Case Report

Perivascular Wall Tumor in the Brain of a Dog

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A 9-year-old spayed female German shepherd mixed-breed dog presented for seizures. Magnetic resonance imaging revealed an irregularly margined intraparenchymal cerebral mass. Microscopic examination of brain tissue collected postmortem demonstrated perivascular whorling and interwoven bundles of spindle-shaped cells. On immunohistochemistry, the tumor cells tested positive for vimentin and negative for factor VIII-related antigen, CD18, CD45, CD3, CD20, GFAP, S-100, and desmin. Immunohistochemistry results, in combination with histopathologic morphology, were suggestive of a perivascular wall tumor. To the authors’ knowledge, this is the first case report to utilize both histopathology and immunohistochemistry to describe a perivascular wall tumor in the brain of a dog.

1. Introduction

Canine perivascular wall tumors are a group of soft tissue sarcomas that arise from structural and supportive cells of the vascular wall [1]. Prior to a report in 2007, the term hemangiopericytoma was widely used to describe all canine perivascular wall tumors [2]. As these tumors may have a range of histologic origins other than the pericyte, the broader term of “perivascular wall tumor” has been suggested [2]. The group encompasses tumors derived from various types of vascular mural cells excluding endothelial cells [2]. The cell of origin of the tumor includes the pericyte, myopericyte, myofibroblast, smooth muscle cell, and fibroblast [2]. Specific types of canine perivascular wall tumors include hemangiopericytoma, myopericytoma, angiomyofibroblastoma, angioleiomyoma, and angiofibroma [2]. When citing references on canine hemangiopericytomas in the following report, the authors infer that this information is also applicable to perivascular wall tumors. Since these tumors are described as a morphologic continuum, they can be difficult to subtype [1]. Utilization of an extensive panel of immunohistochemical markers has been described, in an attempt to subtype canine perivascular wall tumors based on human subclassification schemes [2].

Canine hemangiopericytomas have traditionally been recognized histologically by the presence of whorls of spindle-shaped cells arranged in concentric layers around blood vessels [3]. However, canine perivascular wall tumors can show other histologic patterns such as bundles [2]. Hemangiopericytomas and other perivascular wall tumors most commonly occur in the skin and subcutis of dogs [4, 5]. However, there have been reports of primary hemangiopericytomas and perivascular wall tumors in the lung [6], orbit [7], spleen [8], pelvic cavity [9], mesentery [10], nasal cavity [11], frontal sinus [12], and nasopharynx of dogs [13].

To the authors’ knowledge, this is the first case report written in the English language describing a perivascular wall tumor in the brain of a dog or any other nonhuman species. The diagnosis was made utilizing histological appearance combined with immunohistochemistry. A previous case report, written in Polish, describes a hemangiopericytoma in the brain of a dog [14]. However, in that paper...
2 Case Reports in Veterinary Medicine

the diagnosis was based solely on histopathological characteristics; immunohistochemistry was not performed [14].

2. Case Presentation

A 9-year-old spayed female German shepherd mixed-breed dog presented to Washington State University (WSU) Veterinary Teaching Hospital for an acute onset of seizures. Three generalized seizures had occurred 2.5 weeks prior to referral to the veterinary teaching hospital. A complete blood count and chemistry profile showed no significant findings. The patient was prescribed phenobarbital (2.3 mg/kg orally every 12 hours). Upon presentation to WSU, physical and neurologic examinations were normal; no abnormalities were detected on urinalysis or thoracic radiographs.

Magnetic resonance (MR) imaging by use of a 1.0 Tesla magnet (Philips Gyroscan, Philips Medical Systems, Andover, Massachusetts, USA) revealed an irregularly marginated intraparenchymal mass located within the right piriform lobe. The mass measured 1.5 × 1.3 cm in diameter. On T1-weighted images obtained following the intravenous administration of gadolinium DTPA-dimeglumine (Magnevist, Bayer Healthcare Pharmaceuticals, Wayne, New Jersey, USA), the lesion had heterogeneous contrast enhancement (Figure 1). There was significant parenchymal hyperintensity involving both the white and the gray matter on both T2-weighted and Fluid Attenuated Inversion Recovery (FLAIR) imaging, suggestive of perilesional edema (Figure 2). A mass effect was also observed at the level of the interthalamic adhesion resulting in compression of the right lateral ventricle, in addition to the right rostral and caudal colliculi. The major differentials for this lesion included neoplasia versus an inflammatory lesion.

Analysis of cerebrospinal fluid (CSF) collected at the atlantooccipital site revealed an elevated microprotein level of 104.5 mg/dL (reference range < 30 mg/dL) with a normal cell count of 1 nucleated cell/μL (reference range < 5 cells/μL). CSF cytology results were normal with very rare lymphocytes and erythrocytes observed. Prednisone (0.5 mg/kg orally every 12 hours), fluconazole (4 mg/kg orally every 12 hours), trimethoprim sulfamethoxazole (10 mg/kg orally every 12 hours), and clindamycin (11 mg/kg orally every 12 hours) were commenced while awaiting the results of infectious disease testing. Negative results were obtained on bacterial and fungal cultures of CSF and urine and fungal and protozoal blood and CSF titers. This included the failure to detect Coccidioides, Histoplasma, Blastomyces, and Aspergillus antibodies in serum by immunodiffusion, Cryptococcus neoformans antigen in serum by latex Cryptococcus agglutination, Toxoplasma gondii antibody in serum and CSF by enzyme-linked immunosorbent assay (ELISA), and Neospora caninum antibody in serum and CSF by immunofluorescence assay (IFA).

A brain biopsy was performed using a modified Brain-sight stereotactic system as previously described [15]. Microscopic examination was suggestive of a perivascular wall tumor with prominent perivascular whorling of spindle-shaped cells. Due to the whorling pattern of the cells, the diagnosis of an unusual and infiltrative meningioma was also considered.

Abdominal ultrasound performed during the initial screening process prior to MR imaging had revealed an enlarged left medial iliac lymph node. Histologic evaluation of an ultrasound guided Tru-Cut biopsy of the lymph node was consistent with a neuroendocrine carcinoma. At a later date, thoracic and abdominal computed tomography (CT) were performed with images obtained before and after contrast, in order to attempt to identify the location of the primary neuroendocrine tumor. However, no primary neuroendocrine tumor was identified via CT. CT also did not reveal any evidence of metastatic lesions arising from the primary brain tumor.

Two months following diagnostics and prior to the initiation of any specific oncologic treatment, the dog was euthanized due to acute necrotizing enteritis of unknown etiology and disseminated intravascular coagulation (DIC). Decisions regarding surgery, radiation therapy, and/or chemotherapy to address the brain tumor had been delayed pending immunohistochemical results.

A complete postmortem examination was performed. Brain tissue samples were collected and fixed in 10% neutral
buffered formalin for histopathologic examination. After fixation, an approximately 2.5 × 2.0 × 1.0 cm focus of malacia in the right piriform lobe was identified on the cut surface of the brain (Figure 3). Multifocal hemorrhages were observed within the gastric serosa, gastric and jejunal mucosa, pancreas, and mesentery. These hemorrhages were considered consistent with changes associated with DIC. The underlying cause for DIC was undetermined. In the region of the left medial iliac lymph node, there was a 5.0 × 3.5 × 3.0 cm irregular, mottled tan to gray mass.

Figure 3: Macroscopic appearance of the cut surface of the brain at the level of the midbrain on postmortem examination. A focus of malacia is identified in the right piriform lobe.

Tissue specimens were processed routinely and stained with hematoxylin and eosin for histopathologic examination. The focus of malacia in the brain was characterized microscopically by a broad area of cavitating necrosis within the neuropil in the region of the right piriform lobe. Within this focus there were severe rarefaction, mild gliosis, and infiltration of large numbers of large macrophages with foamy cytoplasm. Near the dorsal margin of this focus there was a densely cellular, poorly defined mass infiltrating the adjacent neuropil. In some regions the mass was composed primarily of interwoven bundles of spindle-shaped cells (Figure 4), while in other areas the predominant pattern was perivascular whorling of the proliferative cells (Figures 5-6). The perivascular whorls varied from three to ten cells in thickness. Nuclei of the proliferative cells varied from round to oval in shape and from medium to large in size and had finely stippled chromatin and small nucleoli. Mitoses averaged one per five 400x fields. The malacia and proliferative tissue did not extend to the meningeal surface of the brain, and no communication of the mass with the superficial leptomeninges was evident grossly or microscopically. These microscopic findings were similar to the antemortem biopsy samples with the exception of very limited necrosis in the antemortem sample.

Figure 4: Perivascular wall tumor; right piriform lobe. The majority of the mass is comprised of spindle cells arranged in haphazardly oriented bundles. H&E ×40. Bar = 1 mm.

Immunohistochemical staining was performed both on brain tissue samples collected antemortem via brain biopsy and also on postmortem tissue. Staining procedures were performed at Washington State University (Washington Animal Disease Diagnostic Laboratory) and Michigan State University (Diagnostic Center for Population and Animal Disease Diagnostic Laboratory).

Figure 5: Perivascular wall tumor; right piriform lobe. The margins of the mass frequently have spindle cells predominantly arranged in whorls surrounding blood vessels infiltrating beyond the primary mass. H&E ×40. Bar = 1 mm.

Figure 6: Perivascular wall tumor; right piriform lobe. Higher magnification demonstrating perivascular whorling of proliferative cells. H&E ×600. Bar = 200 μm.
Figure 7: Perivascular wall tumor; right piriform lobe. The proliferative tumor cells displayed a positive reaction for vimentin.

Figure 8: Perivascular wall tumor; right piriform lobe. The proliferative tumor cells displayed a positive reaction for vimentin.

Health). All immunohistochemistry procedures were run concurrently with positive control tissues; the test and control samples were run with positive and irrelevant negative primary antibodies.

Sections were tested with antibodies to vimentin, factor VIII-related antigen, CD3, glial fibrillary acidic protein (GFAP), S-100, desmin, synaptophysin, chromogranin A (Dako, Carpinteria, California, USA), CD18, CD45 (Leukocyte Antigen Biology Laboratory, Davis, California, USA), and CD20 (Thermo Scientific, Fremont, California, USA). The proliferative tumor cells tested positive for vimentin (Figures 7-8) and negative for factor VIII-related antigen, CD18, CD45, CD3, CD20, GFAP, S-100, synaptophysin, chromogranin A, and desmin. These immunohistochemistry results indicated that this tumor had a mesenchymal cell of origin. In combination with the histopathologic morphology, this suggested that the tumor was of perivascular wall origin.

3. Discussion

Immunohistochemistry was utilized in this case to confirm a diagnosis of perivascular wall tumor and rule out other major differentials. Positive vimentin staining demonstrated that the proliferative cells were of a mesenchymal or round cell origin [16]. Negative staining for factor VIII-related antigen and GFAP ruled out an endothelial cell of origin (hemangiosarcoma) and astrocytic cell of origin (astrocytoma), respectively [16]. Negative staining for CD18, CD45, CD3 (T-cell), and CD20 (B-cell) ruled out a leukocytic cell of origin (histiocytic sarcoma and lymphoma) [16].

Negative staining for GFAP and S-100 made a peripheral nerve sheath tumor less likely [2]. While being rare, intracranial intraparenchymal peripheral nerve sheath tumors have been reported in dogs, without any association with cranial nerves [17]. However, the observation of spindle cells whorling around blood vessels and the prominence of the whorling pattern also were less supportive of a peripheral nerve sheath tumor [3]. Negative S-100 staining was also more suggestive of a perivascular wall tumor than a meningioma [18]. In a retrospective study of 30 canine intracranial meningiomas, 97% of the tumors were positive for S-100 [18]. In contrast, in a study of 31 canine hemangiopericytomas, all tumors stained negative for S-100 [4]. Additionally, while whorling of spindle-shaped cells around capillaries is recognized in a subset of transitional meningiomas [19], the abundance of whorling of spindle-shaped cells around larger blood vessels would be unusual for a meningioma. Combining the negative S-100 staining, prominent perivascular whorling, and lack of extension to the superficial leptomeninges, a meningioma was considered unlikely [18].

Desmin has been proposed to help in the subtyping of canine cutaneous perivascular wall tumors [2]. However, the negative result for desmin was not specific for any one type of perivascular wall tumor [2]. Synaptophysin and chromogranin A staining were also performed to investigate whether the brain tumor was related to the neuroendocrine tumor of the left medial iliac lymph node. Negative synaptophysin and chromogranin A staining confirmed that this was not a neuroendocrine tumor of the brain and that the two tumors found in the patient were unrelated.

Although canine perivascular wall tumors have only rarely been reported outside the skin and subcutis, the histopathologic appearance and immunohistochemical results of this intracranial tumor are consistent with those of canine cutaneous perivascular wall tumors [2, 4, 20]. In a study of 20 canine cutaneous perivascular wall tumors, all tumors were intensely vimentin positive and negative for CD18, factor VIII-related antigen, GFAP, and S-100 [2]. Case reports of canine hemangiopericytomas occurring outside the skin and subcutis have also stained positive for vimentin and negative for S-100 [6, 9]. As there are no specific immunohistochemical markers for perivascular wall tumors, a diagnosis is based on histopathologic appearance in combination with immunohistochemical findings [2].

Intracranial perivascular wall tumors have been reported in humans, though they are rare [21]. Hemangiopericytomas account for less than 1% of all central nervous system tumors in humans [22]. Case reports also describe human intracranial myopericytomas and angioleiomyomas [23, 24]. However, these intracranial tumors are seen even less commonly than intracranial hemangiopericytomas in humans [23, 24]. Human myopericytomas and angioleiomyomas are most commonly seen in the subcutaneous tissues of the extremities [23, 25], a distribution similar to that of dogs. Whereas human hemangiopericytomas are also frequently
Case Reports in Veterinary Medicine

seen in the extremities, the retroperitoneal region is the most common site [26]. Middle-aged adults are most frequently affected by these three types of tumors [25–27], which is comparable to the age of the canine patient in this present case report. On MRI, these intracranial tumors are most commonly extra-axial; however intra-axial locations have been reported [21, 23, 25, 28].

Surgical excision and radiation therapy have been employed as the fundamental treatment modalities for intracranial hemangiopericytomas, myopericytomas, and angioleiomyomas in humans [23, 25, 29]. Intracranial myopericytomas and angioleiomyomas show a benign clinical behavior and have a good prognosis with complete surgical resection [23, 25]. In contrast, recurrence and metastasis are commonly seen in intracranial hemangiopericytomas despite complete surgical resection and adjuvant radiation therapy [29].

Canine cutaneous perivascular wall tumors are locally invasive and occasionally recur [30] but are slow-growing and have very low metastatic potential [31]. When tumors do locally recur they are often a long period of latency [5]. While canine cutaneous hemangiopericytomas and perivascular wall tumors are described as having low metastatic potential, reports have suggested that the presence of necrosis in hemangiopericytomas may indicate an increased potential for malignant behavior [3]. A large tumor size (>5 cm) has also been proposed as a significant prognostic indicator in canine cutaneous perivascular wall tumors [5]. Other than extensive necrosis and local invasion, this intracranial perivascular wall tumor did not demonstrate any additional features suggestive of increased malignancy. Specific subclassification of canine cutaneous perivascular wall tumors has been described by use of a large panel of immunohistochemical muscle markers [2]. However, no studies have investigated the significance of subclassification in determining prognosis in canine cutaneous perivascular wall tumors. Additionally, treatment of perivascular wall tumors is currently based on generalized recommendations for the group of soft tissue sarcomas.

In dogs, radical surgical excision has traditionally been recommended for treatment of cutaneous hemangiopericytomas [32]. Recent studies have similarly highlighted the importance of complete surgical excision in treatment of canine cutaneous perivascular wall tumors [33]. One study found that in all cases in which surgical margins for cutaneous perivascular wall tumors were complete, no recurrence was observed [33]. There has been reported success with the use of radiation therapy in cases of nonresectable soft tissue sarcomas [34]; however unfortunately no data is currently available regarding the effectiveness of radiation therapy specifically for canine perivascular wall tumors. Additionally, no veterinary studies have investigated effectiveness of surgical versus radiation treatment in dogs with perivascular wall tumors external to the skin and subcutis. In the case of intracranial tumors in dogs, wide surgical resection is often not feasible. Palliative radiotherapy and combination therapy of marginal surgical resection with radiotherapy would, therefore, be potential treatment options for perivascular wall tumors of the canine brain.

This report additionally presents a case of metastatic cancer of unknown primary, confirmed via abdominal and thoracic CT, and postmortem examination. Despite postmortem histopathologic evaluation confirming the medial iliac lymph node to be a neuroendocrine carcinoma, the primary tumor was never discovered. A retrospective study of 21 dogs with metastatic cancer of unknown primary identified carcinoma to be the most common histological type [35]. Additionally, amongst dogs in this study with carcinoma as the histological type, 67% of dogs had only a single metastatic site [35]. The median survival time for dogs with metastatic cancer of unknown primary was reported to be 30 days [35]. Survival time for the dog in this current report was 56 days following diagnosis of the left medial iliac neuroendocrine carcinoma. However, the reason for euthanasia was necrotizing enteritis, which appeared to be unrelated to the neuroendocrine carcinoma.

4. Conclusion

This case report describes a perivascular wall tumor in the brain of a dog, a tumor type that has been rarely identified in the brain of humans. While being an uncommon neoplasm, perivascular wall tumor should be considered as a differential diagnosis for an intraparenchymal cerebral mass in a dog.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

References


