,13] In addition, malignant histiocytosis of the CNS in dogs has been described as focal and diffuse lesions in the *WHO International Histopathological Classification of Tumors in Domestic Animals*.[8] Therefore, the pathologic features seen in this dog are quite typical for malignant histiocytosis of the CNS.

Among the various inflammatory CNS disorders of dogs, granulomatous meningoencephalitis (GME) must be considered in the differential diagnosis. The pathologic features have been well demonstrated, but the pathogenesis and causes of GME remain unclear.[12] The disease is characterized by unique inflammatory cell accumulation involving lymphocytes, plasma cells, and histiocytes. Leptomeningeal involvement is common, and the lesions occur predominantly in the white matter, particularly the cerebellomedullary regions.[12] In addition, the inflammatory lesions appear multifocally around the blood vessels within the brain parenchyma. In this dog, the lesions were distributed diffusely in the leptomeninges, spinal white matter, and hippocampus, and the infiltrates consisted mainly of histiocytes. Previously, canine GME was sometimes included under the category of CNS reticulosis and the diagnostic term reticulosis was briefly classified under neoplastic and inflammatory reticulosis.[12] The neoplastic form of reticulosis is characterized by histiocytic dominant infiltrates with high mitotic activity. Because the concept of neoplastic reticulosis is the neoplastic infiltrative proliferation of reticulohistiocytes in the CNS, the disease might be considered equivalent to malignant histiocytosis.

Lymphomatoid granulomatosis commonly appears in the thorax and sometimes involves the CNS in humans.[4,6,14] This neoplastic proliferative disease is characterized by the vascular spread of pleomorphic round cells. These tumor cells commonly accumulate within the tunica media of the lesional vessels, and most immunohistochemical examinations

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Fig. 6. Spinal cord (cervical region); dog. Histiocytic cells exhibit morphologic variation around the blood vessel in the spinal leptomeninges. Most cells were typical mononuclear histiocytic cells with clear to eosinophilic cytoplasm, and some mimicked epithelioid cells characterized as polygonal binucleated giant cells with abundant eosinophilic cytoplasm. HE. Bar = 20 μm.

have revealed that the cells originate from lymphocytes. In this dog, the neoplastic round cells frequently accumulated around the tunica adventitia of the arterioles and CD3- and canine IgG-positive cells were rare, suggesting a nonlymphocytic origin. These findings indicate that the disease in this dog was not lymphomatoid granulomatosis. In addition, the lymphoproliferative disorders reported in several dogs[2,9] have included no mention of CNS involvement. Therefore, lymphomatoid granulomatosis was excluded from the differential diagnoses for this case.

The unique CNS lesions in this dog were characterized by diffuse proliferation of neoplastic histiocytes. It remains unclear which diagnostic term should be applied for such conditions in the canine CNS, but we suggest leptomeningeal malignant histiocytosis in this case. To establish adequate classification of such histiocytic tumors in the CNS, a number of further case studies will be needed.

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Request reprints from Dr. K. Uchida, Department of Veterinary Pathology, Faculty of Agriculture, Miyazaki University, Miyazaki 889-2155 (Japan). E-mail: a0d423u@cc.miyazaki-u.ac.jp.