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Epithelioid and spindle-cell haemangioendothelioma in the brain of a dog: a case report

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ABSTRACT: A 9.5-year-old male Belgian malinois dog died after showing clinical symptoms that included fatigue, anorexia and dyspnoea. Necropsy revealed macroscopic findings in the brain and other organs. A solitary, brown-red-coloured mass, approximately 0.5 cm thick and 1.5 × 2 cm in diameter, was detected on the right side of the medulla oblongata, pons and cerebellum. The cut surface showed no invasion of the brain parenchyma. Histologically, the neoplasm was characterised by proliferation of endothelial cells, which showed epithelioid and spindle cell features. Some tumour cells had intracytoplasmic lumen formations containing red blood cells. The nuclei of the tumour cells were large and vesicular. In immunohistochemical experiments the tumour cells stained positive for factor VIII-related antigen, CD31 and CD34. A description is provided of the features of this epithelioid and spindle-cell haemangioendothelioma (EHE) that originated from vessels of the meninges in the subarachnoid space.

Keywords: haemangioendothelioma; spindle cell; CD34; canine; meninges

Epithelioid haemangioendothelioma (EHE) is a unique vascular tumour characterised by an epithelioid or histiocytoid appearance of endothelial cells, with eosinophilic cytoplasm (Weiss and Enzinger 1982). In medical pathology, the term EHE was first used by Weiss and Enzinger (1982) to describe a tumour of low-grade malignancy that was histologically intermediate between a haemangioma and an angiosarcoma (Warren and Summers 2007). Vascular endothelial tumours of animals show similar microscopic features to those of the spectrum of human epithelioid endothelial tumours (Warren and Summers 2007). In addition, the cause of some vascular endothelial tumours in humans and dogs has been reported to be the same. For example, *B. vinsonii* subsp. *berkhoffii* genotype II was described in both a boy with EHE and a dog with haemangiopericytoma (Breitschwerdt et al. 2009).

Spontaneous tumours of blood vessel endothelial cells, such as haemangiomas and haemangiosarcomas, have been commonly described in dogs (Warren and Summers 2007). However, intracranial vascular neoplasms are rare (Gabor and Vanderstichel 2006), and most cerebral tumours are either metastatic angiosarcomas or hamartomas (Cordy 1990). A review of the EHE literature reveals only one case of intracranial involvement in animals, in which a calf brain exhibited features which resembled epithelioid and spindle cell variants of haemangioendothelioma (HE) (Finnie et al. 1993). Other reports of rare variants of HE include kaposiform HE in a dog (Vincek et al. 2004) and cow (Pires et al. 2009), epithelioid HE in the dermis-subcutis of a dog (Warren and Summers 2007) and retiform HE in two dogs (Lombardini and Summers 2013). To the best of our knowledge, intracranial occurrence in dogs has not yet been reported. Furthermore, the gross findings of EHE in the central nervous system of animals have not been documented.

The aim of this report is to describe the gross, histological and immunohistochemical findings of a primary vascular neoplasm of the brain in a dog. This neoplasm included features typical of epithelioid and spindle-cell haemangioendotheliomas that originated from the vessels of the meninges.

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Case description

A deceased 9.5-year-old Belgian malinois male dog was brought to Yuzuncu Yil University, Faculty of Veterinary Medicine, for necropsy. The dog had a history of fatigue, anorexia and dyspnoea. According to the owner's statement, the symptoms of disease had started approximately one year earlier. A complete necropsy was performed and tissue samples were obtained.

The brain and other tissue samples were fixed in 10% neutralised formaldehyde, processed routinely and relevant blocks were embedded in paraffin wax, sectioned at 5 µm and stained with haematoxylin and eosin (HE), Masson's trichrome, toluidine blue and periodic acid Schiff (PAS). Serial sections were subjected to immunohistochemistry. The brain tissue sections were stained with monoclonal primary antibodies against factor VIII-related antigen (Thermo Fisher Scientific Inc; 1 : 150 dilution), CD31 (Cell Marque; 1 : 150 dilution), CD34 (Cell Marque; 1 : 150 dilution), vimentin (Cell Marque; 1 : 150 dilution), Ki-67 (Cell Marque; 1 : 200 dilution) and cytokeratin (Cell Marque; 1 : 200 dilution). The streptavidin-peroxidase method (Histostain Plus Bulk Kit, Zymed, South San Francisco, USA) was used to stain the sections. Tissue sections were incubated overnight at 4 °C with monoclonal primary antibodies. Finally, the reactions were visualised by reacting the sections with diaminobenzidine (DAB). After the development of the DAB reactions, the sections were counterstained with Gill's haematoxylin. We also used negative controls to verify staining.

Grossly, a solitary, brown-red-coloured tumour mass, approximately 0.5 cm thick and 1.5 × 2 cm in diameter, was detected on the right side of the medulla oblongata, pons and basal part of the cerebellum. The mass was found to initiate around the medulla oblongata and then spread to the pons and cerebellum (Figure 1). It was firm and the cut surface was dark in colour (Figure 2). It was not encapsulated. No metastases to other tissues were observed. In addition to the tumour mass, an accumulation of focal white material was observed in the subarachnoid spaces of the brain hemispheres.

The gastrointestinal tract, the stomach, duodenum, jejunum and ileum were filled with bile and appeared dark. Disseminated gray foci were identified in the lung lobes, as well as a large hepatisation area in the caudal lobe. Dilatation observed in the right ventricle of the heart was attributed to probable pneumonia. Severe congestion was detected in the liver. The kidneys were dark-coloured and the capsule was hardened. The spleen was stiff and small, and its capsule was thickened.

Histologically, the borders of the tumour mass were limited by an inflammatory line, and no invasion to the brain parenchyma was observed. Vasculitis, hyperaemia and haemorrhage were found

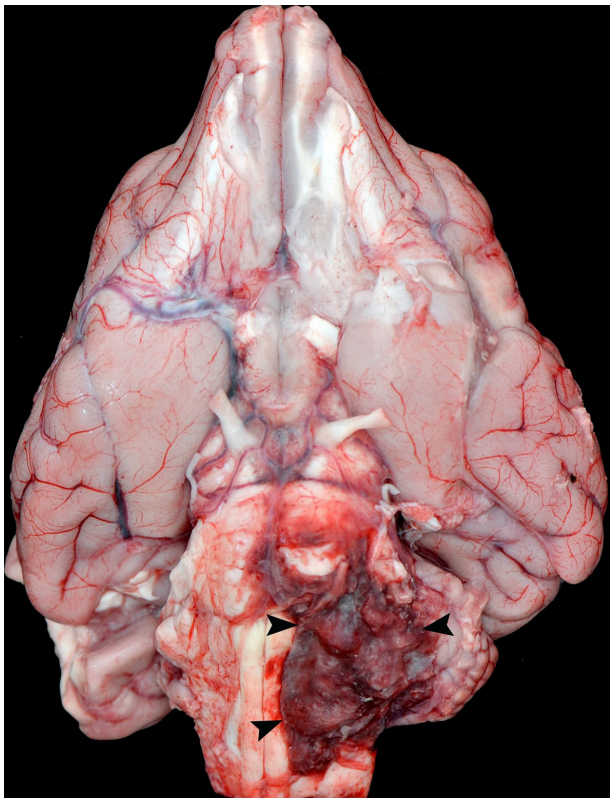

Figure 1. Gross appearance of epithelioid haemangioendothelioma in the brain of the dog (arrowhead)

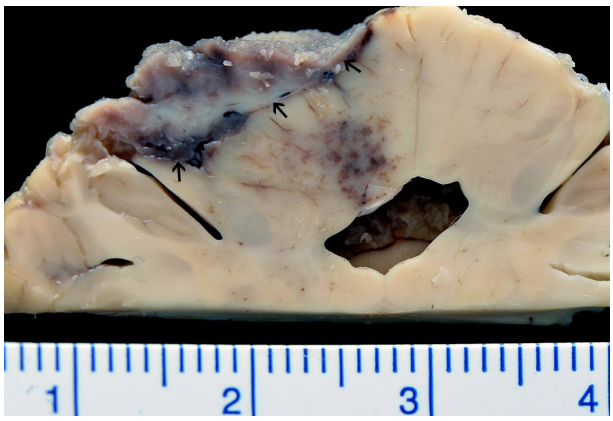

Figure 2. Cut surface of the neoplasm (arrows)

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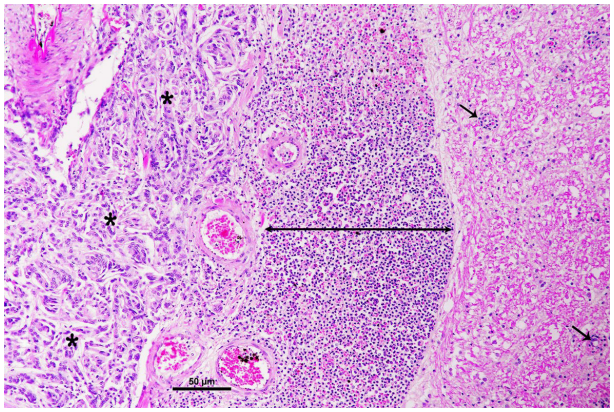

Figure 3. Epithelioid haemangioendothelioma: vasculitis in brain parenchyma (arrows); the double-headed arrow indicates a line of inflammatory cells between the brain and the tumour; neoplastic cells occurred singly or formed clusters of small blood vessels that obscured the lumen in a solid arrangement (stars)

in the brain parenchyma near the mass (Figure 3). In its general structure, the tumour consisted of small proliferating blood vessels lined by endothelial cells. Proliferation of neoplastic endothelial cells with a plump, epithelioid appearance was evident. These neoplastic cells occurred singly or were clustered as short strands, cords or nests in a myxoid stroma. They were polygonal or stellate, with variable amounts of eosinophilic cytoplasm. Endothelial cell nuclei were central or paracentral, large, round-to-oval and vesicular. Some neoplastic cells had single, large, intracytoplasmic lumens, similar to intracytoplasmic vacuoles, which occasionally contained a single erythrocyte. Erythrocytes were also present in the lumens of the primitive vessels and parenchyma of the neoplasm. Some neoplastic endothelial cells that lacked distinct lumens were observed in the structure of the spindle cell. Cell pleomorphism was mild-to-moderate, and mitotic figures were rare (Figure 4). The white material that accumulated in the subarachnoid spaces of the brain hemispheres was hyalinised collagen tissue.

Chronic interstitial pneumonia was detected in the lungs. The interalveolar septum was thickened and fibromuscular hyperplasia was detected in the alveolar walls and propria mucosa of the bronchioles. In the kidney, an increased amount of hyalinised collagen tissue was observed in the renal cortex and intertubular area of the corticomedullary region. Lymphocytolysis, cortical haemorrhage and hyperaemia were observed in the spleen. Similar to the brain and kidney, increases in hyalinised collagen material were evident in the cortex and parenchyma of the spleen. Other histopathological observations included severe capillary hyperaemia and intrahepatic cholestasis in the liver.

Positive immunostaining for factor VIII-related antigen, CD-31 and CD-34 was observed in the cytoplasm of the neoplastic cells, supporting an endothelial origin of the haemangioma (Figure 5). The tumour cells also stained positive for vimentin and Ki-67. Labelling for cytokeratin was negative.

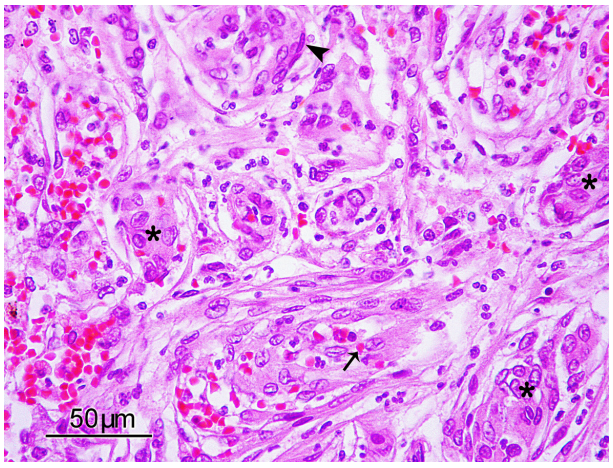

Figure 4. Epithelioid haemangioendothelioma: the tumour shows a mixture of epithelioid and spindle cells (arrowhead); clusters of small blood vessels formed of plump neoplastic cells (stars); some of the neoplastic cells exhibit intracytoplasmic lumens that dislocate the nucleus and include a single erythrocyte (arrow)

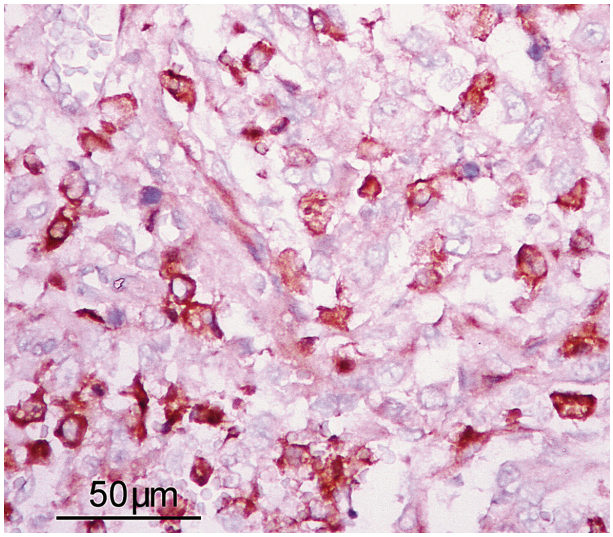

Figure 5. Epithelioid haemangioendothelioma: positive cytoplasmic immunoreactivity for CD34 in neoplastic endothelial cells

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DISCUSSION AND CONCLUSIONS

Endothelial tumours are well recognised and are most commonly classified in humans as epithelioid haemangiomas, haemangioendotheliomas and angiosarcomas (Pulley and Stannard 1990). The pattern of these tumours has recently been described in animals as angiomatosis, haemangioma and haemangiosarcoma (Warren and Summers 2007). HE in animals is defined as a benign vascular neoplasm characterised by hypertrophic endothelial cells that form small hypercellular vascular channels (Robinson and Robinson 2017). Intracranial vascular neoplasias are also well described (Zaki 1977) and common (Thomson et al. 2005) in the CNS of dogs, but primary EHE is rare (Cordy 1979) and unusual (Finnie et al. 1993), typically occurring outside the CNS (Machida et al. 1998). In retrospective studies, CNS tumours of dogs were generally classified as meningiomas, astrocytomas, neuroblastomas, oligodendrogliomas and ependymomas (Foster et al. 1998; Snyder et al. 2006).

Histologically, the neoplastic endothelial cells in this dog's tumour exhibited a plump epithelioid or histiocytic appearance and a slightly differentiated spindled endothelial component, with a myxoid stroma similar to that previously reported in humans (Suster 1992; Zheng et al. 2012) and other animals (Machida et al. 1998; Pires et al. 2010). These neoplastic cells occurred singly or formed clusters of small blood vessels that obscure the lumen in a myxoid stroma (Warren and Summers 2007). Another feature of these tumours was the presence of single neoplastic endothelial cells with intracytoplasmic vacuolisation, which dislocate the nucleus and occasionally contained a single erythrocyte (Finnie et al. 1993; Machida et al. 1998) Erythrocytes were also present in the lumens of the primitive vessels and parenchyma of the neoplasm. Atypia was mild-to-moderate, and mitotic figures were uncommon (Warren and Summers 2007).

In the case presented here, the endothelial lineage was confirmed by the positive immunohistochemical staining for factor VIII-related antigen, CD-31 and CD-34, which are established endothelial markers that support the diagnosis of a neoplasm of endothelial origin (Jennings et al. 2012). CD34 had the highest average immunolabelling intensity in neoplastic endothelial cells, while Factor VIII had the lowest background labelling. These immunohistochemical markers are commonly used and their use for the identification of neoplastic endothelial cells in humans is well described (Heim-Hall and Yohe 2008). Previous studies in dogs (Von Beust et al. 1998; Warren and Summers 2007) and cats (Jennings et al. 2012) have reported that vascular neoplasms exhibit high rates of positive staining for all three antibodies.

This intracranial neoplasia displayed morphological features of both epithelioid and spindle cell haemangioendotheliomas, a pattern that, to our knowledge, has not been previously described in the dog brain. The lack of tumour invasion into the parenchyma leads us to suggest that these tumours may have originated from the meninges. No vascular tumours were found in other sites at necropsy, so this was, in all likelihood, a primary lesion that had arisen in the brain.

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