Published in final edited form as:

J Comp Pathol. 2011 November ; 145(4): 414–418. doi:10.1016/j.jcpa.2011.03.006.

Intracranial meningioma in a baboon (*Papio* spp.)

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Abstract

Meningioma is the most common intracranial nonglial neoplasm of cats, dogs, and humans. Very few spontaneous brain neoplasms have been reported in nonhuman primates. This report describes a naturally occurring meningioma in a captive baboon. Clinical signs exhibited by the animal included head pressing, visual impairment, and vestibular disease. The tumor was arising from the ventral aspect of the cranial cavity and was compressing the superjacent left side of the cerebellum and brainstem. Histologically, the mass was characterized by pleomorphic spindle-shaped to polygonal cells arranged in sheaths, vague whorls, and occasional papillary structures on vascular cores. Nuclear cytoplasmic invagination, syncytial-like cells, and areas of mineralization were also evident. Immunohistochemically, neoplastic cells were positive for vimentin and S-100 protein, and negative for pancytokeratin, GFAP, and EMA. The features of this baboon meningioma are similar to those of meningiomas in other species.

Keywords

Brain; meningioma; nonhuman primates baboon

Meningioma is the most common primary nonglial, intracranial tumor in humans, accounting for 20% to 26% of all primary intracranial neoplasms (Goldstein RA *et al.*, 2005). In veterinary medicine, meningiomas are the most common primary nervous system tumor of dogs and cats but are less frequently reported in other domestic species (Koestner A *et al.*, 2002). Brain tumors have been rarely described in nonhuman primates and most of these were experimentally induced by radiation (Porter BF *et al.*, 2004). Naturally occurring glial tumors include glioblastoma multiforme in baboons (Herring JM *et al.*, 1990; Porter BF *et al.*, 2004), a medulloblastoma in a baboon (Berthe J *et al.*, 1980), a neurohypophyseal astrocytoma in a rhesus macaque (HogenEsch H *et al.*, 1992), and an astrocytoma in a cynomolgus macaque (Yanai T *et al.*, 1992). Nonglial tumors include a lipoma arising from the choroid plexus in a baboon (Fiori MG *et al.*, 1994), and a meningioma in a baboon (McConnell EE *et al.*, 1974). The latter citation was an extensive survey of diseases that were diagnosed among 100 free-ranging baboons and briefly describes the gross and microscopic findings of a lesion interpreted to be a meningioma.

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This case involves a baboon that was housed at the Southwest National Primate Research Center/Southwest Foundation for Biomedical Research (SNPRC/SFBR) in San Antonio, Texas. The animal was a 7-year-old female with a history of head pressing, staggering, visual impairment, and vestibular signs. The baboon was housed in an indoor-outdoor metal and concrete group cage. It was fed commercial monkey diets supplemented with grains, vegetables and fruits. Water was supplied ad libitum. All animal care and procedures were approved by the Southwest Foundation for Biomedical Research Institutional Animal Care and the Use Committee. A complete blood count and chemistry profile were unremarkable. The animal was euthanized after seven days of worsening clinical signs. A neurological examination and neuroimaging tests were not performed. At necropsy, the animal had approximately 10 ml of serosanguineous fluid in the cranial vault and a $3 \times 3 \times 4$ cm, brown, lobular mass that was arising from the floor of the cranial cavity and was subjacent to the cerebellum and brainstem and extended rostrally to the caudal margin of the optic nerves. The mass was adhered to the meninges along the base of the skull, was compressing but could be easily separated from the cerebellum and brainstem (Fig. 1). Marked bilateral hydrocephalus of the lateral ventricles was also present. Complete gross necropsy identified no additional masses.

Tissue samples were fixed in 10% neutral buffered formalin, processed routinely, embedded in paraffin, sectioned at 5 μ m, and stained with hematoxylin and eosin. Selected sections were also stained with periodic acid-Schiff stain (PAS) and Masson's trichrome. Histologically, the bulk of the tumor was composed of pleomorphic spindle to polygonal cells arranged in sheaths and vague whorls (Fig. 2). In a few areas, the cells were more loosely arranged and were occasionally palisading around a central vascular core (Fig. 3). Neoplastic cells had a moderate to abundant amount of eosinophilic, finely granular cytoplasm, round to oval nuclei with a finely stippled chromatin pattern, and one to multiple prominent nucleoli. There was moderate anisocytosis, anisokaryosis, and pleomorphism. Mitotic figures averaged three per ten 40X fields. Nuclear cytoplasmic invaginations and cells having ill-defined margins imparting a syncytial-like pattern were also observed (Fig. 3). Secondary changes included hemorrhage with hemosiderin accumulation, fibrin, edema, and occasional areas of necrosis, as well as multifocal areas of mineralization surrounded by eosinophils and neutrophils (Fig. 4). The mass was compressing but not invading the adjacent hemorrhagic neuropil, which contained aggregates of hemosiderin-laden macrophages. Masson's trichrome-stained slides revealed scattered areas of collagen deposition among neoplastic cells. PAS staining revealed variable amounts of PAS-positive granules in the cytoplasm of cells.

Sections of the brain containing the tumor were stained immunohistochemically using a streptavidin-biotin system (LSAB2 System-HRP, DakoCytomation, Carpinteria, California) according to the manufacturer's instructions. The primary antibodies used included vimentin (monoclonal, dilution 1 in 500, Dako, Carpinteria, California), S-100 (Polyclonal, dilution 1 in 1,000, Dako, Carpinteria, California), pancytokeratin (monoclonal, dilution 1 in 500, Dako, Carpinteria, California), epithelial membrane antigen (EMA) (monoclonal, dilution 1 in 1,000, Dako, Carpinteria, California) and glial fibrillary acidic protein (GFAP) (polyclonal, dilution 1 in 1,000, Dako, Carpinteria, California). Neoplastic cells stained positively with vimentin (cytoplasm) and S-100 (cytoplasm and nucleus) protein and negatively with pancytokeratin, EMA, and GFAP. On the basis of the morphologic features and immunohistochemical staining pattern, a diagnosis of intracranial meningioma was established.

As a group, meningiomas are typically considered benign tumors, and the clinical signs that they incite are the result of compression of neighboring structures, and thus depend upon the tumor's location (Perry A, 2006; Summers BA *et al.*, 1995). Differing from the most

commonly reported locations of intracranial meningiomas of humans (cerebral convexity and falx/parasagittal regions), dogs (olfactory bulb and frontal lobes), and cats (dorsal and lateral convexities), this meningioma was located at the base of the skull (Koestner A *et al.*, 2002; Perry A, 2006). In this case, head pressing in response to first reviewer's comment: is likely secondary to the hydrocephalus. Ventral compression of the brainstem by the mass likely impaired adequate cerebrospinal fluid flow, which led to its accumulation within lateral ventricles. Visual deficits and vestibular disease were probably related to edema and pressure from the neoplasm, although histologic examination of the optic nerves and vestibular nerve was not done. Apart from its location, the neoplasm shared many of the gross findings observed in veterinary and human cases, including a well-demarcated mass that compresses the adjacent brain. However, hyperostosis of the adjacent bone in response to pressure caused by the physical presence of the tumor, a hallmark of human cases that has occasionally been described in animals (Summers BA *et al.*, 1995), was not evident in this case.

Although meningiomas are typically associated with the dura matter, the century-old histogenetic viewpoint is that they arise from arachnoidal cap cells, and the location of the tumor reflects the location of the arachnoid granulations, where this type of cell is clustered. The microscopic appearance of meningiomas is remarkably diverse, and this is attributed to the ability of arachnoidal cells to perform many diverse functions within the leptomeninges, resulting in the development of structural features of both mesenchyme and epithelia (Koestner A *et al.*, 2002; Perry A, 2006; Summers BA *et al.*, 1995). The World Health Organization (WHO) classification for human tumors currently describes 15 variants of meningiomas, which are separated on the basis of behavior into grades (Louis DN *et al.*, 2007). The most recent veterinary classification scheme describes nine histologic patterns that possess similar histologic features as the human categories (Koestner A *et al.*, 1999). Histologically, this baboon meningioma was composed of areas that had features resembling both the transitional and papillary patterns that are described in human meningioma. Histological features similar to those seen in cases of human transitional meningiomas included meningotheelial cells, spindle cells, occasional syncytial-like cells, whorls, necrosis, and mineralization. Areas of meningotheelial cells radiating around a central core in papillary formation is the most common finding of the papillary type. The tumor described in the McConnell's survey (McConnell EE *et al.*, 1974) resembled the meningotheelial subtype.

In humans, a histologic grading system that correlates several morphological features with prognostic values has been published by the WHO, which classifies meningiomas into three grades: grade I - benign meningioma, grade II - atypical meningioma, and grade III - anaplastic (malignant) meningioma (Louis DN *et al.*, 2007). The majority of histologic subtypes are considered grade I tumors. The strongest criterion for classifying a meningioma into grades 2 and 3 is the proliferation index, defined as four mitoses per ten 40X fields. The diagnosis of an atypical (grade II) tumor requires either increased mitotic activity or at least three of the following criteria: patternless sheet-like growth, small cells with a high nuclear:cytoplasmic ratio, macronucleoli, hypercellularity, and 'spontaneous' or 'geographic' necrosis (Perry A, 2006). Anaplastic (grade 3) tumors have malignant features greater than those seen in grade 2 tumors, including a markedly elevated mitotic index (20 or more mitoses per ten 40X fields) (Perry A, 2006). The tumor of this report shares features of both grade I tumors (proliferation index < 4 mitoses per ten 40X fields, and morphological similarities with tumors subtypes) and grade II tumors (macronucleoli, and large areas of necrosis). Comparison of this tumor with human meningiomas using the WHO grading system has questionable relevance given the low number of meningiomas reported in this species.

Meningiomas do not have a definitive cytologic marker, and the pathologic diagnosis is usually made on the basis of tumor cytoarchitecture. In humans, EMA and vimentin are usually the most reliable immunohistochemical markers, although many tumors are also positive for cytokeratin (Perry A, 2006). S-100 protein immunostaining is variable and GFAP expression is rare (Summers BA *et al.*, 1995; Wanschitz J *et al.*, 1995). In a study that compared the immunohistochemical pattern of 15 canine meningiomas, all of the tumors were positive for vimentin and 12 of 15 (80%) for S-100 (Barnhart KF *et al.*, 2002). The intensity of the S-100 staining in these cases was rarely marked and the distribution of positive cells was highly variable. In this baboon case, tumor cells were stained strongly with vimentin and S-100. Similar to human cases, (Barnhart KF *et al.*, 2002) the positive staining with S-100 was detected in both cytoplasm and nucleus, however, its strong positive staining pattern differs from the weak/inconsistent pattern described for human and canine tumors (Barnhart KF *et al.*, 2002). Unlike most human cases, EMA immunostaining was negative both in the tumor and in the skin, therefore the specificity of this antibody in the baboon is questionable.

In humans, meningiomas are solidly associated with a cytogenetic alteration, that of monosomy 22, with mutation and/or deletions of the NF2 gene being described as an early tumorigenic event in 50–80% of sporadic and the majority of NF2-associated meningiomas (Perry A, 2006). The fact that approximately 40% of meningiomas display neither NF2 gene alterations or chromosome 22 allelic loss suggests that additional meningioma tumor suppressor genes may exist (Perry A, 2006; Rutledge MH *et al.*, 1994). In response to first reviewer's request: The following sentence in parenthesis has been deleted (Multiple growth receptor signaling pathways have been described as playing roles in the molecular pathogenesis of meningiomas. Platelet derived growth factor B (PDGF-B) and its receptor PDGFR is one of the more commonly over expressed growth factors. Another is epidermal growth factor receptor (EGFR), which is commonly expressed in meningiomas, but not in normal meningotheial cells (Perry A, 2006)).

Meningiomas are most commonly seen in middle-aged to older adults and are roughly two times more common in women than men (Perry A, 2006). As with humans, meningiomas in dogs have an increased prevalence with age and among females (Koestner A *et al.*, 2002; Summers BA *et al.*, 1995). Women have an apparent predisposition to develop meningiomas during pregnancy or the luteal phase of the menstrual cycle, so a hormonal source of stimulation has long been suspected (Perry A, 2006). In response to first reviewer's request: The following sentences in parenthesis have been deleted (Several steroidal and nonsteroidal hormone receptors have been detected in meningiomas. The most documented among these is the progesterone receptor (PR), and support for PR activation in these tumors is based on the fact that PR expression is higher in meningioma cells than in normal arachnoidal cells (Perry A, 2006). Additionally, progesterone has been shown to stimulate the *in vitro* growth of some meningioma cell lines, and PR antagonists are known to inhibit growth of some of these cells. PR expression appears to be most consistent in benign tumors, being roughly inversely proportional to both tumor proliferation and histologic grade (Perry A, 2006)). Although this case and the one described by McConnell and collaborators involved female animals, more cases will need to be described before meaningful conclusions can be made on the age and sex prevalence in this species.

Although rare, meningiomas should be included in the differential diagnosis list of intracranial neoplasms in baboons.

Acknowledgments

The authors wish to thank Marie Silva, Michelle Hohmann, Antonio Perez and the personnel of the Armed Forces Institute of Pathology for pathology support. The authors also thank Dr. Andy Ambrus of the Veterinary Pathobiology Department at Texas A&M University for his assistance with the immunohistochemistry.

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Fig. 1. Cranial cavity; baboon. A brown lobular mass is present on the floor of the cranial vault and compressing the left lateral aspect of the cerebellum (black arrow) and brainstem (white arrow).

Fig. 2. Meningioma; baboon; histopathologic appearance. Pleomorphic spindle to polygonal cells arranged in sheaths and vague whorls. Neoplastic cells have moderate to abundant cytoplasm, round to oval nuclei with prominent nucleoli (inset). HE. x 200. **Bar, 50 μ m.**

Fig. 3. Meningioma; baboon, histopathologic appearance. Loosely arranged cells that are palisading around a central vascular core, and occasional cells having ill-defined margins that imparted a syncytial-like pattern (inset). HE. x 200. **Bar, 50 μ m.**

Fig. 4. Meningioma; baboon, histopathologic appearance. Secondary changes composed of necrosis, hemosiderosis, and areas of mineralization surrounded by inflammatory cells (inset). HE. x 20. **Bar, 500 μ m.**