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Thalamic astrocytic hamartoma and associated meningoangiomatosis in a German shepherd dog

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ABSTRACT

The present paper describes an astrocytic thalamic hamartoma associated with tectal meningoangiomatosis in a 3-month-old female German shepherd dog showing strabismus, opistotonus, circling, and fore limb hypermetria.

MR images of the brain showed a well-defined intra-axial mass in the tectal region. The mass was hypointense to gray matter on T2-weighted images and hyperintense to gray matter on precontrast T1-weighted images. Histologically, glial cells arranged in a multinodular pattern characterized the mass. More caudally the lesion merged with subpial abnormal newly formed plaque-like shaped tissue characterized by thick branching bundles of spindle-shaped cells surrounding a central vessel. In the nodules, GFAP and vimentin were diffusely expressed. In the vascular proliferation Factor VIII-positive reaction was limited to endothelial cells while the remaining spindle-shaped cells were diffusely SMA-positive. The glial nodules did not express lysozyme and MAC387, nor neurofilaments and nestin.

Hamartomas are mass lesions characterized by disorderly overgrowth of tissue elements. They differ from neoplasms since they are not autonomous and their growth is finite (Cook, 1977). Usually, the use of the term "hamartoma" implies the presence of the lesion at birth, with subsequent growth paralleling that of the animal, but ceasing with maturity (Smith and Van Winkle, 2001). Hamartomas reported in animals include vascular, mesenchymal, pulmonary microcystic, muscle, melanotic, bile duct, ovarian interstitial cell, cutaneous annexe, and collagen types (Saunders, 2007; Scott et al., 1984).

In the human, cerebral hamartomas are lesions usually composed of a combination of mature, disorganized, glial and neuronal cells (Marucci et al., 2011), or of vascular tissue (Summers et al., 1995). They typically rise in the hypotalamus, often associated with symptoms of precocious puberty and/or drug resistant epilepsy with gelastic seizures and behavioral disturbances (Marucci et al., 2011). However, hamartomas have been reported to occur in almost any location within the central nervous system, including spinal cord (Marucci et al., 2011).

In canine nervous system, vascular (Cordy, 1979; Ide et al., 2009; Smith and Van Winkle, 2001), neuronal (Cook, 1977), and peripheral nerve fibers (Saunders, 2007) hamartomas have been described. To the author's knowledge this is the first report of an astrocytic cerebral hamartoma in the dog unusually associated with meningoangiomatosis.

A 3-month-old female German shepherd dog was referred to the Portoni Rossi Veterinary Hospital with a history of divergent strabismus, sudden onset of bilateral mydriasis, abnormal posture of the head, and tilted upward. The dog had been treated with prednisone and amoxicillin, with no effect. In the following days, postural reaction deficits in all four limbs and abnormal wide head movements appeared, followed by progressive depression, lack of appetite, and dysphagia.

At neurological examination, the dog had a depressed and disorientated mental status. Bilateral circling and front limb hypermetria were seen at gait analysis. Postural reactions were abnormal in all four limbs. The head was tilted upward and the vestibulo-ocular reflex was not evocable. A divergent strabismus was seen in both eyes due to abnormal conformation of the skull. Menace reaction was bilaterally absent. Spinal reflexes were normal on all four limbs. Cutaneous trunci reflex was normal. Based on the clinical findings, a brain stem lesion was suspected. However, a forebrain lesion could not be ruled out. Routine hematologic and serum biochemical examinations, including dynamic bile acids, were unremarkable. The main differentials included malformations, inflammatory, and degenerative diseases.

A brain magnetic resonance imaging (MRI) was advised and performed under general anesthesia using a 0.22 MR scanner

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(MrV, Paramed, Genoa, Italy). MR images of the brain were abnormal with a 1.0 × 1.0 × 0.7 cm. well-defined mass in the middle fossa, just caudal to the third ventricle, in the tectal region. The mass had a homogeneous structure, and was hypointense to gray matter on T2-weighted images and hyperintense to gray matter on pre-contrast T1-weighted images (Fig. 1a). On post-contrast T1-weighted images, the mass homogenously enhanced (Fig. 1b). Moreover, the mass was believed to be intra-axial causing light compression of the cerebellum. The lateral and third ventricles were severely dilated. Periventricular hyperintensity, likely due to edema, was present on T2-weighted images. Differential diagnoses for the mass included neoplasia and granuloma. Based on the poor prognosis, the owners declined biopsy and the dog was euthanized.

After death, the brain was promptly fixed in buffered 10% formalin and paraffin-wax embedded for routine histological examination. Furthermore, Masson's trichromic and reticulin silver impregnation stains were carried out. Paraffin-embedded brain sections were also submitted to avidin–biotin peroxidase complex staining for glial fibrillary acidic protein (GFAP, rabbit polyclonal antibody, 1:500, Dako, Carpenteria, CA, USA), vimentin (mouse monoclonal antibody, clone V9, 1:200, Dako), S-100 protein (rabbit polyclonal antibody 1:1000, Dako), Factor VIII (rabbit polyclonal antibody anti-human VonWillebrand factor, 1:400, Dako), smooth muscle actin (mouse monoclonal antibody anti-human SMA, clone 1A4, 1:500, Dako), lysozime (rabbit polyclonal antibody anti-human lyzozyme, 1:50, Dako), MAC387 (mouse monoclonal antibody anti-human myeloid/histiocyte antigen, clone MAC387, 1:40, Dako), neurofilaments (NF, mouse monoclonal antibody anti-neurofilament triple proteins, clone 13AA, 1:200t, Plymouth-meeting, PA, USA, Byomol International, LP), and nestin (rabbit polyclonal anti-nestin neural stem cell marker, 1:700, Abcam, UK).

Macroscopic examination of tranverse brain sections confirmed the severe extension of the lateral and third ventricles. In the region of pretectal diencephalic nuclei a focal round discolored area with haemorrhagic borders was found (Fig. 1c). It extended caudally involving both the rostral colliculi and assuming a plaque-like shape (Fig. 1d). At this site, it was whitish in color and about 1 cm in length. The mesencephalic aqueduct was severely stenotised. Histologically, disorganized nodular aggregates of glial cells with round to oval vesicular nuclei characterized the lesion observed at the thalamic pretectal region. Occasionally the glial cells exhibited multilobulated or megalic nuclei with prominent nucleolus. The central part of the glial cell aggregates showed a variable number of large foamy cells with eccentric nucleus. The nodules were generally defined by bleeding newly formed small vessels (Fig. 2a). More caudally the nodules of glial tissue merged with subpial abnormal tissue that deformed the mesencephalon dorsal profile towards the subarachnoid space. This tissue was characterized by thick branching bundles of spindle-shaped cells (Fig. 2b). They surrounded a central vessel and showed numerous mitotic figures. This lesion produced a marked aqueduct stenosis.

In the nodules, GFAP was diffusely expressed except for the foamy cells (Fig. 2c). The nodules of glial tissue were also vimentin-positive, while they did express neither NF nor nestin. The vascular proliferation showed a diffuse vimentin reaction, while Factor VIII-positive reaction was limited to endothelial cells (Fig. 2d). The remaining spindle-shaped cells were diffusely (80% of cells) SMA-positive. Occasionally, scattered spindle cells were positive for S-100 protein. GFAP IHC-reaction was found in the neuropil adjacent to the vascular proliferation. The immunohistochemical study for lysozyme and MAC387 was negative in both the lesions as well as in the neuropil. Moreover, in the vascular lesion Gomori's silver impregnation highlighted the presence of abundant reticular fibers, mingled with collagen fibers, revealed with Masson's staining.

Based on clinical and pathological findings, we considered the lesions consistent with an astrocytic thalamic hamartoma and meningoangiomatosis, respectively.

In medicine literature, it is assumed that hamartoma presents as disorganized but benign-appearing masses composed of mature cells indigenous to the particular site (Robbins and Cotran, 2010). It is also assumed that this term implies the presence of the lesion at the birth, with subsequent growth paralleling that of the animal but ceasing with maturity (Smith and Van Winkle, 2001). The thalamic lesion under study was conforming to these statements. In fact, the lesion consisted in indigenous glial elements abnormally arranged in disorganized nodular aggregates giving to the lesion a multinodular pattern. Similar histological features have been reported for a human case of cortical oligondroglial hamartoma (Marucci et al., 2011). A so characterized newly formed tissue was well defined and it did not infiltrate the adjacent tissue as glial neoplasms usually do. The occasional nuclear atypia we observed in the glial cells of nodules have been regarded as a reactive change, as reported for astrocytes (Poirier et al., 1990), instead of as a tumour feature. Moreover, the age of the affected dog was more significantly consistent with a developmental malformation than true glial neoplasm, commonly occurring in mature dogs

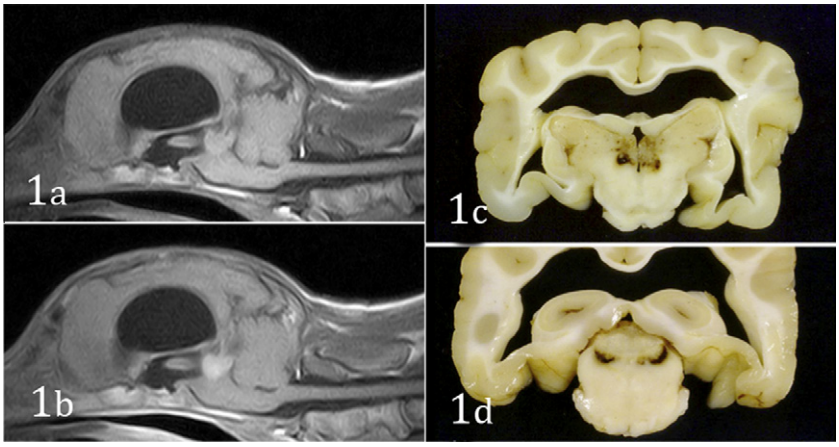

Fig. 1. Magnetic resonance imaging and gross pathology findings. Sagittal T1-weighted pre- (a) and post-contrast (b) images of the brain. The thalamo-mesencephalic mass is detectable as a focal isointense/slightly hyperintense and homogenously contrast enhancing lesion. (c) Transverse brain section at level of pretectal nuclei. An area of discoloration adjacent to the third ventricle is defined by a haemorrhagic halo. (d) A plaque-like lesion of firm tissue develops at the level of rostral culliculi. Also in this case the lesion shows haemorrhagic edges.