

Advanced reactive astrogliosis associated with hemangioblastoma versus astroglial-vascular neoplasm (“angioglioma”)

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Folia Neuropathol 2007; 45 (3): 120-125

Abstract

Hemangioblastomas of the central nervous system are often accompanied by a cyst exhibiting an extensive astroglial reaction. The cyst’s wall might be composed of various astroglial elements including reactive pilocytic or gemistocytic and hypertrophic astrocytes. The small tissue samples composed of compact gliotic tissue are sometimes nonrepresentative for primary hemangioblastoma tumour and might be confused with both pilocytic and diffuse infiltrative astrocytoma. Moreover, vascular anomalies of hemangioblastoma-like pattern could be combined with true neoplastic glial proliferation. Such association of glioma with certain types of vascular anomalies has been designated as angioglioma.

In the current study we evaluated a series of hemangioblastomas accompanied by advanced astrogliosis of adjacent brain tissue. In some cases the histopathological features of pilocytic gliosis with numerous Rosenthal fibres and eosinophilic granular bodies strongly suggest the diagnosis of pilocytic astrocytoma. One tumour was identified as an angioglioma exhibiting a combination of hemangioblastoma-like tissue and pilocytic astrocytoma. The recognition of such an entity is important in differential tumour diagnosis and prognosis.

Key words: capillary hemangioblastoma, pilocytic gliosis, angioglioma.

Introduction

Capillary hemangioblastomas are relatively uncommon, vascular-rich tumours of uncertain histogenesis often associated with well-known von Hippel-Lindau (VHL) familial syndrome [2,30]. Hemangioblastomas are regarded as benign tumours of grade I according to the WHO grading system [16].

They are often associated with VHL disease, a hereditary multisystem neoplastic disorder characterized by development of retinal angiomas, hemangioblastomas of the central nervous system (CNS) and various visceral tumours, including renal clear cell carcinoma, pheochromocytoma, pancreatic microcystic adenoma, cyst adenoma or endolymphatic sac tumour [17,22,23,27,30]. CNS hemangioblastomas

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are usually located in the cerebellum but they may arise in the medulla, spinal cord or cerebrum. In the majority of cases the tumours appear well-defined and cystic.

Hemangioblastomas associated with a cyst might exhibit an advanced astroglial reaction in adjacent brain tissue or the cyst wall. Sometimes the surgeons may fail to reject the primary hemangioblastoma nodule. The small biopsies obtained from the cystic wall might contain only solid gliotic tissue closely resembling neoplastic process of astroglial origin. The dense glial tissue is often composed of various forms of astroglial cells including reactive pilocytic or gemistocytic/hypertrophic astrocytes and morphologically atypical ones. The gliotic tissue samples, non-representative for primary tumours, are sometimes misleading, with both well-differentiated astrocytoma and diffuse infiltrative gliomas. Especially in the cases with intensive pilocytic gliosis the incorrect diagnosis of neoplastic glial process of pilocytic type might be mistakenly established.

There are also tumours exhibiting association of hemangioblastoma-like tissue and true neoplastic proliferation of astroglial cells. The combination of vascular anomalies and gliomas is often defined as angioglioma [1,11,14,19,26]. Vascular anomalies might be associated with diverse glial components including fibrillary astrocytoma [20], pilocytic astrocytoma [19], astrocytoma with a papillary growth pattern [28], pleomorphic xanthoastrocytoma [18], oligodendroglioma [5,6], mixed oligo-astrocytoma [26] or ganglioneuroma [4]. These astroglial tumours are usually associated with vascular anomalies such as arteriovenous malformation (AVM) or cavernous angioma.

In the current study we evaluated the histopathological features of gliotic tissue adjacent to the hemangioblastoma nodules in a series of 28 neurosurgical cases. One case was identified as angioglioma composed of a dense vascular network of predominant hemangioblastoma-like pattern and pilocytic astrocytoma. The aim of the study was to stress the difficulties in interpretation of massive pilocytic astrogliosis associated with hemangioblastoma-like vascular component.

Material and methods

The study was performed on formalin-fixed and paraffin-embedded biopsy tissues of 28 cases of

hemangioblastomas obtained during neurosurgical resection. In 23 cases the tumour was located in the cerebellum, in 5 cases in the spinal cord. The paraffin sections were routinely stained with haematoxylin-eosin (H&E) and Gomori's method. Immunohistochemical analyses were performed on paraffin-embedded specimens according to the labelled streptavidin-biotin complex method with DAB as chromogen using antibodies against glial fibrillary acidic protein (GFAP), vimentin and Ki67 (all antibodies from Dako).

Results

The hemangioblastomas showed a histopathological picture of reticular or cellular pattern. The majority of tumours consisted of numerous small, capillary-like vascular channels and typical stroma composed mainly of vacuolated, foamy cells (Fig. 1). Silver impregnation evidenced the abundant reticulin fibres (Fig. 2). The stromal cells displayed lipid-rich, vacuolated cytoplasm, resulting in its typical foamy or 'clear cell' morphology. The cells varied in size and occasionally showed atypical and hyperchromatic nuclei. The Ki67 index was low.

Among 28 cases of hemangioblastomas, the cyst wall and/or surrounding brain tissue was available in 15 tumours. The adjacent brain tissue often exhibited diffuse, massive gliosis (Fig. 3). Some fragments of cyst wall were formed exactly by compact pilocytic gliosis composed of spindle-shaped pilocytic astroglial cells and abundant Rosenthal fibres and/or granular bodies (Fig. 4). The cytoplasm of these cells was strongly stained for GFAP (Fig. 5).

In a few cases large areas of the cerebellum displayed diffuse proliferation of astroglial cells with atypical features that more or less resembled well-differentiated astrocytoma (Fig. 6).

One tumour was composed of two distinct tissue components: abnormal vascular elements and astroglial stroma. The astroglial component exhibited mainly spindle-shaped, pilocytic astrocytes, numerous eosinophilic granular bodies and Rosenthal fibres (Fig. 7). This histological and GFAP immunohistochemical appearance of the glial component was compatible with true pilocytic astrocytoma rather than reactive astrogliosis. Numerous vascular channels including capillary-like vessels were observed among the tumour cells. Some of the vascular com-

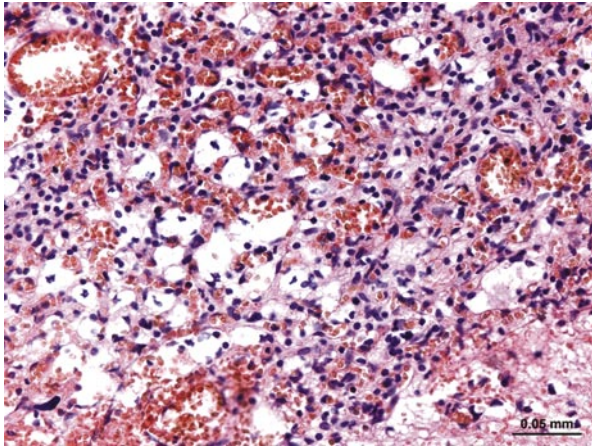


Fig. 1. Hemangioblastoma consisting of small, capillary-like vascular channels and typical foamy stromal cells. H&E

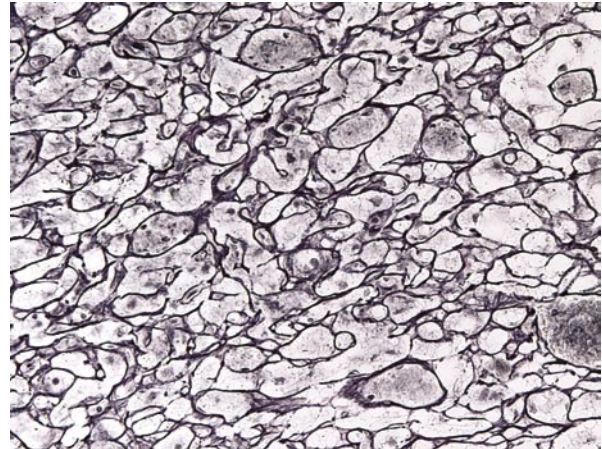


Fig. 2. Dense network of reticulin fibres. Gomori's method

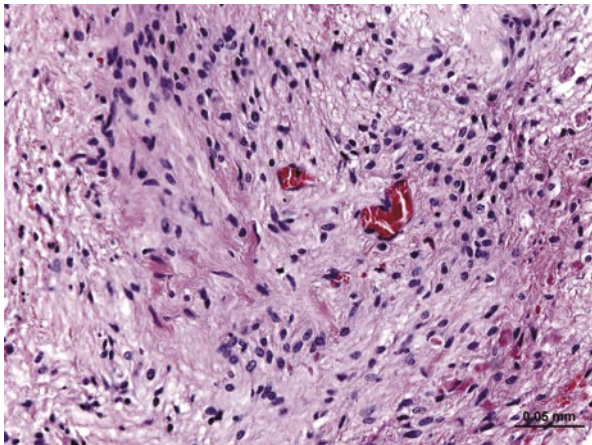


Fig. 3. Brain tissue adjacent to hemangioblastoma exhibiting advanced astrogliosis. H&E

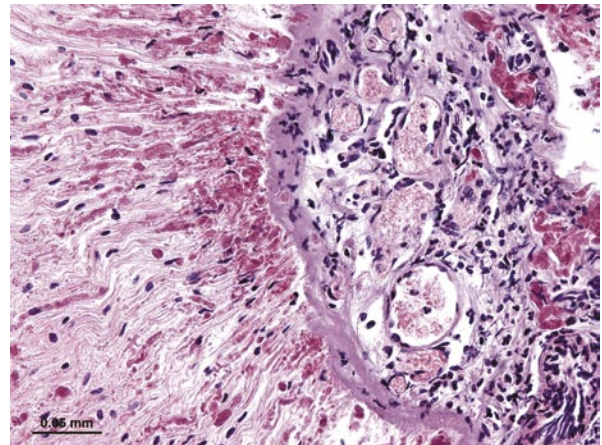


Fig. 4. Cyst wall of hemangioblastoma composed of compact pilocytic gliosis with numerous Rosenthal fibres. H&E

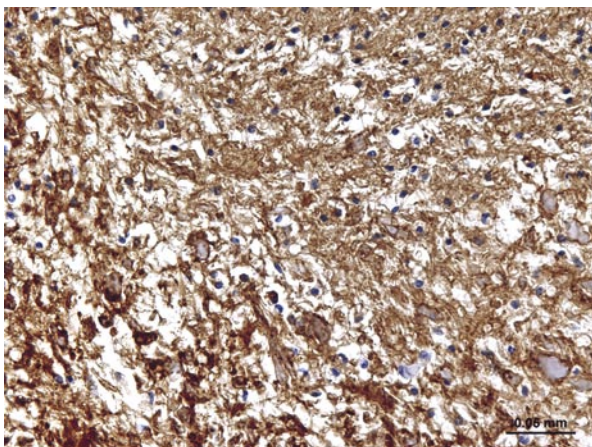


Fig. 5. Strong GFAP expression in pilocytic reactive astrogliosis. H&E

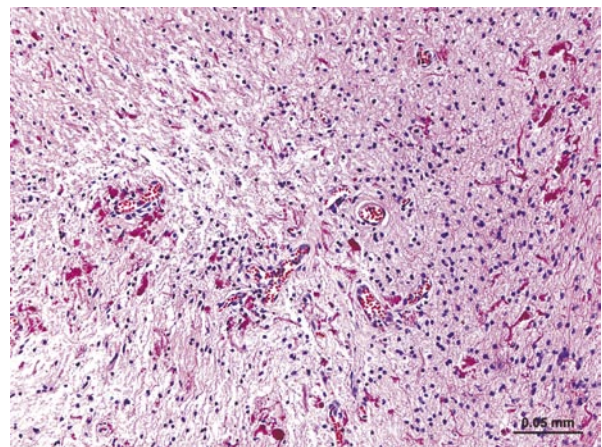


Fig. 6. Diffuse proliferation of astroglial cells with focal atypical features. H&E

ponents displayed a distinct hemangioblastoma-like pattern (Fig. 8). Large parts of the tumour exhibited an abundant vascular component composed of both capillary-like vessels and dilated vessels of different size (Fig. 9). Abnormally enlarged vein-like vessels and arteries, resembling arteriovenous malformation, were also seen (Fig. 10). Immunohistochemically, the main glial component was strongly positive for glial fibrillary acidic protein (GFAP) and vimentin. This tumour with components of pilocytic astrocytoma and abundant, predominantly hemangioblastoma-like vascular elements was identified as angioglioma.

Discussion

Capillary hemangioblastomas of CNS are included in the group of tumours of uncertain origin in the updated World Health Organization (WHO) histopathological classification [16]. Hemangioblastomas might exhibit a wide spectrum of microscopic appearance [2,3]. They are composed of an abundant capillary network and characteristic stromal cells which are considered to be a true neoplastic element. However, the problem of histogenesis of stromal cells still remains unclear [13,21]. It has been documented that some stromal cells, mainly in the cellular variant

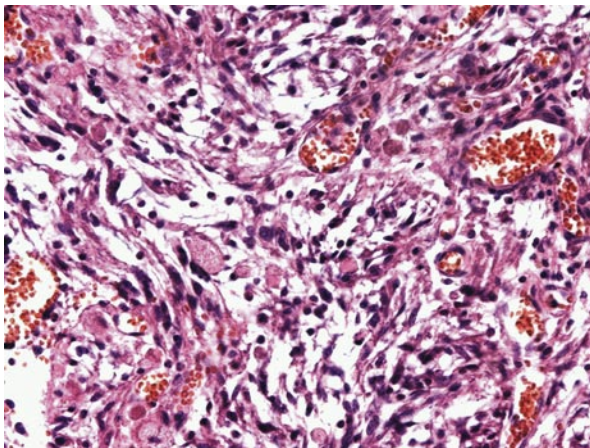


Fig. 7. Tumour designed as angioglioma with two distinct components: pilocytic astrocytoma with numerous granular bodies and abundant vascular elements. H&E

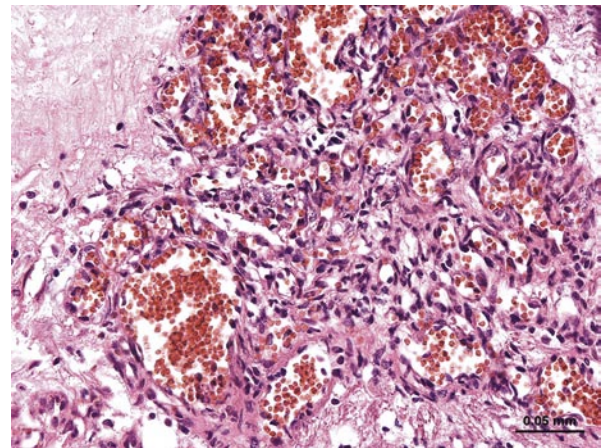


Fig. 8. Vascular component of angioglioma exhibiting hemangioblastoma-like pattern H&E

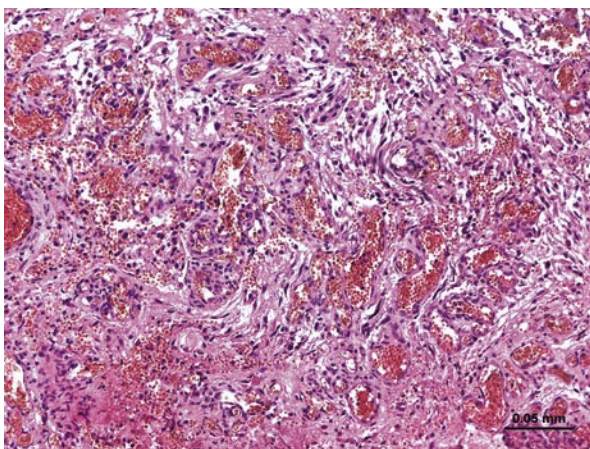


Fig. 9. Highly vascularized part of pilocytic astrocytoma with abundant blood vessels of various size. H&E

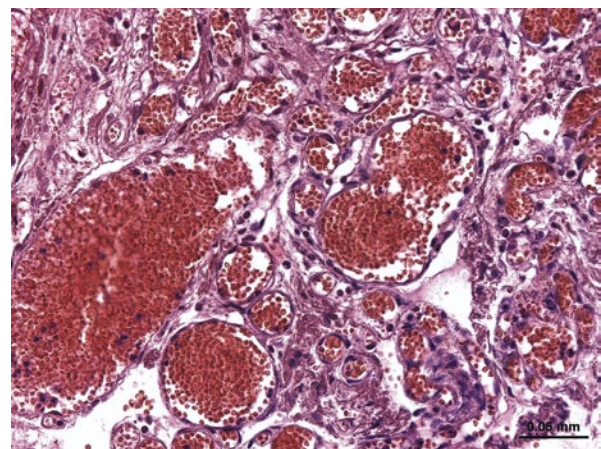


Fig. 10. Abnormally enlarged vessels consisting of dilated vein-like vessels and arteries, resembling arteriovenous malformation. H&E

of hemangioblastoma, exhibited immunoreactivity for glial fibrillary acidic protein (GFAP) [7,12,15,25].

In the present report we demonstrated various histopathological features of compact gliotic tissue associated with hemangioblastomas in a series of 28 cases. The brain tissue adjacent to the primary hemangioblastoma tumour exhibited a more or less advanced astroglial reaction that was predominantly of pilocytic type with numerous Rosenthal fibres and eosinophilic granular bodies. Considering the origin of gliotic tissue, the most important issue is to distinguish the reactive astroglial cells from true neoplastic astrocytes. The individual cells might be identified by their nuclear shape, size and heterogeneity. The most common pilocytic form of astrogliosis in hemangioblastoma is strikingly similar to astroglial neoplastic process of pilocytic origin. A misleading diagnosis is possible as pilocytic astrocytomas and hemangioblastomas share the main clinical and neuroradiological features. Young and middle-aged adult patients are most often affected in both tumours. Hemangioblastomas and pilocytic astrocytomas are most commonly located in the cerebellum or spinal cord and are usually accompanied by a large cyst with mural nodule. Genetic analysis demonstrated allelic deletion of the VHL allele in the stromal component of the hemangioblastoma, whereas the reactive glial tissue does not show this gene deletion, which is consistent with the assessment that the glial component represents a reactive process [24].

Some biopsy specimens lack the representative fragment of hemangioblastoma tissue necessary for the correct diagnosis. In such cases the microscopic features of massive reactive gliosis of pilocytic type developing within the cyst wall of hemangioblastoma might strongly suggest the diagnosis of pilocytic astrocytoma. Reactive gliosis is also a frequent feature of brain tissue surrounding some other tumours, i.e. craniopharyngiomas [16,29]. However, the authors indicated that differentiation of anisomorphic and isomorphic gliosis is impossible by cytological examination.

In our few cases large areas of the cerebellum displayed marked fibrillar gliosis resembling well-differentiated astrocytoma. The chronic glial reaction displaying gemistocytic and hypertrophic form of astroglia might be confused with gemistocytic subtype of diffusely infiltrative astrocytoma. The correct diagnosis is essential, as the appropriate treatment

and prognosis of diffusely infiltrative astrocytomas and hemangioblastoma are different.

Hemangioblastomas are not always easily distinguished from other tumours with an exceptionally abundant vascular component, i.e. highly vascularized astrocytomas. Astrocytomas quite frequently occur in combination with various vascular anomalies. Tumours composed of an extensive vascular component and glioma tissue are sometimes designated as angiogliomas. This is a rather enigmatic entity without confirmation in the WHO brain tumours classification [16]. Since the early descriptions of Bonnin et al. [1] and Fisher et al. [9], other reports of cases designed as angioglioma have been described [4-6,8,10,11,26]. The glial components of such tumours were diverse. The most common vascular anomalies were AVM [4,6,10] or cavernous angioma [5,11,26]. However, some authors have suggested that only true neoplastic vascular neoplasm as hemangioblastoma combined with glioma might be designated as angioglioma [1]. Such a combination was documented in one tumour from our series that was composed of a dense vascular network mainly of hemangioblastoma-like pattern and distinct pilocytic astrocytoma. The histogenesis of such a combination within one tumour is unclear. Such tumours might arise from ordinary pilocytic astrocytoma with extremely extensive vascular proliferation or from vascular tumours of hemangioblastoma origin that undergo neoplastic transformation of the glial component.

This study documents certain difficulties in the interpretation of pilocytic astrogliosis associated with a hemangioblastoma-like vascular component. In some cases of such combination the recognition of angioglioma should be taken into consideration. It is noteworthy that only the representative biopsy samples warrant the correct diagnosis.

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