

# Heterogeneity of histopathological presentation of pilocytic astrocytoma – diagnostic pitfalls. A review

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## Abstract

*Pilocytic astrocytomas (PAs) are the most frequent primary astroglial tumours affecting children and adolescents. They occur sporadically or in association with a genetically determined syndrome – neurofibromatosis type 1. Classic PA usually manifests as a well-circumscribed, often cystic, slowly growing tumour, which corresponds to WHO grade I. The majority of pilocytic tumours arise along the neuraxis, predominantly in the cerebellum. They are associated with favourable long-term outcome or spontaneous regression, even after incomplete resection. However, the behaviour and prognosis might also be related to tumour histology and location. Pilomyxoid astrocytoma (PMA) represents a variant of classical PA with more invasive growth and increased risk of recurrences and dissemination. Typically, PAs exhibit distinct histology with biphasic architecture of loose, microcystic and compact, fibrillary areas. However, some tumours arise in an uncommon location and display heterogeneous histopathological appearance. The morphological pattern of PA can mimic some other glial neoplasms, including oligodendroglioma, pleomorphic xanthoastrocytoma, ependymoma or diffuse astrocytoma. Not infrequently, the advanced degenerative changes, including vascular fibrosis, and recent and old haemorrhages, may mimic vascular pathology. Sometimes, the neoplastic piloid tissue can resemble reactive gliosis, related to long-standing non-neoplastic lesions. Not infrequently, PA exhibits histological features typical for anaplasia, including necrosis, mitoses and glomeruloid vascular proliferation that can suggest a diffuse high-grade glioma. However, even those PAs that lack distinct histological features of anaplasia can behave unpredictably, in a more aggressive manner, with leptomeningeal spreading. Genetic alterations resulting in aberrant signalling of the mitogen-activated protein kinase (MAPK) pathway have been considered to underlie the development of PAs. The most commonly identified KIAA1549-BRAF fusion is important for appropriate tumour molecular diagnosis.*

*In this paper we summarize the clinicopathological presentation of PAs, with emphasis on their heterogeneous morphology, based on our own experience in the field of surgical neuropathology and the literature data. Diagnosis of pilocytic tumours requires careful analysis of clinical, histopathological and molecular features to avoid misinterpretation of these benign neoplastic lesions.*

**Key words:** pilocytic astrocytoma, pilomyxoid variant, low-grade glioma, heterogeneous morphology.

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## Introduction

Pilocytic astrocytoma (PA) is a well-circumscribed, well-differentiated, slowly growing tumour, corresponding to WHO grade I. It is included in the group of “other astrocytic tumours” in the revised 4<sup>th</sup> edition of the current 2016 WHO Classification of Tumours of the Central Nervous System [25]. Typically, PAs exhibit a non-diffuse pattern of cell growth, although they may locally infiltrate leptomeninges or adjacent brain tissue.

The vast majority of cases are associated with benign clinical behaviour and a favourable long-term outcome, particularly those of cerebellar location and complete surgical resection [27-29,60]. However, some tumours, despite their benign histology, may behave more aggressively. The pilomyxoid variant of pilocytic astrocytoma (PMA) is suggested to represent a subtype with more invasive growth and increased risk of recurrences [49,50]. Occasionally, the classic PA may exhibit the distinct histological features of anaplasia such as necrosis, mitoses and vascular proliferation [10,25,31,53,82,90,101]. Some other factors, including partial resection, brainstem location and adult age, are also associated with a worse prognosis [27].

Generally, PA is characterized by distinct clinicopathological features, but not infrequently it manifests heterogeneous appearance, including older age of patients, uncommon location, lack of classical biphasic pattern, presence of nuclear atypia, mitoses, necrosis and vascular glomeruloid changes. In such cases the accurate diagnosis may be challenging [60]. Moreover, the biological behaviour of pilocytic astrocytomas, independently of their clinical course and morphology, is not always predictable.

This report evaluates our own experience in the field of surgical neuropathology of PA and reviews the literature. The correct diagnosis of PA has important therapeutic and prognostic implications; thus the careful analysis of clinical, histopathological and molecular features is required to avoid misinterpretation in differential diagnosis.

## Incidence

Pilocytic astrocytomas occur most commonly in paediatric and young adults in the age group 0-19 years [71], constituting 10% of cerebral and 85% of cerebellar tumours. They are often associated with neurofibromatosis type 1 (NF1), especially those cas-

es developing in the optic/chiasmatic region. The latter account for at least 40% of cases associated with NF1 [58]. Pilocytic astrocytomas are rarely encountered in patients older than 50 years [20,37,59]. The oldest patients with pathologically confirmed PA were an 86-year-old woman [63] and an 85-year-old man with post mortem diagnosis of PA in the brainstem [20].

## Localization

Pilocytic astrocytomas may arise along the entire neuraxis. They affect preferentially the cerebellum but may arise in the optic pathway, hypothalamus, brainstem and spinal cord [27,60]. Less commonly they are located in the basal ganglia and cerebral hemispheres. In the paediatric age group, PAs develop preferentially in hemispheres of the cerebellum, followed by the brain stem and spinal cord. Occasionally, PA may develop in the neurohypophysis/suprasellar region [79] and pineal gland [8]. Brain stem tumours usually appear as a compact dorsal exophytic mass lesion [5]. Exceptionally, paediatric PA may occur as a cerebellopontine angle mass, well separated from the brain stem [65,92].

In adult patients, the majority of PAs are located supratentorially [14,18], less commonly in the cerebellum [96,100], cervicomedullary region [103] or other parts of the spinal cord [37,74,86]. Occasionally, PA in adult patients are associated with haemorrhages and manifest as spontaneous intracranial haemorrhage [57,59].

## Clinical and radiological findings

The clinical presentation of PA depends on tumour location. The neuroimaging findings of PAs, including conventional and advanced magnetic resonance imaging (MRI) sequences, depend on the tumour size, location and tendency to infiltrate the surrounding structures [22]. Typically, PA occurs on computed tomography (CT) and MRI as a well-demarcated, contrast-enhancing lesion that reveals characteristic solid and micro- or macrocystic components [98]. The cyst with an enhancing mural nodule is a classic radiological feature. The solid part usually shows homogeneous contrast enhancement. On MRI, the tumour appears as hypo- or isointense lesion on T1-weighted images and hyperintense on T2-weighted images [55]. Tumour calcifications occur only occasionally.

In some PA cases, the neuroradiological images may be unusual, including small cyst formation, heterogeneously or irregularly enhancing tumour nodules and internal haemorrhages [68]. Uncommonly, the radiological features of PAs can resemble high-grade gliomas.

## Histopathology

The borders of PAs are usually well-defined, but sometimes the neoplastic infiltration of adjacent brain tissue can be seen (Fig. 1A). Tumours of cortical location may demonstrate invasion of the leptomeninges with extensive desmoplastic reaction (Fig. 1B).

Typically, PA exhibits a well-recognizable biphasic pattern with a mixture of loose microcystic and more compact regions (Fig. 1C, D). Such distinct biphasic architecture is particularly evident in tumours of cerebellar location. Numerous small cysts of different size and shape, filled with eosinophilic, myxoid material, could be seen (Fig. 1E, F). The microcystic, loose-textured areas contain stellate astroglial cells resembling protoplasmic astrocytes and globular, mulberry-shaped, eosinophilic granular bodies (EGBs) or hyaline globules (Fig. 2A). Eosinophilic granular bodies are formed by aggregates of tiny granular bodies (Fig. 2B) situated within the astrocytic processes. They exhibit periodic acid-Schiff,  $\alpha_1$ -antichymotrypsin and  $\alpha_1$ -antitrypsin reactivity. The compact parts of the tumour are mostly composed of bipolar piloid cells with delicate “hair-like” processes. Some more solid areas may contain a large amount of eosinophilic structures corresponding to EGBs and/or hyaline droplets (Fig. 2C) or Rosenthal fibres (Fig. 2D). The latter appear as eosinophilic, hyaline, corkscrew-like structures (Fig. 2E), which accumulate within the tumour cell processes. Ultrastructurally, they are electron-dense granular masses surrounded by intermediate glial filaments. Rosenthal fibres are composed of  $\alpha$ -B-crystallin and do not express glial fibrillary acidic protein (GFAP) positivity or exhibit only peripheral immunostaining. Some regions are composed entirely of a large number of Rosenthal fibres. It is well known that both EGB and Rosenthal fibres are not specific for PA; nevertheless, they can serve as a suitable marker of slow-growing lesions. Eosinophilic granular bodies are often present in other non-diffuse glial and glioneuronal tumours, including ganglioglioma and pleomorphic xanthoastrocytoma. Rosenthal fibres are also

a frequent component of chronic reactive piloid gliosis associated with other neoplastic brain lesions, i.e. craniopharyngioma, cerebellar haemangioblastoma or spinal ependymoma. Similar looking gliosis might also be encountered in the pineal cyst and various non-neoplastic lesions associated with the reactive response of astroglia. It is noteworthy that both EGBs and Rosenthal fibres are not required for the diagnosis of PA.

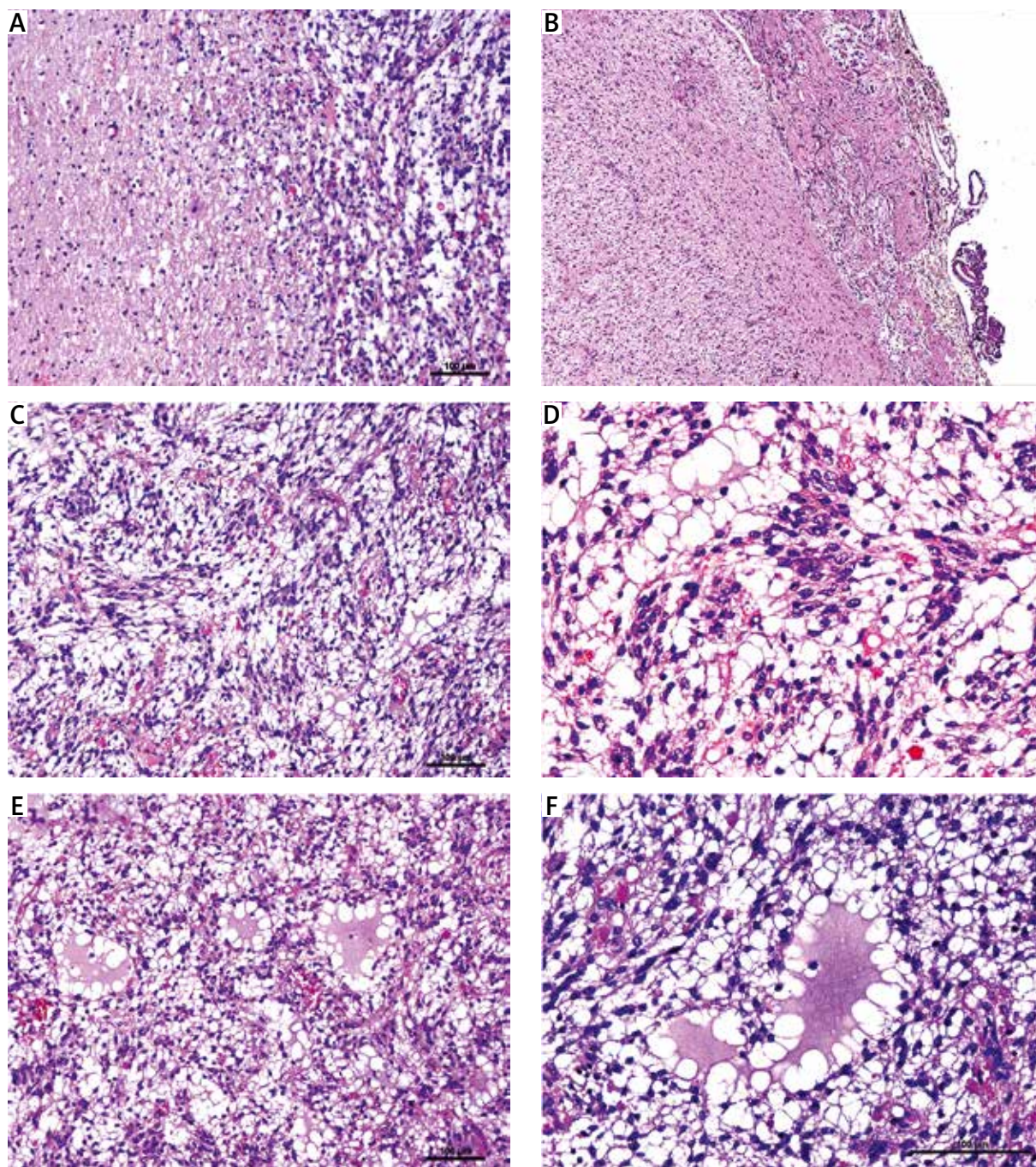
Immunohistochemically, the neoplastic cells of PAs show strong GFAP immunoreactivity (Fig. 2F), S-100 protein and OLIG2 positivity.

The classic biphasic architecture was evident in the majority of PAs cases. However, some tumours are composed predominantly or even entirely of one growth pattern. They display either microcystic or solid appearance, with or without EGBs or Rosenthal fibres. Such monomorphic morphology can be confusing and challenging for neuropathologists.

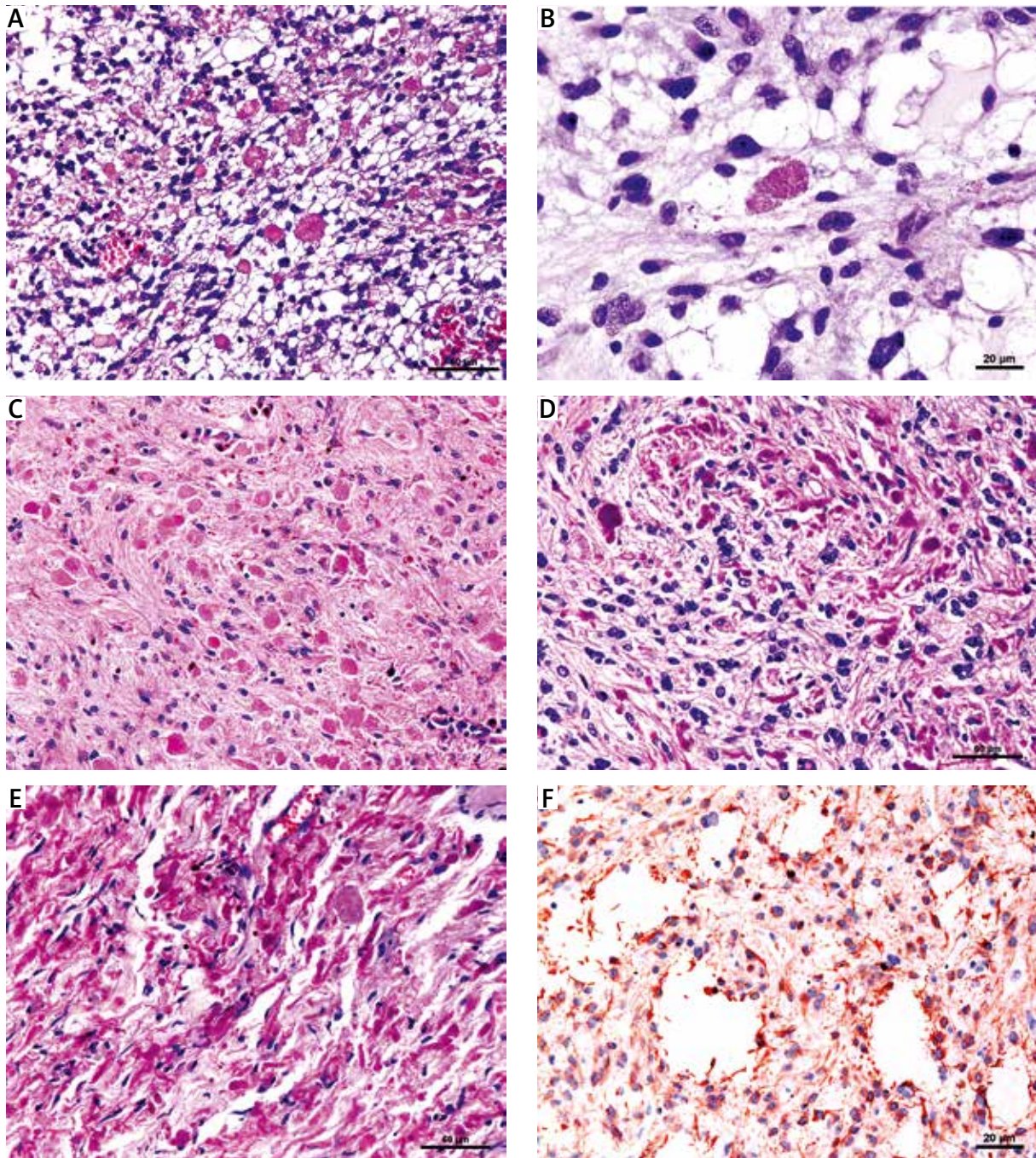
Not infrequently, PAs contain areas of oligodendroglioma-like pattern (Fig. 3A) with a honeycomb picture formed by uniform cells with a clear perinuclear halo (Fig. 3B). Such morphology mimicking oligodendroglioma predominates in the histological picture of some pilocytic astrocytomas [95].

Pilocytic astrocytomas usually show signs of degenerative changes, typical for slowly growing, long-standing lesions. They include not only presence of Rosenthal fibres and EGBs, but also focal increase of cellularity with nuclear hyperchromasia (Fig. 3C) and cellular pleomorphism (Fig. 3D). Large, pleomorphic, often multinucleated cells reflect advanced degenerative changes which have no prognostic significance (Fig. 3E). Some cells, corresponding to the cells known as “pennies-on-a-plate”, exhibit multiple nuclei arranged circumferentially in the cytoplasm (Fig. 3F). Occasionally, thin or psammomatous calcifications can be found (Fig. 3G, H). It is a frequent finding in optic nerve, hypothalamic/thalamic and superficially located cerebral tumours. Densely calcified PAS of the brainstem [15] and unique cases of intraventricular PA with densely calcified tissue and psammomatous bodies were reported [47,52].

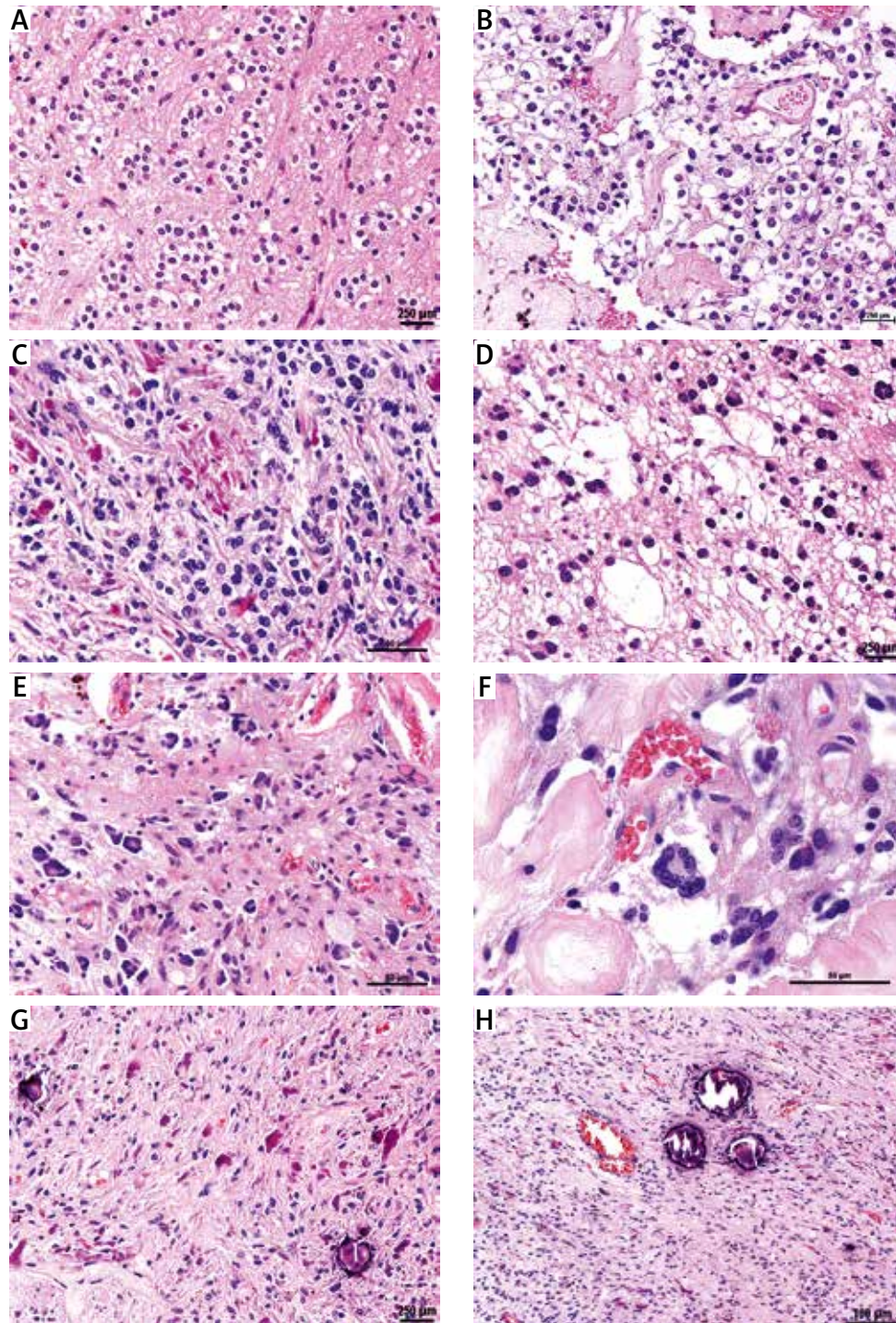
Some tumours exhibit a focal angiocentric pattern with ependymoma-like perivascular arrangement of neoplastic cells (Fig. 4A). Such a pattern might be seen in oligodendroglioma-like areas (Fig. 4B). Occasionally, the neoplastic cells are arranged in ribbons or palisades (Fig. 4C). The fibrillary pattern of neoplastic tissue, resembling diffuse astrocytomas,



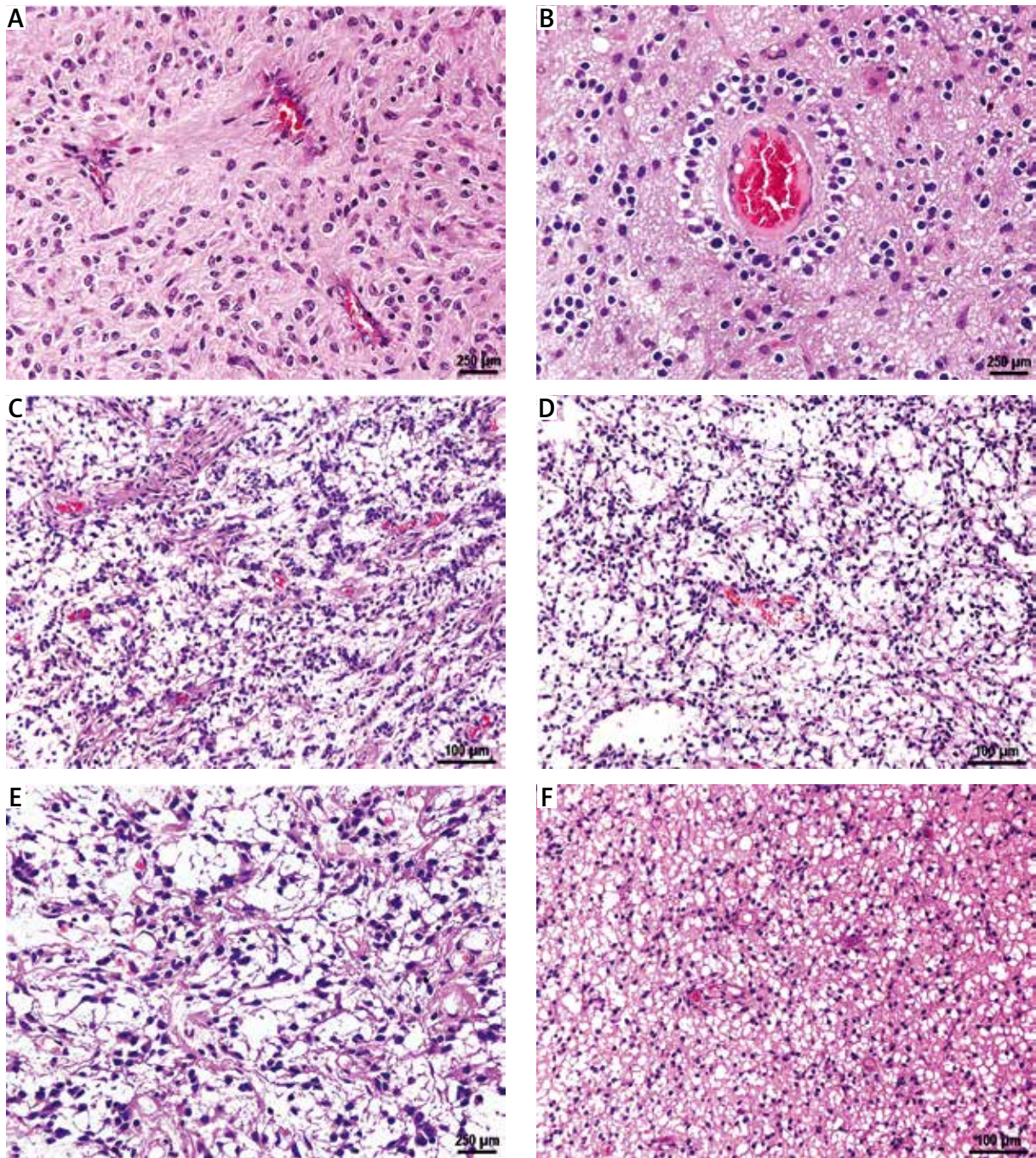
**Fig. 1.** Morphology of pilocytic astrocytoma. **A)** Well demarcation of the tumour from the surrounding tissue with only limited infiltration along the border zone. **B)** Superficially located tumour with leptomeningeal tumour growth. **C)** Classic biphasic pattern with microcystic tissue. **D)** Biphasic architecture with loose, spongy component and compact, fibrillary elements. **E)** Small cysts of different size and shape within loose, microcystic background. **F)** Microcyst filled with eosinophilic, myxoid material.



**Fig. 2.** Typical histopathological features of pilocytic astrocytoma. **A)** Microcystic, loose-textured areas containing eosinophilic granular bodies (EGBs) and hyaline droplets. **B)** Eosinophilic granular bodies formed by the aggregates of tiny granular bodies. **C)** Eosinophilic, compact region with numerous eosinophilic structures corresponding to EGBs and/or hyaline droplets. **D)** More solid component with increased cellularity and focal accumulation of Rosenthal fibres. **E)** Compact, fibrillary tumour tissue with numerous Rosenthal fibres. **F)** Glial fibrillary acidic protein expression in neoplastic cells.



**Fig. 3.** Heterogeneous pattern of pilocytic astrocytoma. **A)** Pilocytic astrocytoma with predominant oligodendrogloma-like architecture. **B)** Oligodendrogloma-like pattern with uniform cells exhibiting clear perinuclear halo. **C)** Compact tissue with increased cellularity, nuclear hyperchromasia and atypia. Rosenthal fibres are present. **D)** Spongy tissue with pleomorphic cells displaying degenerative nuclear atypia. **E)** Large, pleomorphic, often multinucleated cells. **F)** Cell with multiple nuclei arranged circumferentially in the cytoplasm, corresponding to “pennies-on-a-plate”. **G)** Compact, fibrillary tissue with Rosenthal fibres and tiny calcifications. **H)** Fibrillary tissue with psammomatous calcifications.



**Fig. 4.** Patterns of pilocytic astrocytoma mimicking other glial neoplasms. **A)** Ependymoma-like perivascular arrangement of neoplastic cells. **B)** Angiocentric arrangement of neoplastic cells resembling oligodendroglioma cells. **C)** Ribbons or palisaded arrangement of neoplastic cells. **D)** Tumour tissue resembling diffuse astrocytomas. **E)** Neoplastic cells with cytological atypia, nuclear hyperchromasia and fine fibrillary background. **F)** Slightly spongy tissue composed of uniform neoplastic fibrillary astrocytic cells mimicking diffuse astrocytoma.

is not unique (Fig. 4D). Sometimes, the fine fibrillary background is accompanied by cytological atypia, uneven cell distribution and nuclear hyperchromasia (Fig. 4E). Slightly spongy tissue composed of uniform neoplastic fibrillary astrocytic cells may mimic diffuse astrocytoma (Fig. 4F).

Pilocytic astrocytomas often appear as highly vascular tumours. The blood vessels may exhibit advanced fibrosis and/or hyalinization of vascular walls (Fig. 5A). Sometimes, the closely packed, sclerotic, largely hyalinized vessels can resemble vascular malformations, i.e. cavernous angioma (Fig. 5B). The neoplastic tissue may be scant and dispersed between conglomerates of thickened, hyalinized blood vessels (Fig. 5C, D), thus more mimicking reactive piloid gliosis around a lesion of vascular pathology than true neoplastic proliferation. In such cases the misleading diagnosis of cavernous angioma might be established. The advanced angiomatous proliferation might resemble capillary haemangioma, and the diagnosis of so-called angioglioma has been proposed [62]. In chronic lesions, the hemosiderin deposits of old haemorrhages and calcifications are often seen. An unusual case of pigmented cerebellar PA, presenting with posttraumatic haemorrhage in a 38-year-old man, has been described [93]. Advanced vascular abnormalities are sometimes associated with infarct-like necrosis. Other vascular changes are associated with proliferation of microvessels. Such microvascular proliferation often appears as linear arrays (Fig. 5E), especially within the cyst wall of the tumour. Typical glomeruloid changes of the vessels with hyperplasia of endothelial cells might suggest the diagnosis of high-grade gliomas (Fig. 5F). However, the microvascular proliferation of glomeruloid type in PAs should not be considered as a sign of anaplasia. Nevertheless, the careful analysis of clinicopathological findings supported by the molecular profile is required to distinguish PA from diffusely infiltrating gliomas.

Additionally, nuclear atypia, mitosis, necrosis, vascular proliferation and spread into leptomeninges and/or surrounding tissue, mimicking high-grade diffuse gliomas, may be rarely observed. Only occasionally, tumours with brisk mitotic activity, necrosis and marked nuclear pleomorphism have been diagnosed as anaplastic PA [82]. It has been documented that anaplastic/malignant transformation of PA occurred most often in association with previous ionizing radiation [75] or surgery alone [88],

whereas spontaneous malignant transformation was unique [10,72,90]. The majority of anaplastic cases have been described in adults [10,101]. Nevertheless, PAs with anaplastic features do not always exhibit a clear correlation between morphology and tumour behaviour. Only some cases of malignant PA have been documented to progress extremely rapidly [53].

Occasionally, the pre-existing neurons may be entrapped in the neoplastic tissue. Such lesions with residual neuronal elements should be distinguished from true gangliogliomas with a piloid astroglial component.

### Histological variant

The pilomyxoid variant (PMA) of pilocytic astrocytoma exhibits different histological features and behaves more aggressively than PA [50]. It demonstrates piloid cells within a markedly loose, myxoid background that lacks Rosenthal fibres or EGB, characteristic for classic PAs (Fig. 6A). Bipolar tumour cells are arranged radially around blood vessels, thus resembling the angiocentric arrangement or perivascular pseudorosettes seen in ependymomas (Fig. 6B). Some tumours revealed intermediate features of both PMA and classic PA.

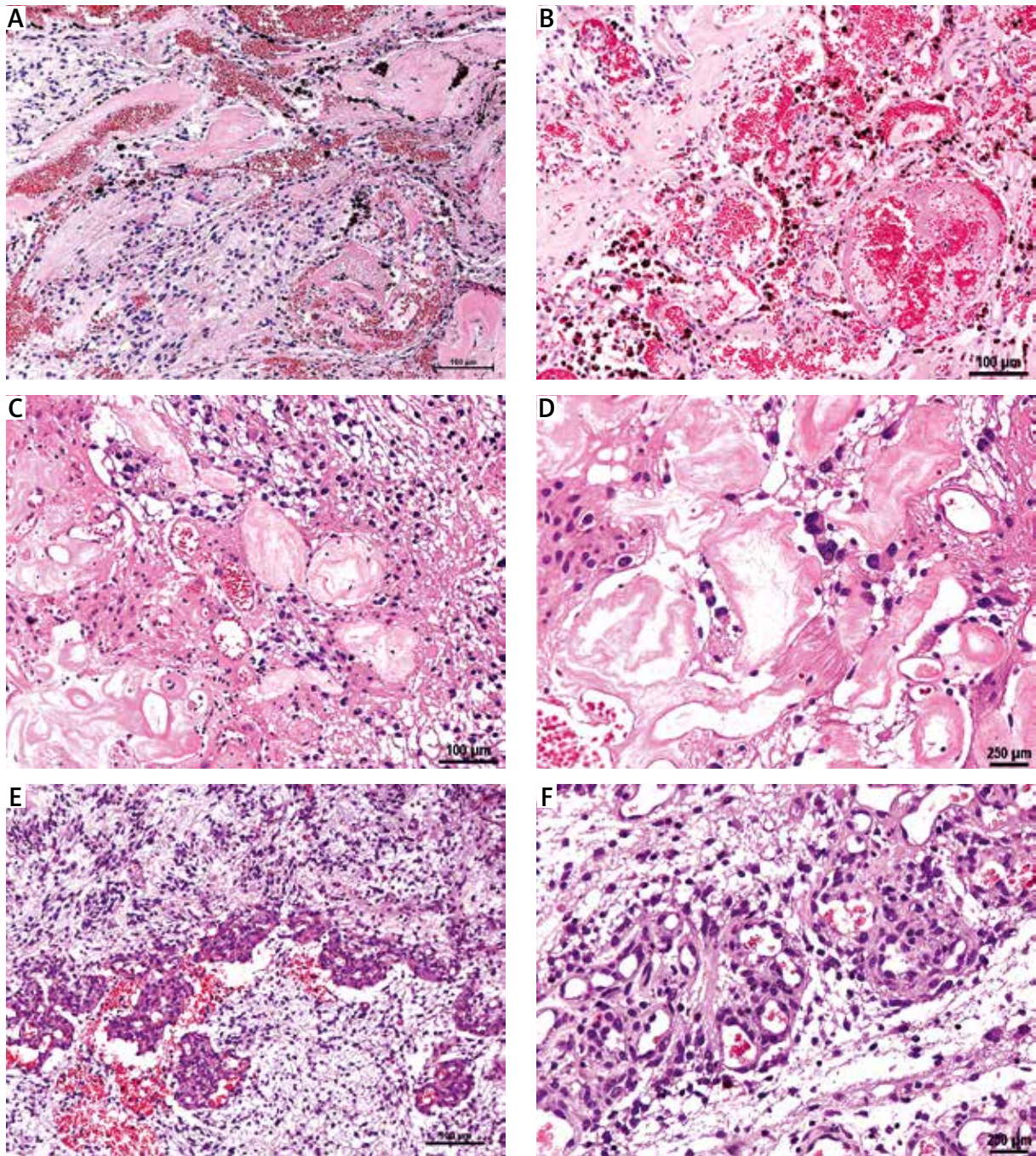
Pilomyxoid astrocytoma usually develops in the hypothalamic region, optic chiasm and third ventricle in infants and young children, less commonly in the thalamus, posterior fossa, brain stem, temporal lobe and spinal cord [49]. It has been suggested that PMAs ought to be included in the differential diagnoses of the lesions invading the sella turcica [3].

The clinical behaviour of PMAs is unpredictable. Usually, they behave more aggressively than conventional PAs. Pilomyxoid astrocytoma was classified as a tumour of grade II in the 2007 WHO classification of tumours of the central nervous system [17], but in the current revised 4<sup>th</sup> edition of the WHO 2016 classification, the determination of its grade of malignancy is not recommended.

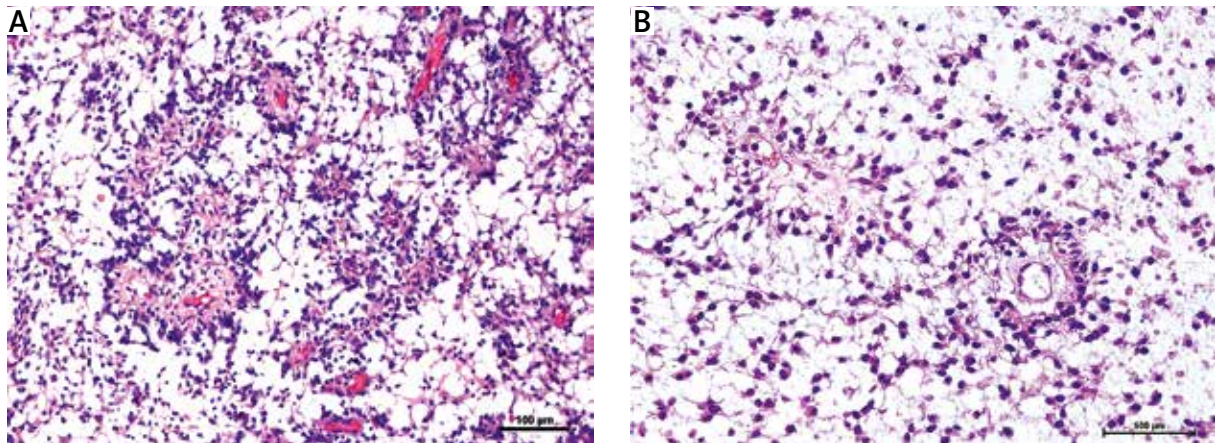
### Immunohistochemistry

Pilocytic astrocytomas express markers from the astrocytic lineage. They show strong GFAP immunostaining, S-100 protein and OLIG2 positivity. The Rosenthal fibres are strongly positive for  $\alpha$ -B crystallin and exhibit only peripheral GFAP staining. Synaptophysin immunoreactivity could be found





**Fig. 5.** Vascular changes in pilocytic astrocytomas. **A)** Neoplastic tissue with advanced vascular abnormalities associated with intratumoural bleeding. **B)** Conglomerates of hyalinized vessels and hemosiderin deposits. **C)** Vessels with considerably thickened, fibrous walls. **D)** Severe vascular hyalinization surrounded by a few neoplastic cells dispersed between conglomerates of vessels. **E)** Linear arrays of proliferating microvessels. **F)** Glomeruloid changes of the microvessels with hyperplasia of endothelial cells mimicking high-grade glioma.



**Fig. 6.** Pilomyxoid astrocytoma. **A)** Markedly loose, myxoid background with angiocentric arrangement of neoplastic cells. **B)** Bipolar tumour cells arranged radially around blood vessels in loose, myxoid tissue.

focally. The Ki-67 proliferative index is usually low, sometimes with a focal increase. Immunohistochemistry for R132H-mutant IDH1 protein is absent in all PAs and helps to distinguish PA from diffuse astrocytomas. Unfortunately, the majority of paediatric diffuse astrocytomas also lack *IDH1* and/or *IDH2* mutations. Phosphorylated MAPK immunostaining with V600E-mutant BRAF positivity could be detected.

### Molecular findings

There are some genetic alterations that are considered to underlie the development of PAs, with a key role of dysregulation/activation of the mitogen-activated protein kinase (MAPK) pathway, particularly through a tandem duplication leading to an oncogenic *BRAF* fusion gene [76,83,102]. Mitogen-activated protein kinase pathway abnormalities are found in the vast majority of PA cases; thus PA is considered as a one-pathway disease [24]. Recent studies have pointed towards the role of activation of the PI3K/AKT pathway in addition to MAPK/ERK signalling pathways in histologically anaplastic and biologically aggressive PA variants [81].

In sporadic PAs the most common genetic alteration is a tandem duplication at chromosome 7q34, which results in fusion between *KIAA1549* and *BRAF* genes. This tandem duplication is found in 60-94% of PAs and leads to downstream activation of the MEK/MAPK/ERK/p16 pathway [12,23,85]. The *KIAA1549-BRAF* fusion is more commonly encountered in PAs originating in the cerebellum [40]. These molecular alterations are more frequent in

children than in adults [87]. However, their prognostic significance is unclear. *KIAA1549-BRAF* fusion causes a deletion of the amino-terminal domain of *BRAF* and constitutive activation of its kinase activity [44]. A proteomic study confirmed the predominance of the MAPK pathway for childhood PA and introduced novel findings regarding ERK-2 expression [6].

The genetic association between neurofibromatosis type 1 and PA is well known. Patients with NF1 demonstrate inactivation of the tumour suppressor gene *NF1*, which encodes neurofibromin (NF1), a protein involved in the MAPK and mTOR-pathway through RAS-RAF signalling. Loss of neurofibromin leads to an increase of the active form of Ras and negative regulation of the RAS/ERK pathway and activation of the mammalian target of rapamycin mTOR/AKT pathway [21]. The Ras/ERK pathway is also involved in cell differentiation responsible for slow tumour growth. Mechanisms of tumourigenesis in low-grade gliomas with and without NF1 are different, including the different signalling pathways and tumour microenvironment [38].

The molecular changes can be used as diagnostic markers [26]. *KIAA1549/BRAF* fusion is common in PA but infrequent in diffuse gliomas, whereas *IDH1* mutation is common in diffuse astrocytomas in adults and uncommon in PA. Such molecular differences can help to establish the correct diagnosis [51]. Moreover, molecular targeted therapy might be considered as a possible novel therapeutic treatment, particularly in patients suffering from tumours with an unfavourable anatomical location preventing their complete surgical resection.

## Treatment

Cerebellar and superficial cerebral pilocytic tumours are usually surgically treated by gross total or subtotal resection. Deeply situated lesions can be only partially resected. Disseminated PA lesions are usually treated by multi-modal therapy, including surgical resection, chemotherapy, and radiotherapy with extended-field radiation [16]. It is noteworthy that PAs are generally indolent tumours and attention should be paid to avoiding aggressive therapy [80].

## Prognosis

Pilocytic astrocytomas are typically well-circumscribed, slowly growing WHO grade I lesions that are generally associated with excellent prognosis, favourable long-term outcome or spontaneous regression with a 10-year survival rate of more than 95% cases. Total or even subtotal removal is an effective treatment in cerebellar and superficial cerebral pilocytic tumours [29]. The long-term functional outcome is generally favourable, in the absence of post-operative complications and brain stem involvement [2]. The surgery is usually followed by tumour stabilization even when the tumour is only partially resected and the patient does not receive complementary radiation. Deeply located lesions are usually associated with worse prognosis and risk for local recurrence. However, some superficial tumours might also exhibit an unexpected clinical course with recurrences.

Spontaneous involution of PA has been reported in children, particularly in cases associated with NF1 [19,33,36,56,73,84]. It has been documented that the optic pathway/hypothalamic gliomas, treated by subtotal resection, biopsy and radiotherapy or radiation alone, might stabilize or even completely disappear on serial MR images [39]. This phenomenon has rarely been observed in adults, especially without NF1 [11]. Nevertheless, postoperative MRI monitoring seems to be important both in adults and in children.

Clinical behaviour is often unpredictable, and PAs may recur locally after incomplete resection or disseminate to the leptomeninges, especially when they are located in the hypothalamic region [1]. It must be noted that recurrences of PA are not associated with histological malignant progression. Some data suggest that PAs in adult patients behave more aggressively than in children and might be associated with recurrences, progression and higher mortal-

ity [31,43,91,94,99]. The possibility of rapid tumour recurrence and malignant transformation indicate the need for careful post-operative follow-up for adult patients with PAs [30].

Additionally, dissemination into the subarachnoid space occurs in a small percentage of cases, most often related to local recurrences. Dissemination of cerebellar PAs can be associated with obstructive hydrocephalus leading to an unfavourable prognosis [32,41,42]. Leptomeningeal dissemination of the cerebellar tumours into the spinal cord might occur many years after primary surgery [45,66,78]; less commonly the meningeal seeding appears at the initial presentation [67]. Spread into the spinal meninges can be observed in PAs of the spinal cord [1,9] and optic chiasm [4,48]. Extremely rarely, spinal cord PA can spread via the cerebrospinal fluid pathway (CSF) to the cerebral meninges [69]. Metastases of juvenile PA to the left cerebellar tonsil and lumbosacral region were also reported in PA of the hypothalamic region [70]. Only occasionally, the tumour may exhibit multifocal recurrences and extensive dissemination [7]. An unusual case of recurrent supratentorial intraventricular PA with local recurrence and disseminations along the complete neuraxis in a short period of one year after primary surgery was described [77].

A particular clinicopathological presentation of PAs might be associated with fatal haemorrhages, which are most often subarachnoid (SAH) [34,46,54,61,64]. Such tumour manifestation is less commonly observed in PMA [35,89]. The haemorrhages likely result from vascular abnormalities, often observed in PAs. Tumour haemorrhage should be considered in the differential diagnosis of spontaneous intracerebral haemorrhage [97].

## Differential diagnosis

The correct diagnosis of PA and its differentiation from diffuse gliomas is important as it is related to different prognosis and specific therapy based on the molecular signal pathways. The diagnostic criteria include age of patients, MRI findings, tumour location and typical histology with biphasic picture, presence of piloid cells and degenerative changes with EGBs and Rosenthal fibres. The majority of cases meet these criteria, but some of them present unusual clinicopathological features, including uncommon location, older age group, misleading histological appearance or inadequate biopsy spec-

imens. Histologically, the diagnosis of PA can often be challenging. The microscopic pictures of PA may mimic some other neoplasms, including pleomorphic xanthoastrocytoma, diffuse astrocytoma and glioblastoma or even piloid reactive gliosis typical for long-standing, non-neoplastic pathological processes. Distinction from all these lesions bears important therapeutic and prognostic implications. Caution is required to avoid misinterpretation; however, in small and/or non-representative biopsy specimens it can be difficult or even impossible. The frequent mutation of *IDH1* and *IDH2* in diffuse gliomas, which is usually not seen in PAs [51], allows tumours of different prognosis and treatment to be distinguished. Only one case of a 72-year-old woman with a right cerebellar PA of WHO grade I and *IDH1* mutation has been reported so far [13].

## Conclusions

Pilocytic astrocytoma is a tumour of distinct clinicopathological features, but not infrequently it presents with atypical features, including older age of patients, uncommon location and lack of classic biphasic morphology. The different histopathological pattern, presence of nuclear atypia, vascular changes, mitoses, necrosis and glomeruloid microvascular proliferation can lead to misdiagnosis. Moreover, the biological behaviour of PAs independently of their morphology is not always predictable. In conclusion, the diagnosis of PA may be challenging, and careful analysis of clinical, histopathological and molecular features is required to avoid misinterpretation followed by inadequate therapy.

## Disclosure

Authors report no conflict of interest.

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