Cerebellar Astrocytomas: Pathology

28

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28.1 Pathology

Although gross and microscopic features of central nervous system (CNS) tumors are identical regardless of the age of the patient, the incidence of various specific histological tumor types varies widely in those 18 years or under in contrast to adults. Whereas the most common tumors in adults are high-grade astrocytic tumors, meningiomas, and metastases, in children astrocytic tumors are the most common CNS neoplasms, account for 47.3 % of lesions, and tend to be low grade [1]. At the same time particular entities can be almost exclusively found among children, e.g., pilocytic and pilomyxoid astrocytomas. Another fundamental difference between adult and childhood CNS tumors lies in the site of origin. Whereas the cerebrum is the favored site among adults, the infratentorial compartment including the cerebellum gives rise to between 21.7 and 60.2 % of all primary brain tumors in children aged 15–17 years and 3–5 years, respectively, with an overall rate throughout childhood of 46.7 % [1].

Cerebellar astrocytomas are common tumors in children, accounting for approx. 5–6 % of all gliomas, 20 % of all pediatric CNS tumors, and 30–40 % of the tumors developing within the posterior cranial fossa [2]. They are predominantly tumors of early life with three-quarters of them occurring in children and adolescents with a main peak incidence between 6 and 9 years of age and a second lower peak in young adulthood, with nearly 90 % being low-grade tumors. Although some series have shown a slight female preponderance, in most larger series the gender ratio is approx. 1:1 [2]. The most common subtype of glioma in childhood is pilocytic astrocytomas, the majority of which are located in the cerebellum (69 %); they can usually be cured by surgery alone and tend not to recur when totally resected [3]. High-grade astrocytic tumors of childhood, on the other hand, are less frequently encountered in the posterior fossa with 13 % of pediatric anaplastic astrocytomas and glioblastomas occurring in the cerebellum [3].

28.1.1 Pilocytic Astrocytoma (WHO Grade I: ICD-O Code 9421/1)

28.1.1.1 Definition

A relatively circumscribed, slowly growing, often cystic astrocytoma occurring in children and young adults histologically characterized by a biphasic pattern with varying proportions of compacted bipolar cells associated with Rosenthal fibers and loose-textured multipolar cells associated with microcysts and eosinophilic granular bodies/hyaline droplets [4].

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M.M. Özek et al. (eds.), *Posterior Fossa Tumors in Children*,
DOI 10.1007/978-3-319-11274-9_28, © Springer International Publishing Switzerland 2015

28.1.1.2 Incidence, Age, Localization, and Sex Distribution

Pilocytic astrocytomas comprise approx. 5–6 % of all gliomas with an incidence of 3.7 per million per year. They are the most common glioma in children in whom the majority (67 %) arises in the cerebellum. Pilocytic astrocytomas most commonly develop without gender predilection in the first two decades of life, comprising 23.5 % of pediatric brain tumors [1]. They are the principal CNS tumor associated with neurofibromatosis NF1 with approx. 15 % of NF1 patients developing a pilocytic astrocytoma [4].

28.1.1.3 Macroscopy

Most pilocytic astrocytomas are soft, gray, and discrete. Intra- or peritumoral cyst formation is common. Chronic lesion may contain calcium or hemosiderin deposits. Primary diffuse leptomeningeal pilocytic astrocytoma is a rarity [4].

28.1.1.4 Histopathology

Pilocytic astrocytomas are tumors of low to moderate cellularity exhibiting an often biphasic pattern with varying proportions of compacted bipolar cells with Rosenthal fibers and loose-textured multipolar cells with microcysts and eosinophilic granular bodies/hyaline droplets (Fig. 28.1). This classical biphasic pattern is best seen in cerebellar tumors. Rare mitoses, hyperchromatic and pleomorphic nuclei, glomeruloid vascular proliferation, infarct-like necrosis, and infiltration of leptomeninges are compatible with a diagnosis of

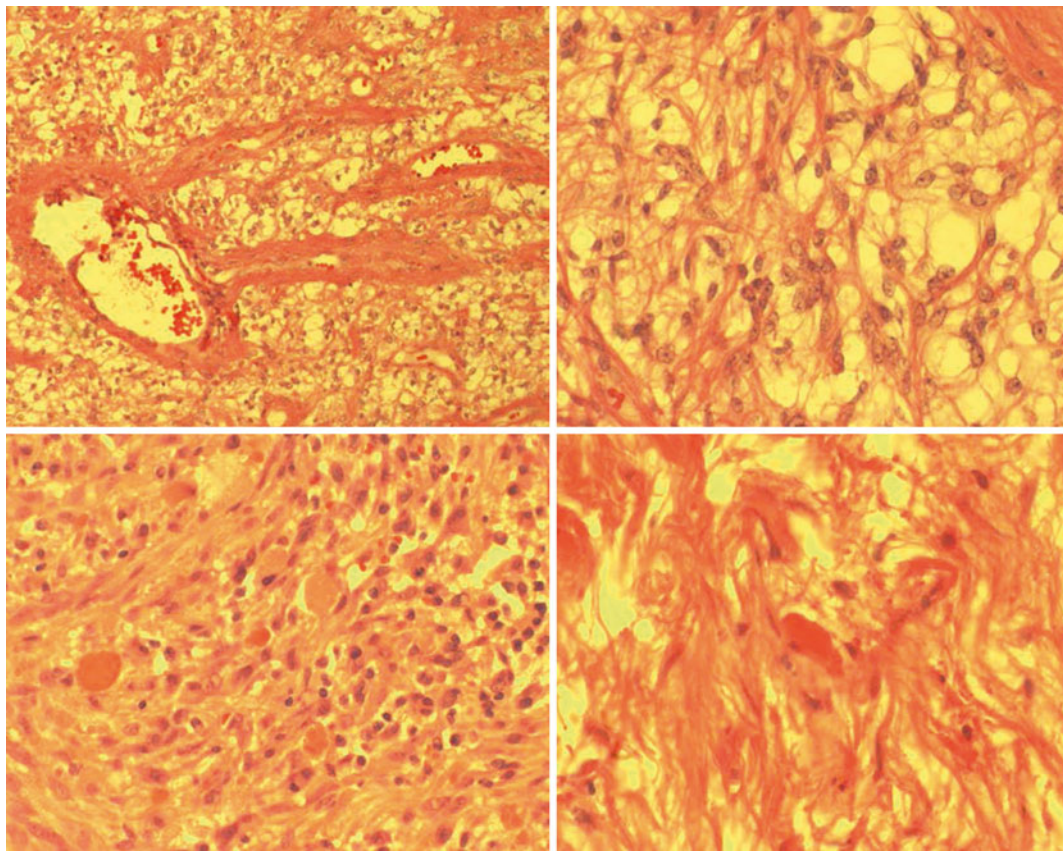

Fig. 28.1 Pilocytic astrocytomas are tumors of low to moderate cellularity exhibiting an often biphasic pattern with varying proportions of compacted bipolar cells (*top left* and *right*) with Rosenthal fibers (*bottom right*) and loose-textured multipolar cells with microcysts and eosinophilic granular bodies/hyaline droplets (*bottom left*). Hyalinized vessels and perivascular lymphocytes are prominent features (*top left*)

pilocytic astrocytoma and are not signs of malignancy. Occasionally, oligodendroglioma-like cells may be seen, especially in cerebellar examples. A striking feature in some pilocytic astrocytomas is alignment of cells in prominent regimented palisades (in pattern that used to be called "primitive polar spongioblastoma").

Compact portions of the tumor yield bipolar piloid cells, long hairlike processes that often extend across a full microscopic field and Rosenthal fibers. Their nuclei are typically elongate and cytologically bland. Due to their high fibril content, these cells are strongly positive for GFAP. Cells derived from microcystic areas posses round to oval cytologically bland nuclei, a small cell body, and relatively short cobweb-like processes which are fibril-poor and only weakly GFAP positive. This growth pattern is typically associated with eosinophilic granular bodies and/or hyaline droplets. Some pilocytic astrocytomas show considerable hyperchromasia and pleomorphism with mitoses encountered in up to 30 % of tumors. In particular cerebellar lesions show a sometimes more diffuse growth pattern reminiscent of diffuse astrocytoma. Hyalinized and glomeruloid vessels and perivascular lymphocytes are prominent features, and necrosis when seen is often infarct-like and non-palisading. The MIB-1/Ki-67 proliferation indices have been found to be in the range of 0–3.9 % with a mean of 1.1 % [5].

Rosenthal fibers are tapered corkscrew-shaped brightly eosinophilic hyaline intracytoplasmic masses and are most common in compact piloid tissue. Although helpful in diagnosis, their presence is not required nor are they exclusive to pilocytic astrocytoma or even indicative of neoplasia as they are also encountered in gangliogliomas and chronic reactive gliosis. They lie within astrocytic processes and are composed of α-B-crystallin but lack GFAP immunoreactivity.

Eosinophilic granular bodies form globular aggregates within astrocytic processes. They are brightly eosinophilic in H&E and PAS positive and show immunoreactivity for α-1-antichymotrypsin and α-1-antitrypsin. Their intracellular localization is usually not discernible in tissue sections. Eosinophilic granular bodies are an important diagnostic feature of several neoplasms but are in themselves not indicative of neoplasia.

Pilocytic astrocytomas are highly vascular as evidenced by their contrast enhancement. Glomeruloid vasculature may be seen; however, endothelial proliferation (a feature of high-grade astrocytic tumors) is generally not encountered. Such neovascularity often lines cyst walls, thus explaining the narrow band of intense contrast enhancement seen at the circumference of some cysts. Involvement of the subarachnoid space is a common finding, particularly in the cerebellum, and is not indicative of aggressive or malignant behavior nor does it portend subarachnoid dissemination. Surprisingly, otherwise typical pilocytic astrocytomas very occasionally seed the neuraxis, rarely even before the primary tumor is detected; however, even this finding is not a predictor of future aggressive behavior [4].

As a group, pilocytic astrocytomas are remarkable in maintaining their WHO grade I over years and decades with changes being commonly of a regressive rather than anaplastic nature. However, there have been rare examples of pilocytic astrocytomas undergoing malignant transformation [6]. They often feature multiple mitoses per high-power field, endothelial proliferation, and palisading necrosis and warrant the designation of "anaplastic pilocytic astrocytoma" rather than "glioblastoma" as their prognosis is not uniformly grim.

28.1.2 Pilomyxoid Astrocytoma (WHO Grade II: Provisional ICD-O Code 9425/3)

28.1.2.1 Definition

A piloid neoplasm, closely related to pilocytic astrocytoma that has a prominent mucoid matrix and angiocentric arrangement of monomorphous, bipolar tumor cells typically without Rosenthal fibers or eosinophilic granular bodies/hyaline droplets [4].

Earlier reports refer to tumors with similar features as "infantile" pilocytic astrocytoma, and the occasional phenotypical conversion of a

pilomyxoid astrocytoma to a typical pilocytic astrocytoma supports a common origin for these two tumors [4].

28.1.2.2 Incidence, Age, Localization, and Sex Distribution

The incidence of pilomyxoid astrocytomas is not known. They present in the very young (median 10 months) but can occur in older children without gender predilection [4]. Although mostly located in the hypothalamic/chiasmatic region, they can occur in the cerebellum [7]. Two patients with pilomyxoid astrocytomas and neurofibromatosis 1 (NF1) have been reported [8].

28.1.2.3 Macroscopy

Pilomyxoid astrocytomas present as solid gelatinous masses partly infiltrating parenchyma; thus a clear surgical plane may not be identified [9].

28.1.2.4 Histopathology

Pilomyxoid astrocytomas show a markedly mucoid matrix, monomorphous bipolar cells, and a predominantly angiocentric cell arrangement (Fig. 28.2). The tumor typically has a compact, rather solid architecture while others are more infiltrative. The lesion is composed of relatively monomorphous, medium-sized bipolar cells, the processes of which may radiate from vessels in a pseudorosette fashion; cells may also be aligned along the long axis of vessels. When strictly defined,

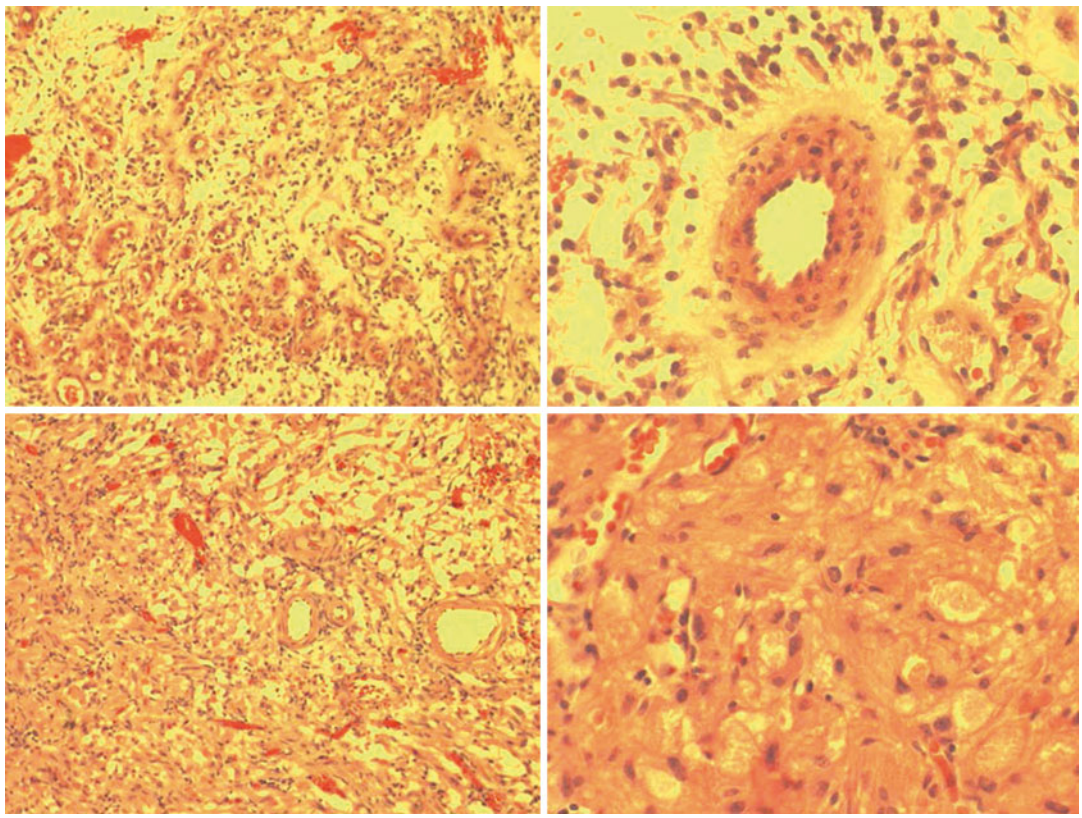

Fig. 28.2 Pilomyxoid astrocytomas show a markedly mucoid matrix (*top left*), monomorphous bipolar cells, and a predominantly angiocentric cell arrangement of cell processes which may radiate from vessels in a pseudorosette fashion (*top right*). Pleomorphic xanthoastrocytomas are characterized by spindly elements intermingled with mono- or multinucleated giant astrocytes with hyperchromatic and pleomorphic nuclei (*bottom left*) as well as the presence of large xanthomatous cells showing intracellular accumulation of lipid droplets (*bottom right*)

the tumor does not contain Rosenthal fibers or eosinophilic granular bodies/hyaline droplets. Mitotic figures and vascular proliferation may be present, and rare examples may be focally necrotic.

Immunohistologically, tumors are positive for GFAP, S-100 protein, and vimentin and may show expression for synaptophysin but are negative for neurofilament protein and chromogranin. MIB-1/Ki-67 labelling indices were found to vary substantially between 2 and 20 % [4].

28.1.3 Pleomorphic Xanthoastrocytoma (WHO Grade II: ICD-O Code 9424/3)

28.1.3.1 Definition

An astrocytic neoplasm with a relatively favorable prognosis typically encountered in children and young adults; characteristic histological features include pleomorphic and lipidized cells expressing GFAP and often surrounded by a reticulin network as well as eosinophilic granular bodies. Lesions with significant mitotic activity (five or more mitoses per 10 HPF) and/or with areas of necrosis may be designated as "pleomorphic xanthoastrocytoma with anaplastic features" [10].

28.1.3.2 Incidence, Age, Localization, and Sex Distribution

Pleomorphic xanthoastrocytomas account for less than 1 % of all astrocytic neolasms. They are mainly encountered in the second decade of life and account for 1.9 % of pediatric brain tumors [1], with two-thirds of patients being under 18 years of age without gender predilection [10]. A superficial location involving the meninges and cerebrum is typical for pleomorphic xanthoastrocytomas; however, they can also occur in the cerebellum [11].

28.1.3.3 Macroscopy

Pleomorphic xanthoastrocytomas are mainly superficial tumors attached to the meninges; they are frequently accompanied by a cyst, sometimes forming a mural nodule within the cyst wall [10].

28.1.3.4 Histopathology

The key histopathological features are contained in its designation: "pleomorphic" refers to the variable histological appearance of the tumor in which spindly elements are intermingled with mono- or multinucleated giant astrocytes with hyperchromatic and pleomorphic nuclei with frequent intranuclear inclusions (Fig. 28.2). "Xanthoastrocytoma" refers to the presence of large xanthomatous cells showing intracellular accumulation of lipid droplets. Granular bodies are an almost constant feature as well as focal collections of small lymphocytes and reticulin fibers visualized using silver impregnation surrounding the individual tumor cells.

Immunohistochemically, tumor cells express GFAP and S-100 protein but also show significant neuronal differentiation (synaptophysin, neurofilament protein, MAP2) as well as CD34 expression. The MIB-1/Ki-67 labelling index is usually <1 % [10].

28.1.4 Diffuse Astrocytoma (WHO Grade II: ICD-O Code 9400/3)

28.1.4.1 Definition

A diffusely infiltrating astrocytoma characterized by a high degree of cellular differentiation and slow growth. The tumor has an intrinsic tendency for malignant progression to anaplastic astrocytoma and, ultimately, glioblastoma [12].

28.1.4.2 Incidence, Age, Localization, and Sex Distribution

Diffuse astrocytomas represent 10–15 % of all astrocytic CNS tumors with an incidence rate of 1.4 per million per year. Fibrillary astrocytomas are fairly rare in childhood and make up 5.0 % of CNS tumors encountered in this period [1]. Epidemiological data suggest that the incidence in children has increased slightly over the past three decades. There is a slight predilection for males (1.18:1), and approximately 10 % occur below the age of 20 years. Localization in the cerebellum is distinctly uncommon [12].

28.1.4.3 Macroscopy

Because of their infiltrative nature, diffuse astrocytomas usually show blurring of the gross anatomical boundaries. There is enlargement and distortion but no destruction of the invaded structures. Smaller or larger cysts, granular areas, and zones of firmness or softness may be seen. Extensive microcyst formation may cause a gelatinous appearance. Focal calcification may be present [12].

28.1.4.4 Histopathology

Diffuse astrocytoma is composed of well-differentiated fibrillary or gemistocytic neoplastic astrocytes in a background of a loosely structured, often microcystic, tumor matrix (Fig. 28.3). The cellularity is moderately increased and occasional nuclear atypia is a typical feature. Mitotic activity is generally absent; however, a single mitosis does not yet allow the diagnosis of anaplastic astrocytoma. The presence of necrosis or microvascular proliferation is incompatible with the diagnosis of diffuse astrocytoma. Histological recognition of neoplastic astrocytes depends mainly on nuclear characteristics of atypia: whereas normal astrocyte nuclei are oval to elongate and vesicular, often with a distinct nucleolus, neoplastic astrocytes show enlarged, cigar-shaped, or irregular hyperchromatic nuclei. Reactive astrocytes, on the other hand, present with stainable cytoplasm while normal and tumor astrocytes show no discernible or scant cytoplasm ("naked nuclei") [12].

28.1.5 Anaplastic Astrocytoma (WHO Grade III: ICD-O Code 9401/3)

28.1.5.1 Definition

A diffusely infiltrating malignant astrocytoma histologically characterized by nuclear atypia increased cellularity and significant proliferative activity. The tumor may arise from diffuse astrocytoma or de novo, i.e., without evidence of a less malignant precursor lesion, and has an inherent tendency to undergo progression to glioblastoma [13].

28.1.5.2 Incidence, Age, Localization, and Sex Distribution

Anaplastic astrocytomas are rare in children and within the cerebellum. They account for 7.2 % of childhood brain tumors [1] and show a male gender predilection with a ratio of between 1.1 and 1.6:1 [13].

28.1.5.3 Macroscopy

Anaplastic astrocytomas have a tendency to infiltrate the surrounding brain without frank tissue destruction which often leads to a marked enlargement of invaded structures such as gyri and basal ganglia. Cysts are uncommon but areas of granularity, opacity, and soft consistency are frequent. On cut surface the higher cellularity of anaplastic astrocytomas produces a discernable tumor mass with a clearer distinction from surrounding structures than in diffuse astrocytomas WHO grade II [13].

28.1.5.4 Histopathology

The principal histological features are those of a diffusely infiltrating astrocytoma with increased cellularity compared with a WHO grade II tumor, distinct nuclear atypia (variations in nuclear size, shape, coarsening and dispersion of chromatin, prominent and multiple nucleoli) and mitotic activity (Fig. 28.3), the latter depending on the size of the sample (one mitosis in stereotactic biopsy sample equals a significant proliferation but not in a large surgical tumor sample; immunohistochemistry for MIB-1/Ki-67 may be helpful which usually ranges between 5 and 10 %). Additional signs of anaplasia are multinucleated cells and abnormal mitoses. By definition, microvascular proliferation (multilayered vessels) and necrosis are absent [13].

28.1.6 Glioblastoma (WHO Grade IV: ICD-O Code 9440/3)

28.1.6.1 Definition

The most malignant neoplasm with predominant astrocytic differentiation; histopathological features include nuclear atypia, cellular pleomorphism, mitotic activity, vascular thrombosis,

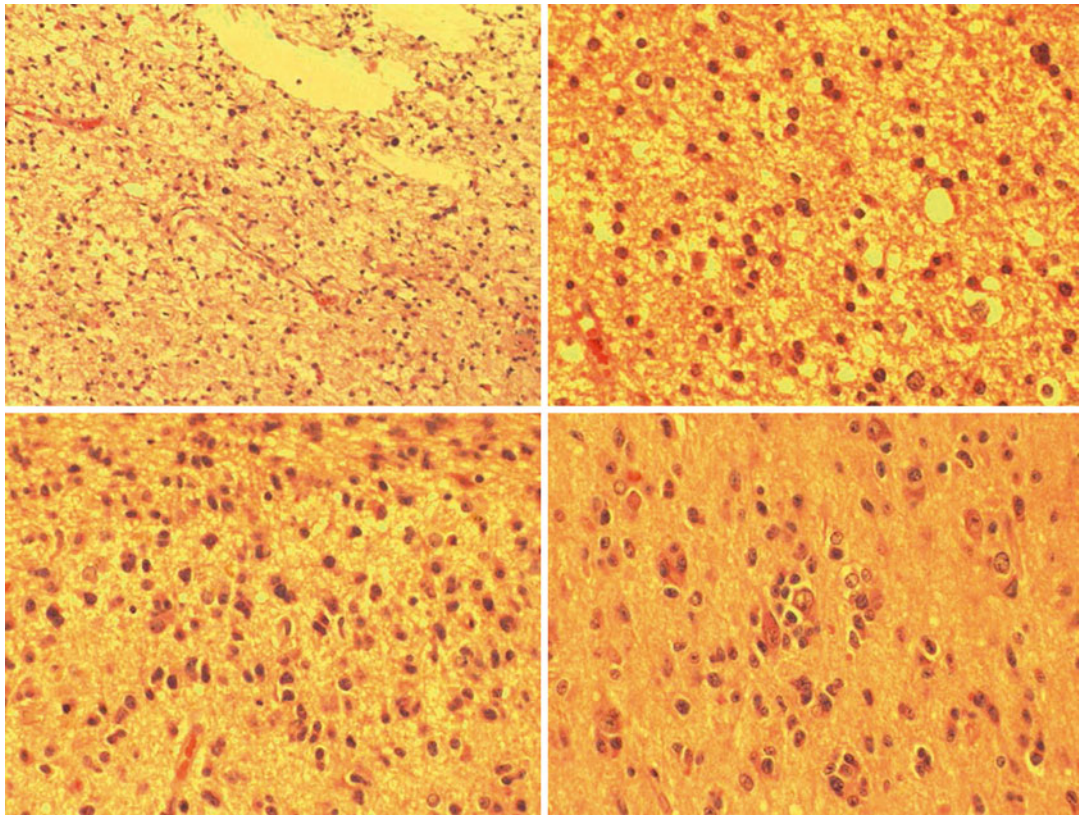

Fig. 28.3 Diffuse astrocytoma is composed of well-differentiated fibrillary or gemistocytic neoplastic astrocytes in a background of a loosely structured, often microcystic tumor matrix (*top left*). The cellularity is moderately increased and occasional nuclear atypia is a typical feature whereas mitotic activity is generally absent (*top right*). In contrast, anaplastic astrocytoma is a diffusely infiltrating lesion with increased cellularity compared with a WHO grade II tumor, distinct nuclear atypia (variations in nuclear size, shape, coarsening and dispersion of chromatin, prominent and multiple nucleoli) and mitotic activity whereas microvascular proliferation and necrosis are absent (*bottom left*). In the cortex, perineuronal satellitosis (tumor cells surrounding cortical nerve cells) is a common feature (*bottom right*)

microvascular proliferation, and necrosis. Most glioblastomas manifest rapidly de novo, without recognizable precursor lesions (primary glioblastoma). Secondary glioblastomas develop slowly from diffuse astrocytoma or anaplastic astrocytoma. Due to their invasive nature, glioblastomas cannot be completely resected. The term "glioblastoma" is used synonymously with "glioblastoma multiforme" [14].

28.1.6.2 Incidence, Age, Localization, and Sex Distribution

Glioblastoma may manifest at any age but is the most frequent CNS tumor in adults, accounting for 12–15 % of all intracranial neoplasms and 60–75 % of astrocytic tumors with an incidence of 30–40 new cases per million per year. The majority (>90 %) develops very rapidly with a short clinical history (usually <3 months): primary or de novo glioblastomas, whereas secondary glioblastomas develop through progression from diffuse (WHO grade II) or anaplastic (WHO grade III) astrocytomas. Glioblastomas are relatively rare in children with 1 % of glioblastomas encountered in patients under the age of 20 years. They account for 7.2 % of childhood brain tumors and are rarely encountered in the cerebellum [1]. The male to female ratio is about 1.26–1.28 [14].

28.1.6.3 Macroscopy

Despite the short duration of symptoms in many cases of glioblastoma, the tumors are often surprisingly large. The lesion is usually unilateral but bilateral symmetrical extension is seen supratentorially due to growth along myelinated structures like the corpus callosum ("butterfly glioma"). Glioblastomas are diffuse and poorly delineated with the cut surface showing a variable color with peripheral grayish tumor masses and central areas of yellowish and red from necrosis, myelin breakdown, and hemorrhage. The central necrosis may occupy as much as 80 % of the total tumor mass and is typically stippled with red and brown foci of recent and remote bleeding; extensive hemorrhages may occur and evoke stroke-like symptoms. Macroscopic cysts contain a turbid fluid and represent liquefied necrotic tissue. Most glioblastomas have their epicenter in the white matter. Multifocal glioblastomas occur in approximately 2.4 % of cases; penetration of the subarachnoid space, dura, venous sinus, or bone is exceptional [14].

28.1.6.4 Histopathology

Glioblastoma is a malignant cellular glioma composed of poorly differentiated, often pleomorphic astrocytic tumor cells with marked nuclear atypia and brisk mitotic activity (Fig. 28.4). Prominent microvascular proliferation (multilayered vessels) and necrosis are essential diagnostic features. Necroses often take the shape of multiple band-like or serpiginous foci surrounded by radially oriented and densely packed tumor cells in a pseudopalisading pattern.

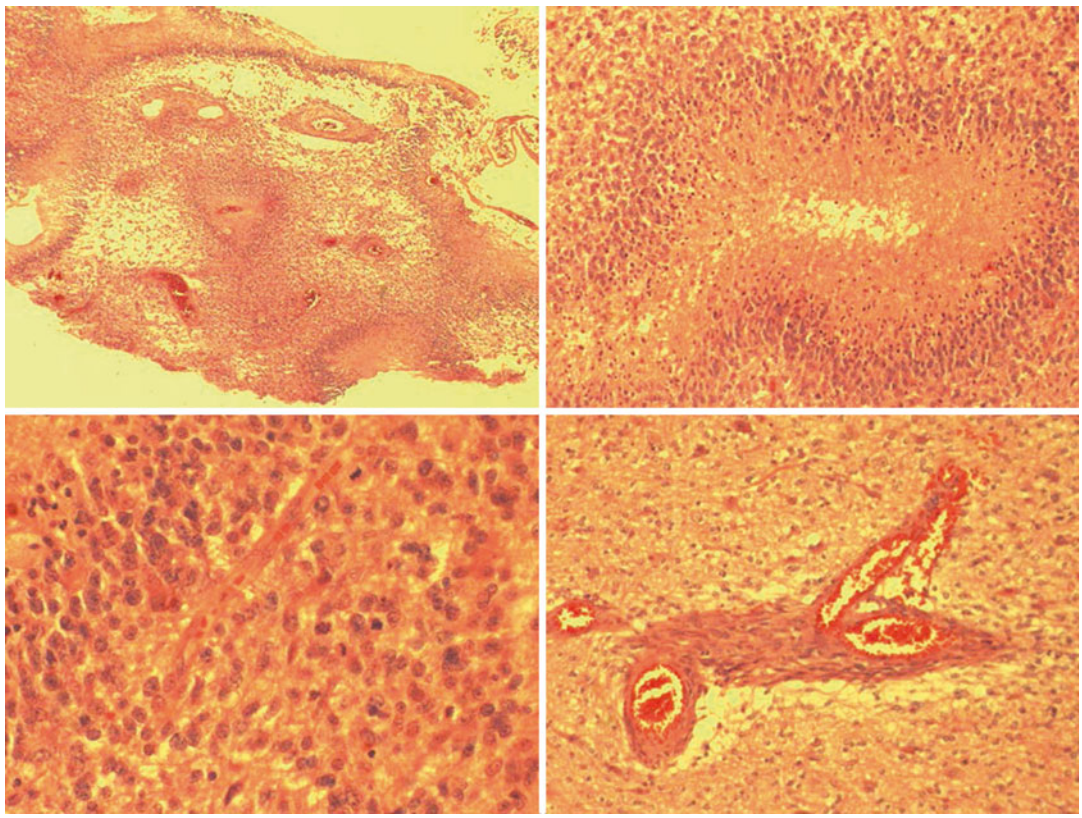

Fig. 28.4 Glioblastoma is composed of poorly differentiated, often pleomorphic astrocytic, tumor cells with marked nuclear atypia and brisk mitotic activity (*bottom left*). Prominent microvascular proliferations/multilayered vessels (*bottom right*) and/or necrosis are essential diagnostic features. Necroses often take the shape of multiple band-like or serpiginous foci surrounded by radially oriented and densely packed tumor cells in a pseudopalisading pattern (*top left* and *right*)

As the term "glioblastoma multiforme" implies, the histopathology of this tumor is extremely variable. While some tumors show a high degree of cellular and nuclear pleomorphism with multinucleated giant cells, others are highly cellular but rather monotonous. The regional heterogeneity of glioblastoma is remarkable and poses challenges to the diagnosis of specimens obtained by stereotactic needle biopsies.

The diagnosis of glioblastoma is typically based on the tissue pattern rather than the identification of certain cell types. The distribution of the diagnostic key elements (highly anaplastic glial cells, mitotic activity, vascular proliferation and/or necrosis) is variable, but large necrotic areas usually occupy the tumor center, while viable tumor cells tend to accumulate in the periphery. The circumferential region of high cellularity and abnormal vessels corresponds to the contrast-enhancing ring seen radiologically. Occasionally, glioblastomas contain foci of glandular epithelial structures which usually can unequivocally be established as being astrocytic in nature. Cellular pleomorphism also includes formation of small undifferentiated as well as lipidized, granular, and large multinucleated giant cells. The latter are often considered a hallmark of glioblastoma; however, they are not an obligatory feature, are not associated with a more malignant clinical course, and are generally regarded as a type of regressive change. If they dominate, a designation of "giant cell glioblastoma" is justified. In addition to necrosis, the presence of microvascular proliferations is a histopathological hallmark of glioblastoma. They typically appear as "glomeruloid tufts" which are most commonly located in the vicinity of necrosis and appear directionally oriented to it. Microvascular proliferations consist of multilayered, mitotically active endothelial cells together with smooth muscle cells and pericytes. Proliferative activity is usually prominent with detectable and frequently atypical mitoses in nearly every high-power field. The growth fraction shows great regional variation with mean MIB-1/Ki-67 values of 15–20 % [14].

28.2 Prognostic Value of Histopathological, Immunohistochemical, Cytogenetic, and Molecular Genetic Features Among Astrocytic Tumors of Childhood

A number of studies have been performed into the predictive prognostic value of morphological features among tumors in general and pediatric CNS neoplasms in particular in order to be able to predict the clinical course, stratify the therapy regimen, or avoid potentially fruitless and deleterious interventions. Not surprisingly, these have yielded wildly diverse and sometimes contradictory results. A plethora of statistically significant histopathological, immunohistochemical, cytogenetic, and molecular genetic parameters has been put forward (Table 28.1), none of which are currently applied in a clinical setting. It comes as little surprise that extent of tumor resection, patient age, and WHO grade still feature most prominently in predicting the clinical course and prognosis of children affected by astrocytic CNS lesions. Significant results are listed in Table 28.1. For a more detailed review of this topic, the interested reader may find these reviews rewarding [15, 16].

28.2.1 General

A study of 30 pediatric astrocytic tumors of various histologies found ploidy to be a statistically significant predictor of survival independent of tumor grade, age, gender, and extent of resection [17]. DNA diploidy was demonstrated in 21 patients and aneuploidy in 9 patients, and of the patients with diploid tumors, 81 % survived compared to only 33 % among patients with aneuploid tumors [17]. Another investigation of 43 astrocytic lesions of different grades evaluated the correlation between outcome and proliferative potential as measured by the bromodeoxyuridine (BrdU) labelling index. A high BrdU labelling index regardless of tumor grade highly correlated with short survival, whereas the association between malignant histology and short

Table 28.1 Summary of statistically significant prognostic histopathological, immunohistochemical, cytogenetic, and molecular genetic factors with their clinical relevance in pediatric astrocytic tumors

Tumor entity				
Source	Feature	Prognostic relevance	*p*	*N*
General				
[18]	High BrdU labelling index	Worse OS	0.0001	43
[17]	Aneuploidy	Worse OS	<0.0011	30
Low-grade astrocytomas				
[18]	Tumor grade (low vs high grade)	Worse OS	0.019	43
[19]	Tumor grade (pilocytic vs fibrillary)	Better 5-year OS	<0.001	132
		Better 10-year OS	<0.001	132
		Better 20-year OS	<0.001	132
[23]	MIB-1 proliferation index >0 %	Worse 5-year CSS	0.005	35
		Worse 5-year PFS	0.006	35
[20]	Tumor grade (pilocytic vs fibrillary)	Better 5-year PFS	<0.001	29
		Better 5-year OS	<0.001	29
Pilocytic astrocytomas				
[25]	Mixed pattern/additional non-pilocytic glial component	Worse OS	0.008	78
[9]	Monomorphous pilomyxoid features	Worse 1-year PFS	0.04	31
		Worse 2-year OS	0.001	31
[28]	MIB-1 proliferation index >2 %	Worse 5-year PFS	0.035	118
[7]	Monomorphous pilomyxoid features	Worse 5-year PFS	ND	78
		Worse 5-year OS	ND	78
Pleomorphic xanthoastrocytomas				
No significant data				
Fibrillary astrocytomas				
[24]	MIB-1 proliferation index >11 %	Worse OS	<0.0001	34
High-grade astrocytic tumors				
[40]	High immunohistochemical expression of bFGF	Shorter median PFS	0.006	27
		Shorter median OS	0.03	27
[35]	Immunohistochemical p53 overexpression	Shorter median PFS	0.019	29
		Shorter median OS	0.013	29
	TP53 mutations	Worse median PFS	0.04	29
[39]	PTEN mutations	Decreased OS	0.006	39
		Worse OS	0.004	17
[36]	MIB-1 proliferation index >25 %	Worse OS	<0.001	33
[29]	Topoisomerase II alpha expression index >12 %	Worse 5-year PFS	0.011	17
		Worse OS	0.004	17
[38]	High immunohistochemical expression of p53	Worse 5-year PFS	<0.001	115
		Worse 5-year OS	<0.001	115
	Overexpression and mutation of p53	Worse 5-year PFS	<0.001	88
		Worse 5-year OS	<0.001	88
[37]	MIB-1 proliferation index >36 %	Worse 5-year PFS	0.003	98
Anaplastic astrocytomas				
[24]	MIB-1 proliferation index >11 %	Worse OS	<0.001	33
[36]	Gain of chromosome 1q	Worse OS	<0.05	10
[37]	MIB-1 proliferation index	Worse 5-year PFS	0.02	98
Glioblastomas				
[36]	Tumor grade (vs anaplastic astrocytoma)	Worse OS	<0.05	23
[37]	MIB-1 proliferation index	Worse 5-year PFS	0.046	98

ND no data available, *OS* overall survival, *PFS* progression-free survival

survival was weaker but still significant, indicating that BrdU labelling index may be a significant predictor of outcome in children with astrocytomas [18].

28.2.2 Low-Grade Astrocytic Tumors

A large cohort of cerebellar low-grade astrocytomas consisting of 105 pilocytic astrocytomas and 27 diffuse astrocytomas revealed that the separation into pilocytic and diffuse histological type was the most significant prognostic factor influencing survival: the 5-, 10-, and 20-year survival rates were 85, 81, and 79 %, respectively, for pilocytic and 7 % each for diffuse astrocytomas [19]. Whereas several additional studies also found better survival rates in children with pilocytic compared to diffuse astrocytomas, one of them highly significantly with children with WHO grade I tumors having a superior progression-free and overall survival than those with grade II tumors [20], histological subclassification of low-grade cerebellar astrocytomas in children was found by other authors to be insufficient for predicting prognosis and biological behavior as both WHO tumor grades I and II showed similar survival rates [21, 22]. Furthermore, among 35 pediatric low-grade astrocytomas, patients with MIB-1/Ki-67-negative tumors, i.e., showing no proliferation, had a 5-year cause-specific survival and progression-free survival of 100 % which declined significantly to 84 and 67 %, respectively, for patients with tumors demonstrating any degree of Ki-67 positivity [23]. Similar results were published from a survey of 34 children with diffuse fibrillary astrocytomas which showed that an MIB-1 proliferation index of <11 % was associated with significantly better overall survival compared with those with MIB-1 >11 % [24].

Cytogenetic analysis was performed on 29 pediatric low-grade astrocytomas and revealed one or more chromosomal abnormalities in eight tumors while normal karyotypes were observed in 21 cases [20]. There was a trend for a better clinical course for tumors with chromosomal changes with 5-year progression-free survivals estimated at 87.5 % for children with abnormal vs 43 % with normal cytogenetics and with 5-year overall survival of 83 % for those with abnormal vs 78 % with normal cytogenetics [20].

28.2.3 Pilocytic and Pilomyxoid Astrocytomas

Several investigations on pilocytic astrocytomas have encountered pilomyxoid features or a mixed pattern with additional non-pilocytic glial components which were found to convey an unfavorable clinical course. One study of 31 cases concluded that pilocytic astrocytomas with monomorphous pilomyxoid features had a less favorable outcome with higher rates of recurrence and CSF dissemination than cases with classical histological features, resulting in 1-year progression-free survival of 38.7 % (vs 69.2 %) and 2-year overall survival of 38.7 % (vs 100 %), thus qualifying as a more aggressive variant and separate entity [9]; this fact was appreciated by including the pilomyxoid astrocytoma as a separate entity in the latest WHO classification of CNS tumors [4]. A study on 58 classic pilocytic astrocytomas and 20 pilomyxoid astrocytomas revealed the pilomyxoid variant to be associated with a worse prognosis in univariate but not in multivariate analysis [7]. A further survey on 78 cerebellar pilocytic astrocytomas revealed a classic pilocytic/microcystic pattern in 62 cases whereas 16 showed a mixed pattern with an additional non-pilocytic glial component which was associated with a significantly poorer survival [25]. The conjunction of mitoses, nuclear atypia, and increased cellularity, designated as “atypical pilocytic astrocytoma,” was found to be rare and less reliably correlated with prognosis than in patients with fibrillary astrocytomas [6].

Several investigations have examined the influence of proliferation upon juvenile pilocytic astrocytomas, using among others the

currently most widely employed proliferation marker Ki-67/MIB-1. No significant differences were encountered between subgroups of pilocytic astrocytomas showing an MIB-1 index <5 % (PFS = 87.4 %) vs MIB-1 >5 % (PFS = 76.3 %) [26], while there was also no association found between survival and MIB-1 labelling index or any histological parameter in 131 pilocytic astrocytomas [5]. Another investigation on 48 cases showed adverse outcome in patients with pilocytic astrocytoma to be related to the extent of surgical resection and not to correlate with histology, MIB-1 labelling indices, or cyclin D1 immunoreactivity [27]. Interestingly, one study on 118 pilocytic astrocytomas found an MIB-1 index of >2.0 % to be associated with shortened progression-free survival; however, restricting evaluation to only incompletely resected tumors resulted in an insignificant trend of patients with tumors showing an MIB-1 index >2.0 % having a shortened progression-free survival [28]. Another group investigated the immunohistochemical expression of topoisomerase II alpha, a marker of cell cycle turnover and determinant of tumor cell resistance to chemotherapy, whose labelling index was found to range from 0 to 11.6 and was closely correlated to the MIB-1 index; however, topoisomerase II alpha expression did not correlate with patient survival or recurrence [29].

28.2.4 Pleomorphic Xanthoastrocytoma (PXA)

PXA are mainly encountered in the second decade of life and have a generally good prognosis despite their pleomorphic appearance. Factors influencing clinical outcome include extent of resection and histological features such as mitotic index, necrosis, and lymphocytic infiltration, whereas necrosis has occasionally been put forward as a hallmark of unfavorable prognosis; additionally, findings of no or rare degeneration, atypical mitoses, as well as high mitotic activity and MIB-1 labelling index seem to correlate with a worse biological behavior of PXA [30]. This is corroborated by two publications which find anaplastic transformation and increased mitotic activity of PXA to confer a much worse prognosis [31], while conversely, a low mitotic index of <5/10 HPF is postulated to be predictive of a more favorable recurrence-free and overall survival [30].

As to the significance of TP53 mutations regarding malignant progression or recurrence, no prognostic value has yet been established in two independent investigations [32, 33]. One PXA revealing multiple genetic alterations after investigation by comparative genomic hybridization (CGH) showed a poor prognosis [34]; however, no large series relating chromosomal aberrations to survival exists.

28.2.5 High-Grade Astrocytic Tumors

A study on 26 patients with high-grade astrocytic tumors found a striking difference in outcome between tumors with MIB-1 indices <12 % and those with indices >12 % [35], another on 33 cases found a prognostically significant cutoff MIB-1 proliferation index of 25 % [36]. Median progression-free survival in the former study was >48 months in the low compared with only 6 months in the high MIB-1 group, whereas median overall survival was >48 months in the low compared with only 16 months in the high MIB-1 group. Although MIB-1 index was found to be associated with histopathological grade, it proved to be a much stronger predictor of outcome than histology [35]. A later study by the same group on 98 high-grade gliomas showed a strong association between MIB-1 labelling and patient outcome: the 5-year progression-free survival was 33 % in 43 patients with MIB-1 indices of <18 %, 22 % in 27 patients with MIB-1 between 18 and 36 %, and 11 % in 28 patients with MIB-1 >36 % [37]. Not surprisingly, a strong association was also observed between tumor grade and MIB-1. Notwithstanding this correlation, a significant association was noted between MIB-1 and progression-free survival even after stratification by

histology. Thus, although histology had an independent association with outcome, the prognostic value of MIB-1 labelling transcended histological subgrouping and was apparent both in anaplastic astrocytomas and glioblastomas, with tumors showing MIB-1 labelling indices >36 % having an almost uniformly poor outcome regardless of histology [37].

The same group also analyzed immunohistochemical expression of p53 in 115 high-grade astrocytic tumors, among which a significant association between p53 overexpression and outcome was found independent of histological features, age, sex, the extent of resection, and tumor location [38]. The rate of 5-year progression-free survival was 44 % among the 74 patients with low p53 expression and 17 % among the 41 patients with p53 overexpression indicating that overexpression of p53 in malignant gliomas of childhood is strongly associated with an adverse outcome, possibly because P53-dependent pathways influence the cytotoxic effects of conventional chemo- and radiotherapy [38]. The study corroborated an earlier investigation by the same authors who had already encountered a significant association between p53 overexpression and a shorter progression-free and overall survival in a smaller cohort [35]. However, while a later study on a group of 39 high-grade astrocytomas found a significant association between PTEN mutations and decreased survival among children regardless of patient age or tumor grade, mutations in TP53 or amplifications of MDM2 and CDK4 were not significantly linked to outcome [39].

Immunoreactivity for basic fibroblast growth factor (bFGF), a mitogenic and angiogenic factor, among 27 malignant childhood gliomas found a significant difference in outcome between patients with high and those with low bFGF expression with median progression-free survival of >66 months in the low and 6 months in the high bFGF group as well as an overall survival of >66 months in the low and 18 months in the high bFGF group, pointing toward a strong association between tumor bFGF expression and outcome in children with high-grade gliomas [40]. The same authors later investigated nuclear DNA topoisomerase II alpha (TII alpha), a marker of cell cycle turnover and determinant of tumor cell resistance to chemotherapy, in a series of 17 pediatric high-grade gliomas [29]. A cutoff labelling index of 12 % was found to define two prognostic subgroups with profoundly different 5-year progression-free (60 % vs 8 %) and overall survival (100 % vs 8 %) for cases with an index >12 % [29].

28.2.6 Anaplastic Astrocytoma

An investigation of the proliferative potential of 33 childhood anaplastic astrocytomas showed a significantly better survival for tumor carriers with an MIB-1 index <11 % compared to those with an index >11 % [24]. Furthermore, a CGH study on 10 anaplastic astrocytomas of childhood found a significantly shorter survival for children whose tumors showed gains of chromosome 1q [36].

28.2.7 Glioblastoma

Within the group of pediatric glioblastomas, the clinical outcome for the giant cell type of glioblastoma seems to be somewhat better than for classical glioblastomas with children surviving up to 11 years, possibly can be due to their less infiltrative nature [41]. Equally, in the setting of Turcot syndrome type 1 (autosomal dominant disorder characterized by colorectal polyps and malignant neuroepithelial tumors), glioblastomas tend to show a remarkably longer survival time (27 vs 12 months) compared with sporadic cases [42].

28.3 Comparative Genomic Hybridization (CGH) in Astrocytic Tumors of Childhood and Adolescence

CGH is a cytogenetic technique that is particularly useful in the study of solid tumors and which was first introduced in 1992. CGH offers

advantages over other cytogenetic and molecular genetic methods like loss of heterozygosity analysis (LOH) and classic karyotyping in that it does not involve in vitro culture of tumor tissue or necessitate healthy tissue or blood from a given patient, allows rapid detection and localization of gains and losses across the entire genome, and offers higher resolution than conventional cytogenetics. DNA from archival material can be used, and CGH can be successfully performed using very small amounts of DNA in the order of nanograms. The entire genome is screened for gains and losses of genetic material relative to the ploidy level in a single experiment, and the method is essentially a modified in situ hybridization. However, there is a limit to the resolution of this technique: losses are only detectable when the region affected exceeds 10 Mb, whereas gains are detected if there is a high-level amplification of approximately 2 Mb, and balanced structural rearrangements like balanced translocations, inversions, and ring chromosomes cannot be detected at all. Once regions of gain or loss have been established, they can be further delineated by FISH or other molecular genetic techniques, e.g., LOH analysis and sequencing in order to identify proto-oncogenes and tumor suppressor genes [43]. A summary of the most common CGH findings in 154 pediatric astrocytic tumors is listed in Table 28.2.

28.3.1 Pilocytic Astrocytomas

Two CGH studies altogether with 50 cases showed very few chromosomal imbalances [44, 45]. The most common aberration affecting a mere 10 % of all tumors consisted of gains of 6q followed by gains of 7q in 8 % of cases whereas the most common loss affects 9q and is found in just 4 % of cases [44, 45]. The last two imbalances are noteworthy in that +7q is encountered in other gliomas like pleomorphic xanthoastrocytomas, ependymomas, and gangliogliomas but also in choroid plexus papillomas, classic medulloblastomas, and PNET, while −9q is the main aberration in pleomorphic xanthoastrocytomas and is also found in anaplastic astrocytomas and astroblastomas [43].

Table 28.2 Summary of the most common CGH findings in 154 pediatric astrocytic tumors

Tumor entity			
Source	*N*	Frequent gains (%)	Frequent losses (%)
Pilocytic astrocytomas			
[44]	9	6q(44),4q(33),5q,7q,11q,13q(22)	1p,9q(22)
[45]	41	7(5),5,6,9(3)	None
Pleomorphic xanthoastrocytomas			
[46]	50	X(14),7,9q,20(8)	9(48),17(10)
[34]	3	7(67),2p,4p,11q,12,15q,19(33)	8p(67),9p,10p,13q(33)
Fibrillary astrocytomas			
[47]	8	9,11,19(13)	2,22q(13)
Anaplastic astrocytomas			
[48]	2	None	None
[36]	10	5q(40),1q(30)	22q(50),6q,9q(40),12q(30)
[49]	3	2q,6q,7q,11q,12q,13q(33)	16p(67)
Glioblastomas			
[36]	13	1q(54),3q(38),2q,17q(23)	6q,8q,10q,13q,17p(31)
[50]	5[a]	17,20q(40)	13q,Y(40)
[49]	10	2q,4q,5q,12q,13q(40),8q(30)	16p(50),17p,19p,22q(40),19q(30)

[a]After radiochemotherapy

28.3.2 Pleomorphic Xanthoastrocytomas (PXA)

Two CGH investigations on 53 cases found loss of chromosome 9 to be by far the single most common aberration affecting 49 % of specimens whereas gains of chromosome X and losses of 7 were far rarer with 14 and 11 %, respectively [34, 46].

28.3.3 Fibrillary Astrocytomas

Only one CGH study of eight cases has been performed and showed no chromosomal aberrations in four tumors whereas the other tumors presented with no distinct pattern of gains and losses [47]. Loss of 22q – the most frequent aberration among anaplastic astrocytomas – was encountered in one tumor.

28.3.4 Anaplastic Astrocytomas

Three studies have investigated altogether 15 anaplastic astrocytomas by CGH [36, 48, 49]. The most common chromosomal aberrations among these tumors were gains of 5q (27 %) and 1q (20 %) as well as losses of 22q (40 %), 9q (33 %), and 12q (27 %) [36]. Interestingly, one study found a significantly shorter survival among patients with anaplastic astrocytomas showing +1q [36], an association that has also been reported for ependymomas which when shown to harbor +1q tended to occur in the posterior fossa of children and behave aggressively [15, 43].

28.3.5 Glioblastomas

Three studies have investigated altogether 28 pediatric glioblastomas by CGH [36, 49, 50], of which five were examined after radiochemotherapy [50]. Similar to anaplastic astrocytomas, the most common chromosomal aberrations were gains of 1q and 2q (25 % each), 3q and 17q (18 % each), as well as losses of 17p (29 %) and 13q (21 %) [36]. Compared with adult cases, gains of 1p, 2q, and 21q as well as losses of 6q, 11q, and 16q were more frequently observed among pediatric malignant astrocytomas showing that chromosomal aberrations do not only differ between pediatric anaplastic astrocytomas and glioblastomas but also between pediatric and adult high-grade astrocytomas, supporting the notion of different genetic pathways [36].

28.4 Extraneural Metastases of Astrocytic Brain Tumors in Childhood

Extraneural metastases from brain tumors are an unusual event; their incidence, however, has increased over the years along with improved patient survival due to more aggressive and effective therapy. As to their pathogenesis, the relationship between surgery and metastasis is unclear: while it is possible that in some cases the appearance of extraneural tumor foci simply reflects prolonged survival time of these patients, the overwhelming majority of patients with extraneurally metastasising brain tumors have undergone some form of prior surgical manipulation of the primary neoplasm, be in the shape of a previous stereotactic or open biopsy, surgery, or a shunt procedure. The diagnosis of extraneural metastases in the pediatric population is of more than just academic interest as these lesions do not necessarily occur in conjunction with a local recurrence of the CNS tumor and the investigating pathologist has to be aware that a tumor at a particular site and in a specific age group could also represent metastatic spread of a cerebral neoplasm.

A survey of extraneural metastases occurring in children under the age of 18 years revealed 245 cases of which 28 (11.4 %) were patients suffering from astrocytic lesions (for references to specific cases see [51]): 14 with glioblastomas (6.9 % of all cases), 6 with pilocytic astrocytomas (2.9 %), t3 each with astrocytomas not

otherwise specified and gliosarcomas (1.5 % each), respectively, and 2 with anaplastic astrocytomas (1.0 %, Table 28.3). Glioblastomas predominantly metastasized to bone (57.1 % of astrocytic tumors), with vertebrae being particularly common targets and 3 out of 14 cases presenting with multiple osseous sites of involvement (Table 28.3). Of all 28 astrocytic tumors, 57.1 % spread to mainly regional, i.e., cervical, lymph nodes, interestingly unrelated to WHO grade of

Table 28.3 Demographic data, tumor histology, metastatic sites, latency, and survival among 28 children with extraneural metastases of astrocytic tumors

		Metastatic sites				
Age/sex	Histology	Bone (including bone marrow)	Lymph nodes	Visceral/others	Latency	Surv
(a) *Metastases after surgical intervention* (*operation*, *biopsy*, *and/or shunt insertion*)						
4/M	PA	–	Cervical	Skin	48	>90
3/M	AA	–	–	Epidural	ND	ND
3/F	GBM	Skull	Pulmonary	Lung, pleura	ND	31
7/F	GBM	Jaw, ver, sca, hum, pel, fem, tib	Supraclavicular	–	12	7
9/M	GBM	Bone NOS	–	–	2	3
9/F	GBM	–	Cervical	–	ND	19
12/M	GBM	Pelvis	–	–	5	ND
12/F	GBM	Bone NOS	Cervical	Lung	ND	7
17/F	GBM	–	–	Lung	24	ND
6/M	GS	–	–	Lung	ND	17
6/M	GS	–	–	Lung	ND	7
11/F	GS	–	–	Lung	1	0
(b) *Spontaneous metastases without prior surgical intervention*						
4/M	PA	–	–	Lung, muscle	0	ND
3/M	AA	–	Cervical	–	0	2
11/F	GBM	Skull, jaw, ver, rib, hum, uln, fem, pel, tib, fib		–		6
(c) *Shunt-related metastases*						
6 m/M	PA	–	–	Peritoneum	2	>106
19 m/M	PA	–	–	Peritoneum	47	10
3/M	PA	–	–	Peritoneum	6	>12
6/F	PA	–	–	Peritoneum	122	5
4/F	A NOS	–	–	Peritoneum	5	1
12/F	A NOS	–	–	Lung, liver	ND	0
17/M	A NOS	Bone NOS	Nodes NOS	Pleura, soft tissue	ND	28
1/F	GBM	–	–	Peritoneum	ND	ND
7/F	GBM	Vertebrae	Pulmonary	Pleura, liver, adre	ND	ND
9/M	GBM	–	–	Peritoneum	9	ND
9/F	GBM	–	–	Peritoneum	2	4
13/M	GBM	–	–	Peritoneum	3	4
14/F	GBM	Vertebrae, rib, sternum	Aorta, mediast	Pleura, lung	ND	13

M male, *F* female, *PA* pilocytic astrocytoma, *A* astrocytoma, *AA* anaplastic astrocytoma, *GBM* glioblastoma, *GS* gliosarcoma; *adre* adrenal, *fem* femur, *fib* fibula, *hum* humerus, *mediast* mediastinum, *pel* pelvis, *sca* scapula, *tib* tibia, *uln* ulna, *ver* vertebrae

Latency interval between brain surgery and extraneural metastasis (in months), *Surv* survival after extraneural metastasis (in months), *NOS* not otherwise specified, *ND* no data available

malignancy. In regard to visceral metastases, there was a clear distinction between shunt-related metastases, of which all 13 cases showed tumor seeding in the compartments that the previously inserted shunt was draining to (pleura, peritoneum), whereas 7 out of the 15 remaining cases showed pulmonary metastases, all bar one of them stemming from glioblastomas or gliosarcomas [51]. Not surprisingly, particularly grave outcomes were found among children with glioblastomas and gliosarcomas, of which all died within a time span of at most 31 months, while long-term survival of between 1 and 11 years was encountered among children suffering from pilocytic astrocytoma [51].

Acknowledgements Many thanks and heartfelt best wishes to my former clinical colleagues at the Royal Children's Hospital in Melbourne (Australia) – may the Hawthorn Hawks win many more flags! Thanks, too, to Werner Paulus for years of teaching, advice, and help.

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