NOTE *Pathology*

Ganglioglioma in the Thalamus of a Puppy

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ABSTRACT. A solitary brain mass of a 4-month-old miniature dachshund showing seizure-like neurological signs was examined histopathologically. At necropsy a white tumor mass, replacing the thalamus, approximately 1.5 cm in diameter, was found. There was cystic space filled with yellowish pale fluid in the central area of the tumor mass. Histopathological examination revealed that the mass consisted of irregularly arranged well-differentiated neuronal and glial cells, and multifocal mineral deposits. The neuronal cells had a large clear nucleus and various amount of Nissl substances in the cytoplasm. Some neural cells were bi-nucleated. Neither mitotic figures nor proliferating cell nuclear antigen (PCNA)-positive nuclei was found in the neuronal cells. Immunostaining for glial fibrillary acidic protein (GFAP) revealed diffuse proliferation of GFAP-positive glial cells and their processes, while these glial cells did not show apparent cellular atypism, mitotic activity, or PCNA-immunoreactivity. Accordingly, the present tumor was diagnosed as ganglioglioma, and hamartomatous histogenesis might be possible.

KEY WORDS: canine, ganglioglioma.

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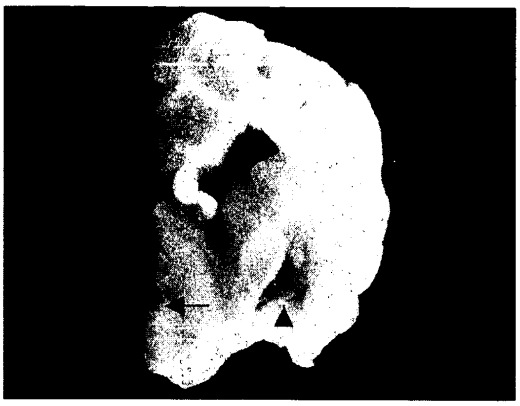
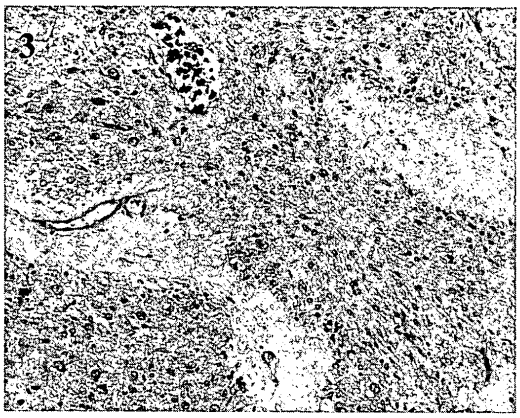
Benign tumors in the central nervous system showing neuronal differentiation are categorized to be gangliocytomas (ganglioneuromas) or gangliogliomas [3, 5, 8, 10]. Although these neuronal tumors are considered to be rare in nonhuman animal species [3], there are a few reports in dogs, horse, calf [2, 4, 7–10], and some rodents [1, 6]. Majority of human ganglioneuromas and gangliogliomas, occurs in children and young adults, and the most frequent site of the tumor is the cerebrum, including the temporal and frontal lobes [5, 8]. Histological differences between ganglioneuromas and gangliogliomas are not necessarily clear. Ganglioneuromas are characterized by almost uniform proliferation of well-differentiated neuronal cells with a certain degree of cellular atypism. On the other hands, gangliogliomas include proliferation of neoplastic or reactive glial cells in addition to such neuronal cells. This paper describes clinical and histopathological features of ganglioglioma in a 4-month-old miniature dachshund.

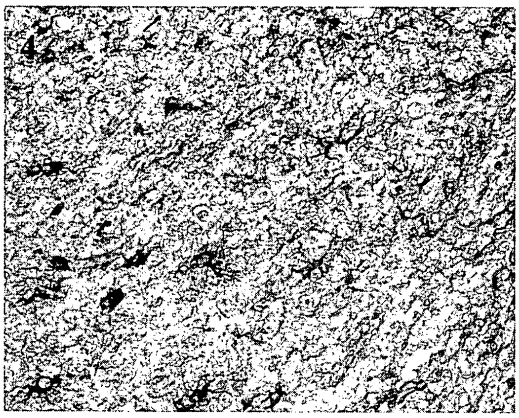
A male miniature dachshund showed seizure-like neurological signs after repeated vaccination for canine distemper, parvo, parainfluenza and adeno viruses, at 3 months of age. The dog was medicated by recombinant interferon for 3 days, antibiotics for a week, and phenobarbital for 2 days, respectively. The clinical signs were exaggerated despise of these treatments and the dog was euthanized at 4 months of age and was necropsied immediately at the private animal hospital. At necropsy, a white mass replacing the thalamus, approximately 1.5 cm in diameter, was observed. The central area of the mass was irregularly cystic filled with yellowish pale fluid (Fig. 1). The right lateral ventricle was moderately dilated and a cleft formation, about 0.5 cm long, was present at the region of the left globus pallidus (Fig. 1). No significant lesions were observed in the other visceral organs, except for moderate congestion in the spleen.

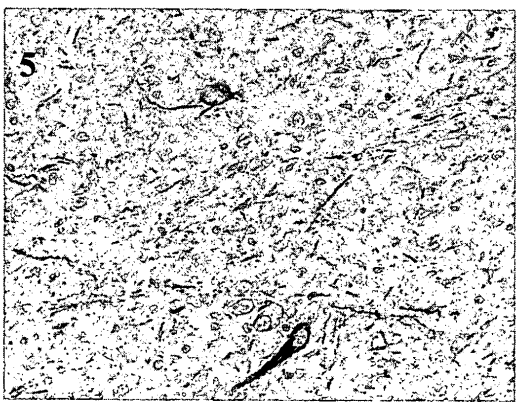
Tissue samples were taken from the brain, lung, heart, liver, kidney, intestines, pancreas, urinary bladder, and lymph nodes, and virus isolation for canine distemper was attempt using fresh tissues, while no virus was isolated from any organs. Histopathological examinations were performed using 10% neutral buffered formalin fixed samples. Paraffin sections of 4 μm were made and stained with hematoxylin and eosin (HE). Some selected brain sections including the thalamic lesion were also stained with Kluver-Barrera (KB), periodic acid Schiff (PAS), and von Kossa silver impregnation. Immunohistochemistry was performed using the Envision polymer reagents (Dako-Japan, Kyoto, Japan). Rabbit antisera against glial fibrillary acidic protein (GFAP, prediluted, Dako-Japan) and proliferating cell nuclear antigens (PCNA, prediluted, Zymed, California, CA, U.S.A.), and monoclonal antibody against neurofilament protein (NF, prediluted, Dako-Japan) were used as primary antibodies, respectively.

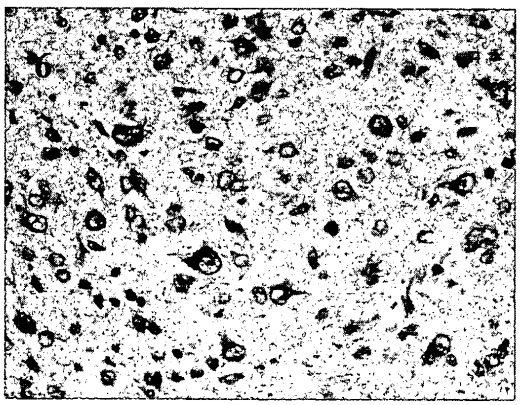
Although the thalamic lesion was well demarcated grossly, the histological border between intact and neoplastic tissues was not clear. The thalamic lesion mainly consisted of irregularly arranged well-differentiated neuronal and glial cells, and perivascular mineral deposits. The ratio of the elements varied according to areas. Adjacent areas of the central cystic space consisted of diffuse proliferation of GFAP-positive glial cells and their processes, and multiple mineral deposits (Fig. 2). These glial cells did not show apparent cellular atypism or mitotic activity. No PCNA-positive nuclei were found in these glial cells. Some mineral deposits were observed around blood vessels and often

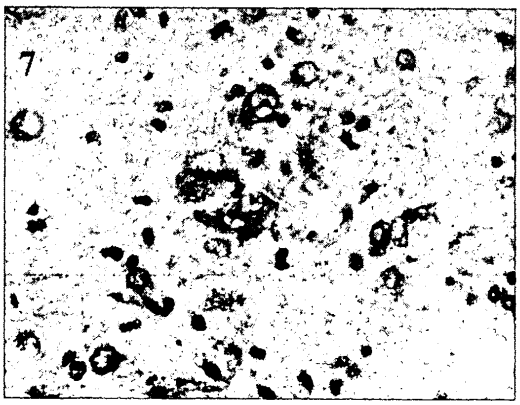


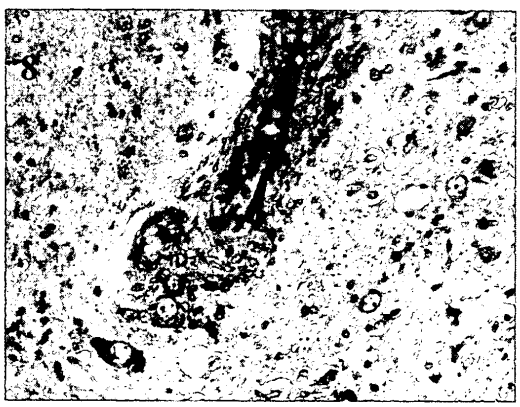












surrounded by loose connective tissues (Fig. 3). The mineral deposits were strongly positive for von Kossa silver impregnation, suggesting the involvement of calcium. Neuronal elements gradually increased from central to peripheral areas of the lesion, and mixed population of GFAP-positive glial cells and NF-positive neuronal cells were observed in the intermediate areas (Figs. 4 and 5). The most peripheral regions mainly consisted of irregularly arranged neuronal cells and occasional perivascular calcification. Only small number of GFAP-positive glial cells was present in the area. The neuronal cells in the area were varied in size and had a large clear nucleus with various amount of Nissl substances in the cytoplasm (Fig. 6). Bi-nucleated large neuronal cells were occasionally found in the region (Fig. 7). In addition, some neuronal cells were closely attached to middle-sized blood vessels with pericytosis (Fig. 8). No mitotic figures and PCNA-positive nuclei were found among the neuronal cells.

Sudden progression of neurological signs, mass formation in the brain and unusual histological appearance of the mass lesion suggest that the thalamic lesion of the present case might be neoplasm. The cleft-formation in the globus pallidus found in the present case is occasionally found in dogs with hydrocephalus [11]. The thalamic mass was enough compressive to cause the increase of brain pressure, subsequent ventricular dilation, and cleft formation, resulting in severe progressive neurological signs. Both neuronal and glial cells in the lesion neither show intense proliferating activity evaluated by mitotic figures or PCNA-reaction, nor severe cellular atypism. These facts indicate benign natures of the present neoplastic lesion. Therefore, the present brain mass was diagnosed as ganglioglioma according to the International Histological Classification of Tumors in Domestic Animals by WHO [3].

The precise histogenesis of the present tumor remains unclear. Apart from previous bovine ganglioglioma reported by Roth *et al.* [7], no immature cells considered as ganglion precursors or apparently neoplastic astrocytes were confirmed within the present tumor. Histological features characterized by irregular arrangement of highly differentiated glial and neuronal cells might indicate hamartomatous histogenesis of the present case, like as suggested in human cases [8].

Multifocal calcification is also characteristic feature of the present case. In human gangliogliomas, such mineral deposits called as microcalcification have been well documented and are the diagnostic hallmark for X-ray, computed tomography (CT) scanning, or magnetic resonance imaging (MRI) examinations, together with cyst formation within the tumor mass [5]. There was few information concerning such distinct mineral deposits within gangliogliomas or ganglioneuromas in domestic animals.

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Fig. 1. Gross view of the cut surface of left cerebrum hemisphere. The arrow indicates thalamic mass with central cystic space. The arrowhead exhibits cleft formation in the globus pallidus. × 1.5.

Fig. 2. Multiple mineral deposits and diffuse proliferation of glial cells in the central area of the thalamic mass lesion. HE. × 40.

Fig. 3. Higher magnification of Fig. 2 with diffuse proliferation glial cells. The blood vessels were surrounded by loose connective tissues and mineral deposits. HE. × 200.

Fig. 4. Mixed population of GFAP-positive astrocytes and neuronal cells in the intermediate area. Immunostaining for GFAP. × 300.

Fig. 5. Same area of Fig. 4. Neuronal cells and their processes showed moderate to intense immunoreactivity for NF. Immunostaining for NF. × 300.

Fig. 6. Peripheral area of the thalamic mass consisting of predominant proliferation of neuronal cells. The neuronal cells varied in size and had a large clear nucleus with various amount of Nissl substances. KB. × 400.

Fig. 7. Bi-nucleated large neuronal cells found in the area of Fig. 5. KB. × 400.

Fig. 8. Neuronal cells closely attached to middle-sized blood vessels with proliferating pericytes. KB. × 400.