

## Case Report

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# Imaging Features and Decision Making in Retrobulbar Neuroendocrine Tumours in Horses – Case Report and Review of Literature

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With 4 figures

Received for publication September 12, 2006

### Summary

A 25-year-old Haflinger gelding was evaluated for chronic-progressive unilateral exophthalmos. Ultrasonographic investigation and magnetic resonance (MR) imaging revealed a retrobulbar space-occupying mass to be the cause of eyeball displacement. Ultrasonographic features were not sufficient to specify the type and extension of the lesion. Magnetic resonance scans, however, clearly displayed an infiltrative intracranial growth pattern but sparing of orbital soft tissues. Based on MR appearance, tentative diagnosis of an orbital soft tissue neoplasia was made and subsequently confirmed by histopathological investigation. The latter revealed a poorly differentiated neuroendocrine tumour. Retrospectively, MR changes resembled those seen with neuroendocrine neoplasms of the human skull. Even if histopathology remains to be elucidated by cytological or histological inspection, MR imaging of equine orbital tumours should provide the criteria necessary for evaluating the therapeutic options and associated prognosis.

### Introduction

Exophthalmos refers to an acquired protrusion of the eyeball due to an increase of orbital contents (Baujat et al., 2006). Usually, the cause of unilateral equine exophthalmos is a tumour, followed by mycotic infections of frontal sinus or guttural pouch, retrobulbar abscess, traumatic haematoma, and retrobulbar hydatid cyst (Cook, 1968; Scott et al., 1974; Barnett et al., 1988; Hubert et al., 1996; Basher et al., 1997). Distinction of benign versus neoplastic aetiology is of outstanding importance for prognosis and clinical management, as is the grading of tumour biology in latter cases. In general, orbital neoplasms can originate from orbital tissues, or invade the orbita from adjacent structures or the blood stream. Reported neoplasia-induced exophthalmos in horses have been caused by neuroendocrine tumours of unclear origin, neuroepithelial neoplasms of the retina and optic nerve, olfactory neuroblastomas, nasal and paranasal adenocarcinomas, paranasal sinus osteoma, squamous cell carcinoma, lipoma, melanoma, malignant lymphoma and microglioma (Lavach and Severin, 1977; Eagle et al., 1978; Bistner et al., 1983; Hill et al., 1989; van Maanen et al., 1996; Basher et al., 1997; Davis et al.,

2002; Stierstorfer et al., 2003; Scotty et al., 2004; Döpke et al., 2005). Apart from lipoma, virtually all these masses are capable of invading the bone and, thereby, entering the multiple cavities of the skull. Moreover, regional tumours like carcinomas, neuroendocrine neoplasms and olfactory neuroblastomas can cause remote metastases (Basher et al., 1997; Davis et al., 2002; Döpke et al., 2005). The risk of tumour cell dissemination via blood stream, however, is minimal compared to the probability of local destructive growth. Diagnostic imaging, therefore, bears useful prognostic implications and could influence the mode and aggressiveness of surgical therapy. The present manuscript highlights the magnetic resonance (MR) and sonographic features of a histologically confirmed neuroendocrine tumour of the orbit with progression into the rostral cranial fossa and paranasal sinuses in a horse.

### Case History

#### History and clinical findings

A 25-year-old Haflinger gelding was presented to the Equine Ophthalmology Service because of progressive proptosis of the right eyeball noticed by the owner about 6 weeks prior to admission. The horse was bright, alert and responsive, and revealed no clinical abnormalities on physical and neurological examination but absence of menace response in the affected eye. Direct and consensual pupillary reflexes were intact. The visual axis of the protruded eyeball was adducted and depressed (Fig. 1a). Palpation of the periorbital region was inconspicuous. There was a painless resistance to retropulsion. Intraocular pressure of the right eye was measured (Tonopen XL<sup>®</sup>, Fa. Medtronic Solan, Düsseldorf, Germany) within physiological limits (20 mmHg). At fundoscopic examination, the optical nerve appeared pale, swollen and edematous. No further abnormalities were seen in the fundus.

A high-frequency ocular sonography was performed to shed light on the retrobulbar compartment and to measure the eyeball diameters. A transpalpebral approach had been chosen, facilitated by application of sterile acoustic coupling medium to the eyelid and the transducers. Ultrasonographic images were obtained using an SONOLINE<sup>®</sup> (Siemens, Erlangen, Germany) Omnia with a VF13-5<sup>®</sup> 12 MHz linear

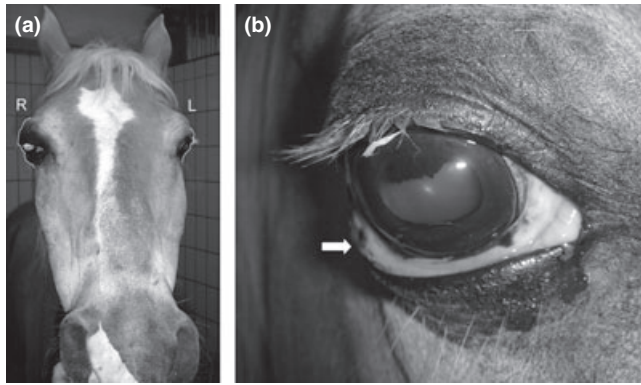


Fig. 1. Proptosis of the right eyeball at first presentation (a) and 1 year thereafter (b). (a) Lateral contours of the right (R) and left (L) eye are outlined. (b) At second admission, a marked edematous swelling of palpebral conjunctiva was present (arrow). Mucopurulent discharge is seen at nasal canthus and the upper eyelashes.

transducer. Control panel settings (power, gain and time-gain compensation slope) were adjusted in accordance with basic sonographic principles and own experiences of normal ocular echogenicity (Cronau, 2004; Cronau and Gerhards, 2004). At that stage, equatorial diameters of both globes did not differ significantly (right: 41 mm; left: 42 mm). Behind the right eyeball, an inhomogeneous and lobulated hyperechogenic soft tissue mass could be demonstrated compressing other orbital structures (Fig. 2). Based on clinical appearance and ultrasound findings, a retrobulbar tumour was diagnosed as a probable cause of the exophthalmos. The owners declined further diagnostic investigations and the animal was sent home without treatment.

One year later, the horse was presented again with severely aggravated proptosis, oedema of palpebral conjunctiva, chemosis and purulent ocular discharge (Fig. 1b). At neuro-ophthalmologic examination, menace response and direct and consensual pupillary light reflexes were absent in the right eye. Slit lamp biomicroscopy and direct ophthalmoscopy disclosed normal transparency of cornea, lense and vitreous body. However, retinal blood vessels appeared attenuated and the optic disc presented with an irregular outline. Sonographic findings were identical to those found at first ultrasound investigation but the right eye's equatorial diameter had decreased to 38.7 mm. Magnetic resonance images of the head were obtained under general anaesthesia using a 1.5 Tesla Siemens Magnetom Symphony® (Siemens, Erlangen, Germany), a human CP spine coil and a human CP body flex coil. The animal was positioned in left lateral recumbency, on a purpose-built, non-ferrous metal table of adjustable height. The head was positioned in the centre of the Magnetom. Magnetic resonance imaging (MRI) scans were performed as proposed by Ramirez and Tucker (2000) for ophthalmic imaging. In short, images were acquired in sagittal, transverse and dorsal planes, and included T1-weighted spin-echo, T2-weighted turbo spin-echo, and fluid-attenuated inversion recovery (FLAIR) sequences. Both T1- and T2-weighted images displayed an irregularly shaped, lobulated, highly infiltrative and osteolytic retrobulbar mass (Fig. 3). It appeared slightly hyperintense to skeletal muscles on T2-weighted images, and isointense to muscles in T1-weighted scans. On both sequences, the abnormal tissue was hypointense to retroorbital fat. At the base of the orbita, multiple blood vessels became prominent in the form of flow-void areas

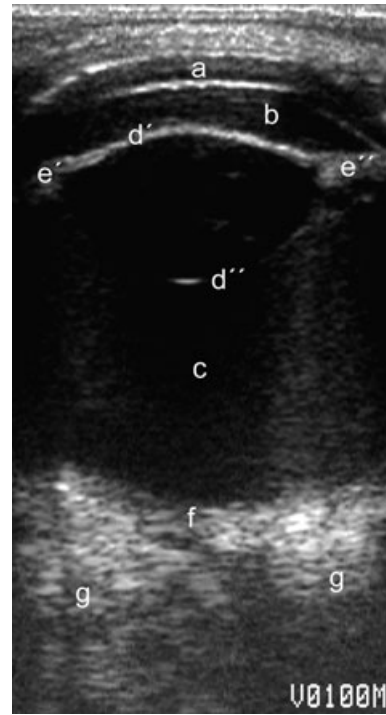


Fig. 2. Dorsal image of the (affected) right eye. The eyeball presents with normal sonographic architecture from anterior to its posterior wall: the cornea appears uniformly echogenic (a); both chambers (anterior, b; posterior, c) are anechoic; in between, the anterior (d') and posterior aspects of the lens capsule (d'') are seen as echogenic bands, perpendicular to the ultrasound beam, nasally and temporally bordered by slightly less echogenic iris and ciliary body [nasal (e'), temporal (e'')]. Retina, chorioid and sclera appear as an echogenic band (f) that, at its most posterior aspects, cannot be distinguished from a lobulated, isoechoic, extra-conal, orbital soft-tissue mass (g).

(Fig. 3d). The mass replaced large parts of the bony orbita, namely the wings of presphenoidal bone and the orbital part of lacrimal bone, and, thus, protruded into both the caudal maxillary cavity (Fig. 3g) and the rostral cranial cavity. Despite its rather aggressive growth, extra-ocular muscles and the optic nerve were not directly infiltrated. Similarly, intracranial portion of the tumour strictly was localized extradurally. The surface of the adjacent frontal lobe (Fig. 3e'') was moderately compressed and its cortical layers as well as the outermost subcortical white matter appeared mildly edematous on T2-weighted images (Fig. 3, arrowhead) and FLAIR sequence. The remainder of the head was within normal limits. Magnetic resonance imaging and sonographic findings were consistent with a highly infiltrative soft-tissue tumour extending into multiple cavities of the skull. The owner elected euthanasia on account of the severity of the lesion and the associated poor long-term prognosis.

The horse was dissected immediately after being put down. Macroscopic examination revealed a highly infiltrative soft tissue mass within the orbita, frontal and maxillary sinuses, and the rostral cranial fossa (Fig. 4A). In spite of exuberant growth, intracranial parts and those protruding into the sinuses were covered by an intact periosteum (Fig. 4A, a'). The tumour mass tightly surrounded the optic nerve without infiltrating its meninges or growing into the optic canal (Fig. 4A, d). Rostral cranial fossa was invaded by penetrating the wings of presphenoidal bone lateral to the cribriform plate (Fig. 4A, b). Tumour mass, then approached the cribriform

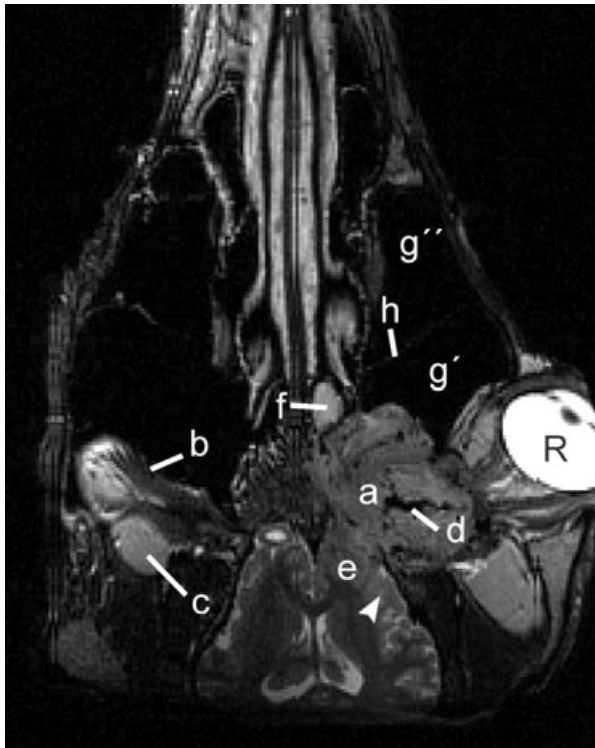


Fig. 3. T2-weighted MR scan in a slightly oblique dorsal (neuro-ocular) plane. Marked protrusion of the right (R) globe. Tumour mass (a) appears slightly hyperintense to extraorbital muscles (b) and hypointense to orbital fat (c). Its texture is not homogeneous but characterized by salt-and-pepper pattern corresponding to microseparation and formation of cell nests. Flow void areas (d) resemble intratumoural blood vessels. Intracranial extension goes along with mild compression of frontal lobe (e), hyperintense brain oedema (arrowhead) and asymmetry of lateral ventricles. Involvement of paranasal sinus (Sinus conchae mediae) is associated with fluid accumulation (f). (g) Maxillary sinus with caudal (g') and rostral (g'') chambers separated by the septum sinuum maxillarium (h).

plate subperiostally and covered 85% of its intracranial surface without evidence of progressing rostrally into the nasal cavity. Intracranial growth was leading to a mild extradural compression of the right frontal lobe. Invasion of the paranasal sinuses occurred through presphenoidal wings and the orbital part of the frontal and lacrimal bones closely to the frontomaxillary aperture but sparing palato- and nasomaxillary openings. At macroscopic inspection, neoplastic tissue appeared soft, greasy and reddish-grey with sparse stroma, and no signs of ossification or cartilage formation. For histology, samples from different parts of the neoplasm were obtained and immersed in 10% buffered formalin, embedded in paraffin, sectioned at 5  $\mu$ m and stained with a panel of neuropathological stains and immunomarkers. Further samples underwent fixation in glutaraldehyde, embedding in epoxy resin and ultrathin sectioning, and were evaluated through transmission electron microscopy. Histology, immunostaining and electron microscopy were consistent with the diagnosis of a poorly differentiated neuroendocrine tumour with osteolytic properties (Fig. 4B).

### Discussion

Retrobulbar tumours account for nearly 4% of all neoplasms in small animals (Gilger et al., 1992). They usually appear in adulthood without gender predisposition and are slightly more

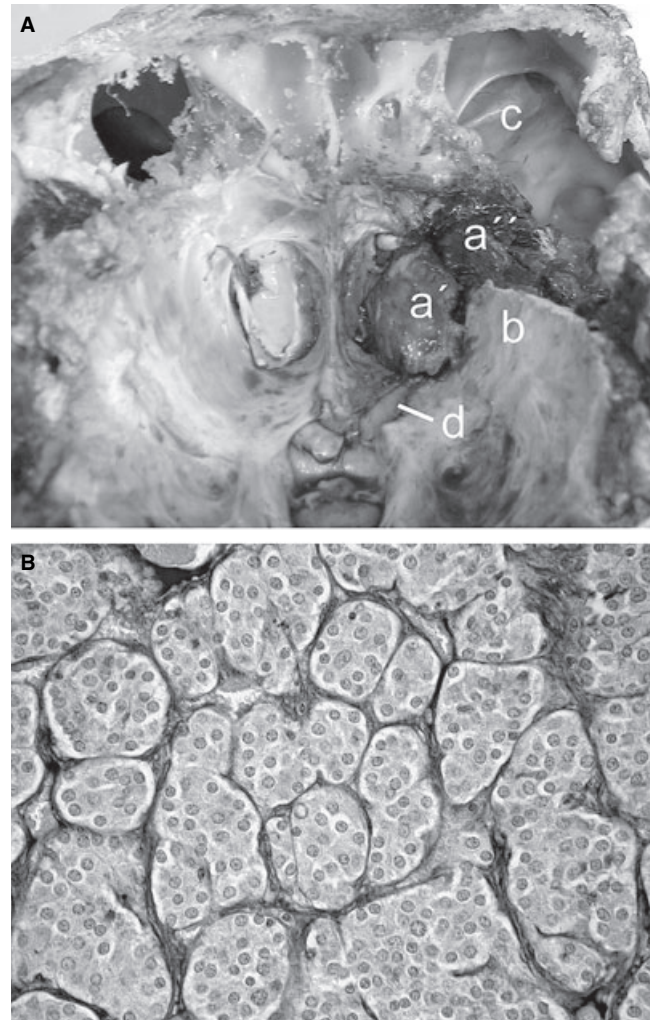


Fig. 4. (A) Macroscopic appearance of the tumour, seen from cranial cavity, with its (a') subperiosteal intracranial portion and (a'') orbital part. At its most rostral area, the presphenoidal wing (b) is replaced by neoplastic tissue. (c) Right frontal sinus. (d) Slightly edematous optic nerve within an unaffected optic canal. (B) Characteristic histological field with multiple neoplastic cell nests separated by mesenchymal microsepta ( $\times 650$ , periodic acid Schiff stain).

frequent in large breed dogs than in other breeds (Attali-Soussay et al., 2001). Albeit epidemiological details are lacking, their prevalence in horses is to be considered lower than in small animals, and lower than equine periorbital neoplasms such as squamous cell carcinoma, sarcoid and malignant melanoma (Lavach and Severin, 1977).

However, for horses presented with unilateral proptosis, orbital mass lesions resemble the most likely aetiology after having ruled out buphthalmos (enlarged globe due to increased intraocular pressure) and exorbitism (protrusion of the eyeball due to a shallow orbit). The combination of static eyeball displacement, protrusion of nictitating membrane, conjunctival hyperaemia, papillary oedema and painlessness on palpation is strongly suggestive of an orbital pressure rise due to neoplasia. Those retroorbital tumours can arise from orbital tissues, extend from adjacent structures, or metastasize to the orbit from remote areas (Attali-Soussay et al., 2001). Irrespective of their origin, nearly all reported retroorbital tumours in horses, and 60% of that in small animals have already invaded the

orbital soft tissues, the calvaria or adjacent cavities of the skull, at the time of admission (Lavach and Severin, 1977; Eagle et al., 1978; Bistner et al., 1983; Barnett et al., 1988; Hill et al., 1989; van Maanen et al., 1996; Basher et al., 1997; Attali-Soussay et al., 2001; Davis et al., 2002; Stierstorfer et al., 2003; Scotty et al., 2004; Döpke et al., 2005). Hence, assessment of growth pattern, rather than of histogenesis, is of major importance for evaluating prognosis and treatment options.

As seen with this case, ultrasonography may be helpful to confirm the presence of a retrolbulbar mass, but it is not suitable for evaluating tumour type or extension (Miller and Carter, 1985). Another draw-back of this technique is the possibility to miss inferomedial masses due to difficult access (Arnold-Tavernier et al., 1997). This diagnostic gap can be easily overcome by an MR imaging that exhibits deep tissue penetration and an excellent spatial resolution. Even if computed tomography is superior in bone imaging, MR scans readily display structures associated with nasal and paranasal sinuses and shed light on the involvement of orbital soft tissues and the brain (Arencibia et al., 2000, 2001; Ramirez and Tucker, 2000; Probst et al., 2004). When staging orbital masses in humans, extension of intracranial and intraorbital involvement are evaluated separately (Iannetti et al., 2005). Intracranial extension is the keystone for predicting the clinical outcome, and planning surgical therapy, whereas staging of intraorbital growth implies whether the eyeball and associated structures have to be removed too. Accordingly, McCary et al. (1996) distinguished: (A) tumours adjacent to the orbit, without infiltration of orbital wall; (B) tumours eroding the orbital wall, without eyeball displacement; (C) tumours eroding and infiltrating the orbital wall, with eyeball displacement but without periorbital involvement and (D) tumours with periorbital invasion. Type A tumours are approached via craniofacial surgery, if the cranial vault is involved, and via paralaronasal route if not, but the bony orbita is spared from being touched. In neoplasms of classes B–D, however, removal of the orbital medial wall is strongly recommended. The question whether or not surgical therapy is indicated in horses with ethmoidoorbital tumours had been discussed by Basher et al. (1997). Their report on two horses that underwent dorsal orbitotomy and cytoreductive surgery revealed survival times over 19 months, with both horses still being alive at the time of paper submission. The main concern was the possibility of cranial vault invasion. Accordingly, absence of neurological signs was considered to render a surgical intervention justifiable (Basher et al., 1997). Today, advanced imaging is prone to contribute largely to this discussion. However, experiences in removing bony structures surrounding the eye in horses is restricted to the zygomatic arch in terms of orbital rim resection (Beard and Wilkie, 2002). Unless further studies are carried out, cytoreduction remains the treatment of choice. Similarly, 75% of retroorbital tumours in dogs and 80% in cats cannot be excised in toto (Attali-Soussay et al., 2001). In the present case, the owners denied any surgical intervention. Although, the survival time in this slow growing tumour exceeded 1 year.

Staging of orbital invasion bears further impact on the surgeon's technical skills as orbital exenteration does not improve survival times in humans unless extraocular muscles, optic nerve, ocular bulb, or the skin overlying the eyelid are involved (Iannetti et al., 2005). Based on a retrospective analysis involving 38 patients with ethmoidoorbital tumours,

Iannetti et al. (2005) recommended the following grading system: (I) tumours eroding and infiltrating the orbital wall; (II) tumours invading periorbital fat; (III) tumours invading the structures listed above. If the neoplasm is graded as II or less an eye-sparing surgery should be considered. However, in stage III, sparing of orbital soft tissues will influence the survival time negatively. Experiences in equine medicine reveal similar results. Neoplastic infiltration of the globe and, sparsely, of the eyelids and conjunctiva necessitates enucleation. In extensive infiltration of the eyelids, conjunctiva, globe, optic nerve and orbital soft tissues, removal of the entire orbital content (exenteration) remains the treatment of choice (Beard and Wilkie, 2002). Both procedures are most commonly performed via transpalpebral technique (Brooks, 1992). Basher et al. (1997) based their decision to perform an exenteration in two horses on adpection of the surgical field after dorsal orbitotomy. In addition to clinical assessment of menace response and pupillary light reflexes and ophthalmoscopic examination, involvement of the globe and optic nerve can be estimated preoperatively through ultrasonography and MR imaging. However, proper assessment of tumour-nerve relationship by ultrasound requires extensive personal experience. It also hampers from poor penetration of large retroorbital masses and from artefacts due to different indices of sound wave refraction in highly heterogeneous tissue (Karim et al., 2004). Whether the optic nerve really escapes from tumour ingrowth can be seldom answered with confidence. The same caveat holds true for infiltration of deep retroorbital contents and the bony part of the orbit. Magnetic resonance investigations, on the other hand, suffer from long acquisition times. In properly anesthetized animals, flickering eyeball motions are readily suppressed and do not cause artefacts or degradation of spatial resolution during scanning time. Early studies on optic nerve imaging in humans emphasize the suitability of turbo spin echo sequences compared to other MR techniques regarding signal-to-noise ratio and contrast (Hennig et al., 1986; Weigel et al., 2006). In particular, T2-weighted images display hyperintense cerebrospinal fluid (CSF) signal and yield high contrast between optic nerve, CSF film and the adjacent intraorbital soft tissue (Weigel et al., 2006). Even if 3.0 Tesla scanners are required for obtaining quantitative nerve parameters, clinical devices with 1.5 Tesla field strength proved suitable for acquisition of morphologic details (Weigel et al., 2006). In the present case, on T2-weighted images, the optic nerve had been surrounded by a contiguous hyperintense lining reflecting an intact and non-invaded subarachnoid space.

Treatment, other than surgery, is dependent on tumour type and biology. Even though the highly infiltrative behaviour of neuroendocrine tumours in horses (van Maanen et al., 1996; Basher et al., 1997) renders the success of surgical interventions questionable, there are no reports on adjuvant therapies. In humans, the best long-term tumour control has been achieved by a combination of surgery and radiation therapy after early diagnosis (Gujrati and Donald, 2005). Even if salt-and-pepper MR appearance of this equine tumour resembles that described in human counterparts, conventional imaging does not offer key clues to deciphering the cellular origin (Sharma et al., 2005). One step forward in the diagnosis of neuroendocrine neoplasms was made by Bustillo et al. (2004) who performed octreotide scintigraphy in the human head and neck tumours. When coupled to a radioisotope, this somatostatin analogue is



actively taken up by cells expressing somatostatin type 2 receptors. This technique yields a remarkable sensitivity of 97% and a specificity of 82%. Other supportive indices may arise from physical examination as neuroendocrine neoplasms regularly go along with mild autonomic dysfunctions. Definite diagnosis in animals, however, is still established by fine-needle aspiration cytology or histopathological examination of excision biopsies harvested at advanced stages of disease (Basher et al., 1997; Attali-Soussay et al., 2001).

### Acknowledgements

We are particularly grateful to Gina Farkas and Karin Stingl for excellent technical assistance. Moreover, we thank Prof. Dr Juergen Schlegel, Division of Neuropathology, Technical University of Munich, for his neurooncological advices, and Dr Christiane Kafarnik for her critical comments that have been incorporated into the final draft.

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