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Diagnostic Evaluation of Diffuse Gliomas

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1. Introduction

Diffuse gliomas are preferentially located in the subcortical or deep white matter of the cerebral hemispheres and are the most frequent CNS neoplasms accounting for approximately 60 per cent of all CNS tumors (CBTRUS 2011). This definition excludes the circumscribed and biological different pilocytic astrocytoma and pilomyxoid astrocytoma which are covered in a separate chapter in this book. Other rare distinct glial neoplasms with a favourable prognosis such as the subependymal giant cell astrocytoma of lateral ventricles and the pleomorphic xanthoastrocytoma of children and young adults also do not belong into the group of diffuse gliomas. Ependymomas indeed are diffuse growing glial neoplasms but are biologically different. Moreover they appear in a different population as astrocytic and oligodendroglial neoplasms. Because of space limitations the current chapter deals only with astrocytomas, oligodendrogliomas, oligoastrocytomas and glioblastomas. These tumors are grouped here under the umbrella term "diffuse gliomas". They have a predilection for frontal and temporal lobes accounting together for more than two third of all cases. However diffuse astrocytomas may be seen in any other region of the brain including cerebellum and spinal cord (Louis et al., 2007a).
Although serious advances in neuroimaging of these brain tumors have been made in the past, histopathologic evaluation of neurosurgically removed tumor specimens is still required for definite diagnosis of diffuse gliomas. These CNS tumors show an extensive variety of histologcial and cytological appearance making diagnosis somewhat difficult for those who are not familiar in working with brain tumors. The current chapter focuses on neuropathological features of the different types of diffusely infiltrating gliomas based on the latest World Health Organization (WHO) classification of tumors of the nervous system. Core features and distinct pattern and variants are also introduced and illustrated. Immunohistochemistry and molecular biology have contributed to an improved classification and shown in some cases to be of prognostic value. The advantages and limitations of the most commonly used antibodies such as GFAP, WT1, MAP2, MIB-1, P53, IDH1R132H; NOGO-A are discussed in the current chapter. Molecular analysis of 1p19q codeletion, MGMT promoter methylation, Tp53 and isocitrate dehydrogenase mutations are presented in detail and their implications are discussed.

2. Incidence and overview

Regional incidences vary with generally higher number in developed countries and are estimated between 2.2 per million people for low-grade lesions (i.e. WHO grade II

neoplasms) and up to 4.6 per 100.000 people for glioblastoma (Ohgaki et al., 2005a). There is a strong correlation between age of presentation and histological tumor grade. The mean age of diagnosis for diffuse astrocytoma grade II WHO is 39 years, for anaplastic astrocytomas grade III WHO is 45 years and 61 years for glioblastoma grade IV WHO. The mean age for oligodendroglioma is 43 years, for anaplastic oligodendrogliomas grade III it is 47 years. Mean age for oligoastrocytomas is 40 years, for anaplastic oligoastrocytomas is 44 years (Louis et al., 2007a). A similar age distribution has been observed in our institution. Less than 10% of astrocytic and less than 2% of oligodendroglial tumors develop in the pediatric age group. Thus, the pathologist should always take patients age into mind when considering possible differential diagnoses. There is a slight predominance of males (Ohgaki et al., 2005b) but in contrast to meningiomas or germ cell tumors this is not of diagnostic relevance. Higher socioeconomic status is also a risk factor**.**

The histologic subtypes are not evenly distributed. Diffuse astrocytomas represent 5-10%, anaplastic astrocytomas approximately 10% and glioblastomas between 75-85 per cent of all astrocytic neoplasms (CBTRUS, 2011). This can be explained by the fact that glioblastomas are a heterogenous group of tumors with distinct genetic features but similar morphology. Diffuse astrocytomas show a tendency to progress to a more malignant phenotype during disease progression within 6-8 years, ending finally as secondary glioblastomas, (10-15% of all glioblastomas). However there is no biomarker that can predict the time to progression in individual patients. The majority of glioblastomas develop without a precursor lesion ("de novo") and are genetically distinct from the secondary glioblastomas (Ohgaki et al, 2007). In primary glioblastomas several activated oncogenic pathways are known, but all share a similiar dismal prognosis. Oligodendroglial tumors account for 5-6% of all gliomas and in this group 70% are diagnosed as grade II oligodendrogliomas and 30% as grade III anaplastic oligodendrogliomas (CBTRUS, 2011). While there is no doubt that oligodendroglioma undergo a similar malignant tumor progression as astrocytic neoplasms, there is still debate about how much of these truly develop into glioblastomas. Because of divergent classification criteria true estimates for mixed gliomas vary between 1 and 10% of all gliomas. According to the more stringent CBTRUS criteria, only 2% of all gliomas meet the criteria for a mixed oligodendroglial – astrocytic neoplasm (CBTRUS, 2011).

2.1 General grading of diffuse gliomas

In 1979 the World Health Organization issued a publication for classification of tumors of the central nervous system which has been updated lastly in 2007. This included a grading scheme based on malignancy behaviour of the tumors. Grading of diffuse gliomas is performed in a four-tiered score ranging from grade I to grade IV, the latter bearing the worst prognosis. Histological factors that influence grading are nuclear atypia, cellularity, mitosis, necrosis and endothelial proliferations. Among diffuse gliomas grade II is assigned to diffuse astrocytoma, oligodendroglioma and oligoastrocytoma. Grade III neoplasms include anaplastic astrocytoma, anaplastic oligodendroglioma and anaplastic oligoastrocytoma. Grade IV is reserved for glioblastoma. This score is used to separate the histologic continuum of diffuse gliomas.

3. Astrocytoma

3.1 Macroscopy

The invaded CNS tissue is usually enlarged, but main anatomical structures remain relatively intact. The overlying cerebral cortex might be affected with a blurred gray-white

junctional zone. Tissue from this area instead of the deeper white matter might be not diagnostic or carries the risk of undergrading the tumor. The fixated tissue appears yellowish to gray and may be of varying texture, either softer or firmer than the surrounding normal appearing brain. Larger cysts are uncommon but when present are usually filled with a clear fluid. In cases with extensive microcystic formations of the tumor, a gelatinous appearance is present. Calcifications within the tumor is not the role. In spinal cord, cystic lesions may extend from the tumor poles.

3.2 Histology

Astrocytomas might display a wide range of cytologic and histologic features so that some autors even state that "astrocytomas are best defined as infiltrating gliomas that cannot be classified as oligodendrogliomas" (Burger & Scheithauer 2007). One important diagnostic marker is the hypercellularity of the CNS tissue. The number of tumor cells is usually slightly increased with a cellularity of two to five times than normal and the distribution of cells is irregular. Neoplastic astrocytes usually exhibit irregular elongated, hyperchromatic nuclei lacking a perinuclear halo with often minimal fibrillar cytoplasm ("naked nuclei"). The tumor cells lie between myelinated axons which can be visualized with luxol fast blue stains. In some cases there is a prominent pink cytoplasm with short stout processes and eccentrically placed nuclei, a so called "gemistocytic appearance". These tumors are prone to perivascular lymphocytic cuffs which are also seen in glioneuronal tumors (Takeuchi et al., 1976). Nuclei in gemistocytic variants are more rounded and less irregular and might show micronucleoli. Since almost all astrocytomas exhibit some gemistocytic tumor cells, a cut off of more than 20% gemistocytes has been proposed for the gemistocytic variant of astrocytoma (Tihan et al., 2006). Tumor margins in astrocytomas are rarely discernible. The neoplastic astrocytes rest on a fibrillary background which often shows some microcystic changes and increased density of cellular processes. These microcavities are usually absent in reactive gliosis. Cases with extensive mucoid degeneration and rarity of glial processes are designated as protoplasmatic astrocytomas. All three morphologies fibrillar, gemistocytic and protoplasmatic are considered histological variants of diffuse astrocytomas. Since a different clinical outcome for these is not firmly established some authors rather consider these as divergent patterns of differentiation (Louis et al., 2007b).

Compared to diffuse astrocytomas, anaplastic astrocytomas exhibit increased cellularity, distinct nuclear atypia and mitotic activity but lack the micovascular proliferation and necrosis of glioblastomas. Multinucleated tumor cells are often diagnostic for a grade III lesion but not required for their diagnosis. One should also be aware of possible previous radiation therapy of the tumor leading to an increase of cell pleomorphism together with a decrease of mitotic activity (Gerstner 1977).

The original St. Anne-Mayo grade system did not allow mitoses in a low-grade lesion. Current criteria suggest that presence of zero or one mitosis do not alter survival and thus is still compatible with a WHO grade II neoplasm (Giannini et al., 1999). Unfortunately the WHO classification allows for a broad range of interobserver variability in borderline cases of low-grade gliomas, as presence of mitotic activity has to be interpreted in regard to the total sample size (Louis et al., 2007). In small specimens such as stereotactic biopsies a single mitosis suggests at least a grade III lesion but in larger specimens the presence of a single mitosis is not sufficient (Giannini et al., 1999). Cases with low cellularity of astrocytic tumor cells but exhibiting several mitoses should be considered as grade III or IV lesions. Diffuse

astrocytomas (WHO grade II) have normal appearing vessels and a vessel density that is only slightly greater than in normal human brain. Compared to grade II lesions the vessel density increases further in grade III astrocytomas (Brat et al., 2001).

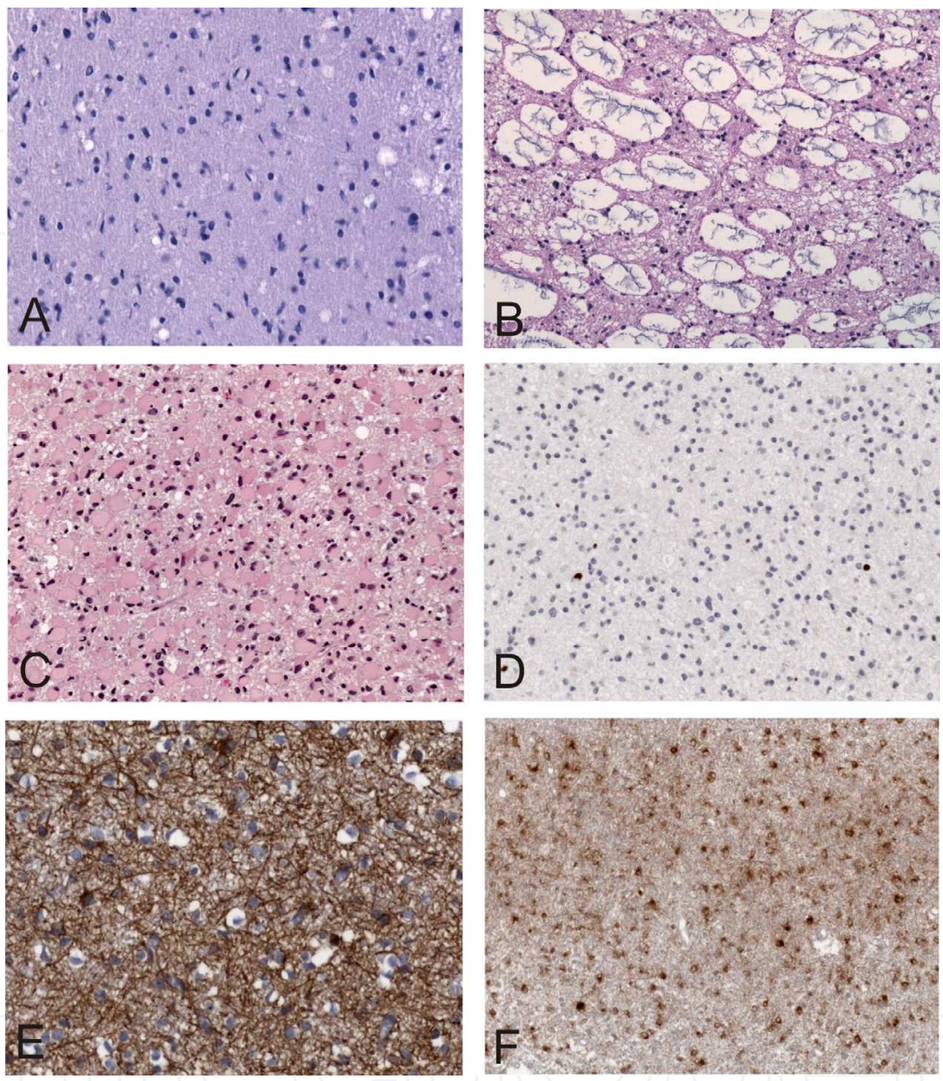

Fig. 1. Histology of **diffuse astrocytoma**: HE stains of (A) fibrillary astrocytoma, (B) protoplasmatic astrocytoma and (C) gemistocytic astrocytoma. The proliferation in these tumors, as determined by MIB-1 nuclear immunoreactivity (D) is low (1-2%). Strong, consistent GFAP expression in neoplastic astrocytes (E). IDH1 mutations are found in up to 70% of these tumors, the most common R132H mutation can be detected immunohistochemically (F).

Differential diagnosis also includes reactive changes of the CNS. In astrocytic neoplasm, tumor cells are morphologically similar but less evenly distributed than reactive cells which are in different stages of activation. In addition reactive astrocytes show longer stellate processes. It is also important to recognize entrapped neurons and differentiate these from the more pleomorphic or even multinucleated neuronal tumor cells of a ganglioglioma.

Ventricular tumors with bizarre giant cells but low mitotic activity are often subependymal giant cell astrocytomas (WHO grade I).

3.3 Immunohistochemistry

Astrocytomas show an expression of glial fibrillary acidic protein in tumor cells (Yung et al,. 1985). Especially the gemistocytic tumor cell cytoplasm and rare interdispersed Rosenthal fibers show a strong immunoreactivity for GFAP (Tascos et al., 1982). In addition the fibrillary neuropil displays almost always shows a diffusely positive background. Fibrillary astrocytes often show a small perinucelar rim, while interdispersed small round cells might be GFAP-negative. In independent studies all examined diffuse astrocytomas, were at least focally positive for GFAP (Cosgrove et al., 1986, Waidelich et al., 2010). Astrocytomas also express consistently S-100 and vimentin (Tabuchi et al., 1982, Yung et al., 1985). While S-100 is also present in the nuclei, Vimentin is often absent in distant cell processes. The malignancy-associated expression of WT1 is less intense than in high-grade astrocytic lesions (Hashiba et al., 2007, Rushing et al., 2010) but usually more prominent as in reactive lesions or oligodendrogliomas. WT1 is expressed in 52% of all diffuse astrocytomas, but tumors with more than 75% positive WT1 cells should prompt the diagnosis of a high grade glioma (Schittenhelm et al., 2009). A single study demonstrated that oligodendroglia-associated marker Nogo-a is absent in grade II and III astrocytomas (Kuhlmann et al., 2008). Caution should be employed when using epithelial antigens, such as cytokeratins and epithelial membrane antigen for differential diagnosis of carcinomas, as variable expression of these markers have been observed in astrocytomas (Franke et al.,1991; Ng et al.,1989). A bcl-2 expression in diffuse astrocytomas is more prominent than in reactive lesions and frequently seen in gemistocytic tumor cells (Hussein et al., 2006).

The microtubuli-associated protein 2 which has once been considered as a neuronal marker is expressed in 92-97% of astrocytomas (Wharton et al., 2002). Cytoplasmic staining is preferentially seen in the larger, more pleomorphic, tumour cells and expression is generally more intense in high-grade lesions than in astrocytomas grade II. Some authors propose, that presence of MAP2-positive ramifying cytoplasmic processes aids in differentiating astrocytomas from oligodendogliomas where MAP2 is expressed in a capped fashion highlighting the rounded cells (Blümcke et al., 2004). MAP2 might also help to distinguish astrocytic tumors from ependymal neoplasms which show usually only solitary MAP2-positive cells in one third of cases examined.

Expression of p53 is seen in 72% of diffuse astrocytomas and more prominent in gemistocytic tumor cells and younger patients (Vital et al., 1998). However we have observed p53 in up to 63% of reactive lesions. The phospho-histone H3 marker might be useful to detect mitoses in tumor specimens with a proposed cutoff of 4/1000 between grade II and grade III astrocytomas (Colman et al., 2006). MIB-1 tumor proliferation is usually between 2-3%, rarely exceeding 4% (Sallinen et al., 1994). In protoplasmatic variants the MIB-1 proliferation index is usually lower than in other tumor variants (Prayson et al., 1996). The MIB-1 proliferative activity of astrocytomas grade III usually ranges between 5-10% and there is an overlap on both sides to grade II and grade IV lesions. Rare astrocytoma cases may show focal islands of small oligodendrocyte-like cells with immunoreactivity for synaptophysin and NeuN between conventional glial tumor cells (Barbashina et al., 2007).

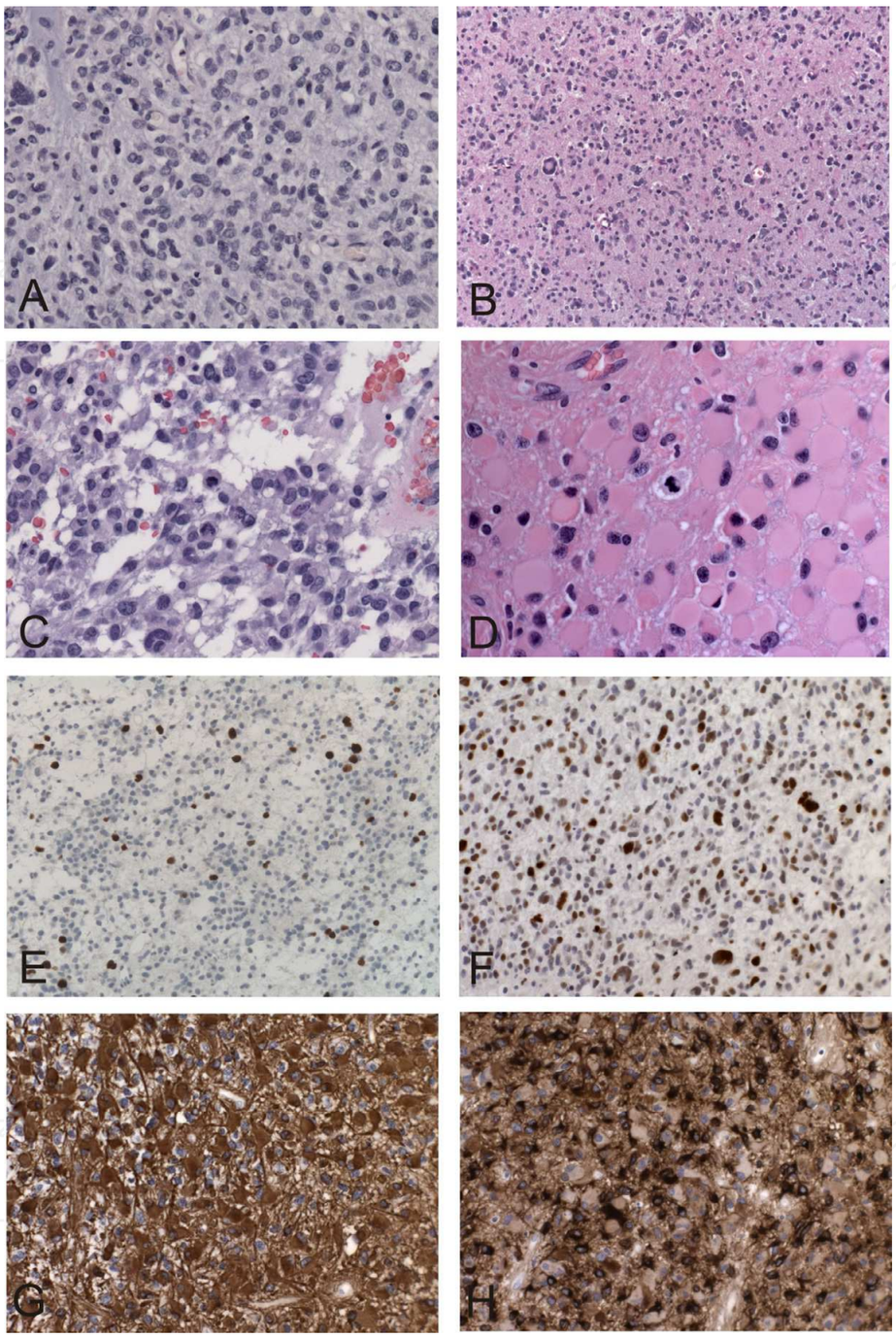

Fig. 2. **Anaplastic astrocytomas** are histologically characterized by (A) increased cellularity, (B) nuclear pleomorphism, (C) presence of several mitoses. Gemistocytic tumors (D) are prone to undergo a more rapid tumor progression. Immunohistochemistry shows increased MIB-1 prolifation index (E). Extensive p53 nuclear immunoreactivity (F) is more frequent in astrocytomas than oligodendrogliomas or glioblastomas. GFAP (G) also marks the elongated tumor cell processes. Anaplastic astrocytomas have a considerably higher presence of MAP2 positive tumor cells (H) than grade II astrocytomas.

3.4 Electron microscopy

Utrastructurally astrocytomas contain abundant 7 to 11nm sized not always parallel aligned intermediate filaments independent of fibrillary, gemistocytic or protoplasmic phenotype of the tumor cells (Duffell 1963). Cells contain dilated cisterns of endoplasmatic reticulum, lysosomes and lipid deposits. Eosinophilic granular bodies display as dense osmiophilic masses between intermediate fibrils. The ultrastructural picture of glioblastomas is similar.

4. Glioblastoma

4.1 Macroscopy

The most malignant astrocytic glioma widely known by its acronym "GBM" was orginally designated as "glioblastoma multiforme" because of extensive variability of tumor histologies. However, individual tumors can also appear quite monorpous on histology. For this reason the "multiforme" is no longer used by the current WHO classification (Burger & Scheithauer, 2007). In our institution we prefer to use the term "multicentric" for single tumors with radiologically or macroscopically separate lesions and the term "multifocal" for true multiple lesions for which no histological continuum between the tumor centers exists. Common tumor spreading routes include fornix, corpus callosum, anterior comissure and radiation optica because of the high affinity of tumor cells for myelinated structures (Burger et al., 1983). Tumors that reach the dura show often marked desmoplasia leading to a firm texture resembling gliosarcoma or meningioma (Stavrinou et al., 2010).

The necrotic center of the tumor is often surrounded by a gray rim and varying yellowish-grayish texture of the surrounding white matter. Black hemorrhagic streaks and thrombosed veins are typically for a grade IV lesion. Symmetric tumors spreading over the corpus callosum are called "butterfly gliomas". Glioblastoma tumor borders are usually diffuse but rare cases (especially giant cell pseudoepithelial glioblastomas) can be very circumscribed mimicking a carcinoma metastasis.

4.2 Histology

The prominent eosinophilic cytoplasm of pleomorphic tumor cells with small fibrillary zones indicates astrocytic heritage of the glioblastoma but this is not the rule for all tumors. Marked nuclear atypia and elevated mitotic activity is common. Either microvascular proliferations or necrosis or both are required to secure the diagnosis. Tumor appearance can be so heterogenous that diagnosis is often based on tissue patterns rather than individual tumor cell morphology. Occasionally perinuclear halos may resemble oligoendrogliomas, however glioblastoma tumor nuclei lack the monotony roundness of true oligodendrogliomas. Small cells with little cytoplasm can appear so monomorphous that small cell glioblastomas mimic anaplastic oligodendrogliomas. Small undifferentiated tumor cells intermingled with gemistocytes are more likely seen in secondary glioblastomas developing from gemistocytic astrocytomas. Some tumors may show prominent perivascular rosettes resembling anaplastic ependymomas but usually lack the more uniform roundness of ependymal tumor cells. Tumor cells can be elongated and arranged in fascicles so that at the first view sarcoma comes into mind.

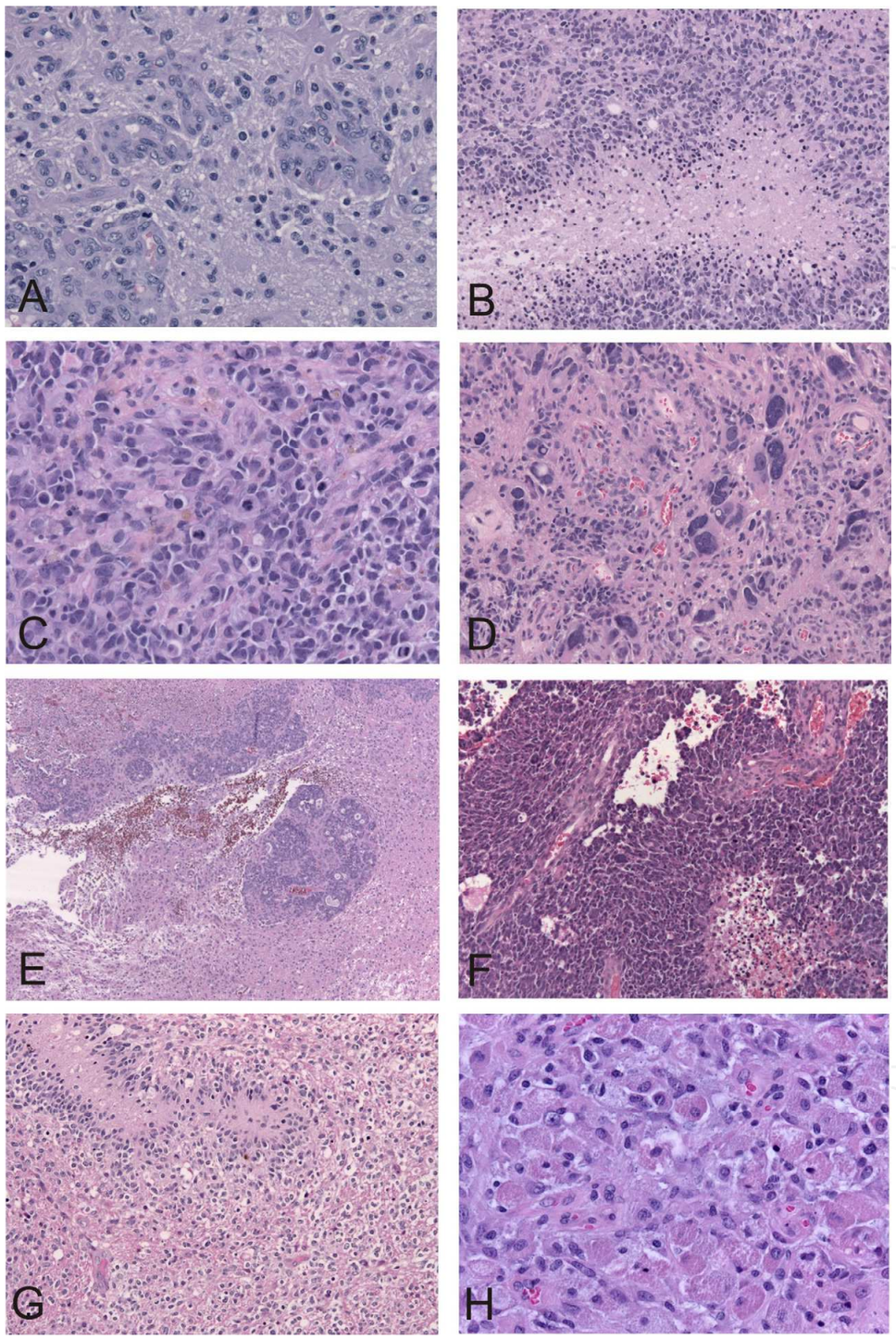

Fig. 3. **Glioblastomas** are defined through microvascular proliferations (A) and pesudopalisading necroses (B). The tumor is mitotically active (C) and may show a high degree of anaplasia (D). Glioblastoma cell composition can be so heterogenous with adenoid epithelial metaplasia (E), small cell component (F), focal oligodendroglial differentiation (G) or granular cells (H) in some cases.

Morphologic variants include granular cell astrocytoma which is characterized by large, PAS-positive cells with a degenerative granular lysosomal content. These look similar to the benign granular cell tumor of the pituitary stalk (Schittenhelm et al., 2010). Another variant is the often subcortical located giant cell glioblastoma showing multinucleated giant cells in more than 50% of tumor cells that can be associated with reticulin deposits (Palma et al., 1989). These tumors need to be distinguished from the more benign subependymal giant cell astrocytomas or pleomorphic xanthoastrocytoma. Another variant contains a biphasic pattern of alternating reticulin-free glial and reticulin-containing mesenchymal deposits and are aptly named gliosarcomas (Louis et al., 2007a). These tumors account for 2% of all glioblastomas (Meis 1991). Metaplastic transformation can be so extensive that chondroid and osseous formations in gliomas are possible (Schittenhelm et al., 2007). Furthermore gliomas can show focal areas of epithelial differentiation that ranges from positive immunreactivity of epithelial antigens to adenoid or squamous formations leading to misdiagnosis of carcinoma (Rodriguez et al., 2008). Rare cases may show a melanotic differentiation (Jaiswal et al., 2010).

In average 3 pseuopalisading necroses are present in a glioblastoma specimen (Brat et al., 2004). Pseudopalisading cells are usually less proliferative and exhibit higher rates of apoptosis due to hypoxic conditions but are usually without a prominent inflammatory infiltrate. More than half of the palisades show a central vascular lumen, in about twenty percent intravascular thrombosis is also seen (Brat et al., 2004). Vascular proliferations may be present throughout the tumor but there is a tendency for these structures to accumulate in the peripheral region of high cellularity corresponding to the contrast-enhancing ring seen in radiological images (Louis et al., 2007a). Tumor vessels in glioblastoma have an increased density and show hyperplasia (Brat et al., 2001). Tumor vessel arrangement in a garland-like fashion is not uncommon. Vascular proliferation in form of glomeruloid bodies in glioblastomas is more frequently than in tumors from any other organ system (Plate et al., 1999).

Infiltrative growth is mostly characterized by small undifferentiated cells growing along axonal structures in the white matter or along the brain surface and blood vessels. These are designated as 'secondary structures of Scherer' (Scherer, 1938). In the spinal cord, tumor cells might extend into the subarachnoid space (Burger & Scheithauer, 2007). Apoptosis of tumor cells is not a major feature but most prominent in areas of pseudopalisading necrosis.

4.3 Immunohistochemistry

The immunoprofile of glioblastomas is in many ways similar to astrocytomas. The vast majority of glioblastomas express the glial markers GFAP and EAAT1 (Waidelich et al., 2010) but these antigens may occasionally lacking (especially in small glioblastomas). S-100 immunostaining is then helpful to indicate a glial origin of the neoplastic cells. Strong MAP2 immunoreactivity is seen in 90% of glioblastomas (Blümcke et al., 2004). Vimentin immunoreactivity is very unspecific. Diffuse growth of gliomas can be supported by identifying axons with neurofilament stains within the tumor, but extensive neurofilament immunoreactivity of the tumor should prompt the diagnosis of an (anaplastic) ganglioglioma. In gliosarcomas, GFAP is lacking in sarcomatous areas. A complementary reticulin staining pattern in these tumors is diagnostic. The proliferation varies greatly, usually 15-25% of the nuclei are MIB-1 positive, but tumors with small cell morphology can show up to 90% proliferating cells. Tumors with previous radiation or gemistocytic

morphology may show little proliferating activity. Because of inconsistent laboratory techniques and varying evaluation methods, MIB-1 immunoreactivity has no established cutoffs between low-grade and high-grade lesions. WT1 expression is consistently expressed in glioblastomas (Schittenhelm et al., 2009). In our experience expression is similar in primary and secondary tumors but expression can be reduced in recurrent tumors. In addition there is evidence that tumors that contain a Tp53 mutation show reduced WT1 levels compared to Tp53 wild type glioblastomas (Clark et al., 2007). IDH1 R132H antibody expression is found in 4% of primary and in 71% of secondary glioblastoma (Capper et al., 2010). Tp53 immunoreactivity is less present than in astrocytomas but can be considerably high in giant cell glioblastomas. Microglial markers such as CD68 are regularly found in glioblastomas and can be very extensive in tumors with granular cell component and need to be distinguished from demyelinating lesions. Cytokeratin expression in glioblastomas (especially in giant cell glioblastomas and glioblastomas with true epithelial metaplasia) is an important diagnostic pitfall (Rodriguez et al., 2008). Dot-like EMA immunoreactivity is less frequently observed in glioblastomas than in ependymomas, where usually more than 5 EMA-positive dots per high-power field are seen (Hasselblatt & Paulus 2003). Immunohistochemistry of EGFR wild type protein is more prominent in primary glioblastomas as in grade II or III gliomas (Simmons et al. 2001).

5. Oligodendroglioma

5.1 Macroscopy

Like all other diffuse growing tumors, oligodendroglioms show diffuse borders. The tumors are usually soft and have a grey to pink color. They may appear hemorrhagic and / or calcified but this is not a specific feature for oligodendrogliomas Superficial growth can expand the cortical grey matter. The anaplastic forms lack a central necrosis typically for glioblastoma but may show focally smaller necroses. Rare disseminating cases may grow as superficial gelatinous mass extending along the spinal cord (Mittelbronn et al., 2005).

5.2 Histology

In contrast to astrocytomas, oligodendrogliomas are dominated by histologic monotony of the round to oval shaped tumor cells which are best seen in smears. Nuclei have a bland chromatin and prominent nucleoli. The very characteristic perinuclear halo – a fixation artefact resulting from autolytic water absorption – is absent in frozen sections or specimens that have been quickly processed resulting from a short fixation time. Delicate branching capillaries and tumor calcifications that also may affect tumor vessels are more frequent in oligodendrogliomas than in other CNS tumors. Overun cortical areas show a perineuronal satellitosis of the tumor cells and tumor cells may concentrate along subpial structures. In addition cortical structures show often smaller microcystic changes.

Anaplastic oligodendrogliomas show increased nuclear pleomorphism that is mostly restricted to focal areas and increased mitotic activity compared to grade II lesions. Some authors prefer a mitotic cutoff of 6 mitoses per 10 high power fields to discriminate between grade II and grade III lesions (Giannini et al., 2001). Focal elevated cellular areas as nodules do not warrant tumor designation as a grade III lesion in absence of other anaplastic features. In contrast to astrocytomas where endothelial proliferations lead to the diagnosis of glioblastoma, vascular proliferations or extended vascular hyperplasia are typical for anaplastic oligodendroglioma grade III. In addition smaller areas of necrosis may be

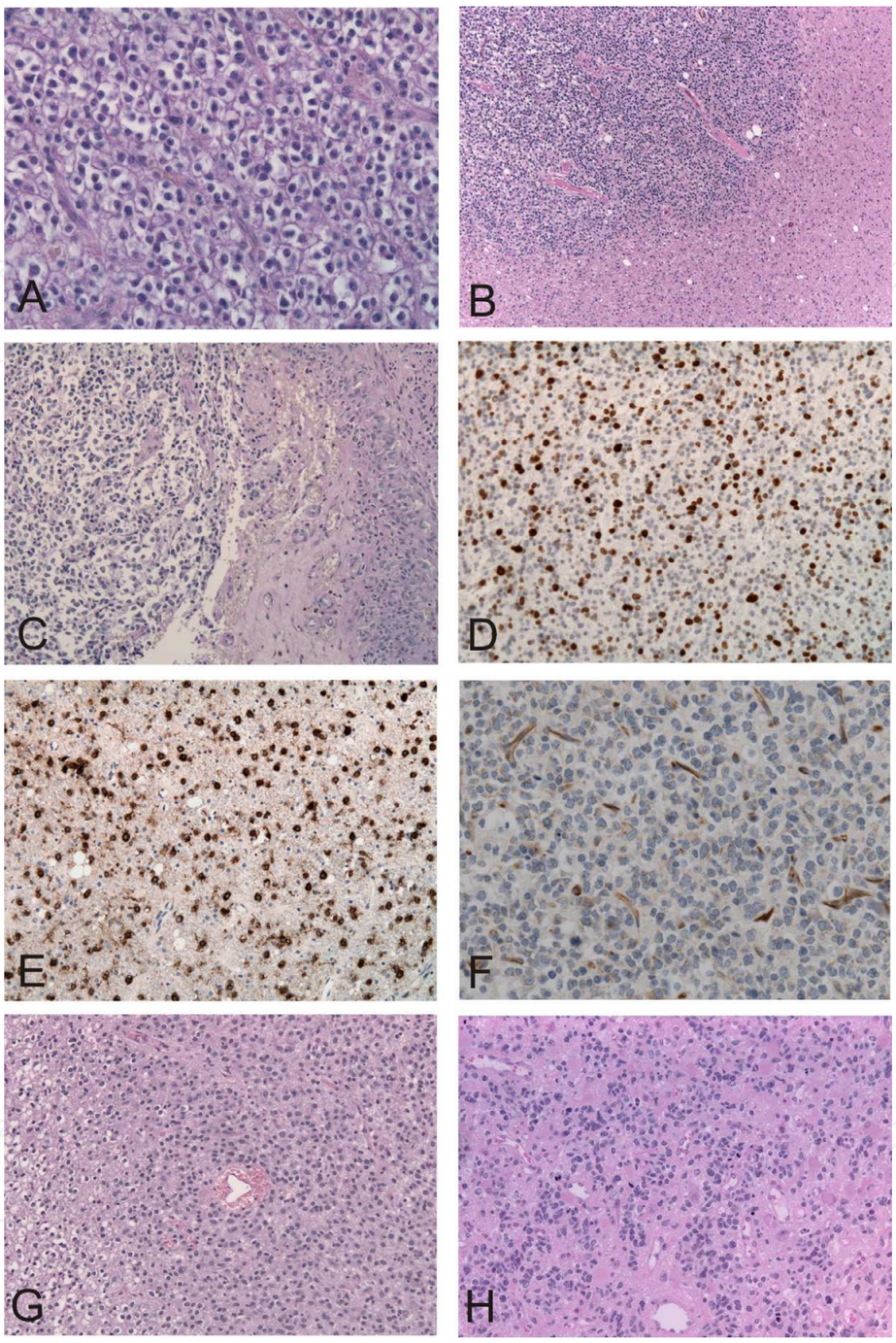

Fig. 4. **Oligodendrogliomas** show a typical honeycomb pattern (A). Tumor borders can be discrete infiltrative (B). Anaplastic oligodendroglioma with endothelial proliferations (C) and increased MIB-1 proliferation index (D). Oligodendroglial tumors typically exhibit a marked perinuclear MAP2 immunoreactivity (E) and show far less WT1 immunopositive cells (F) than astrocytomas. **Mixed oligodendroglioma-astrocytoma** can present either as true biphasic tumors (G) or as strongly intermixed (H) as in this anaplastic oligoastrocytoma with extensive mitotic activity.

present but not typically in the pseudopalisading forms of glioblastoma. The current WHO classification however explicitly allows presence of pseudopalisading necroses in anaplastic oligendrogliomas and thus weakens a sufficient discrimination to glioblastomas with oligodendroglial differentiation. Anaplastic oligodendrogliomas may contain smaller cells with pink cytoplasm and eccentric placed nuclei, so called minigemistocytes and areas with increased fibrillar background and plump process-bearing gliofibrillary oligoendrocytes. These eosionophilic cells are seen more often in grade III than grade II oligodendrogliomas. Finally some oligodendroglioma tumor cells may have sharp delineated borders resembling epitheloid differentiation. In the tumor edges severeal astrocytic cells might be present but unless clearly neoplastic in nature their presence does not warrant the diagnosis of mixed oligoastrocytoma. Focally parallel tumor cell growth may resemble polar spongioblastomas (Louis et al., 2007). Rare cases of oligodendrogliomas may show focally neuopil islands that have to be distinguished from neurocytomas. Tumor cells with signet-ring cell morphology have also been described in oligodendrogliomas (Kros et al., 1997).

5.3 Immunohistochemistry

There is no distinct single antibody availabe to discriminate reliably between oligodendroglial and astrocytic neoplasms. It is adviseable to use a panel of different antibodies for which expression patterns in these neoplasms has been extensively studied. In our institution we stain routinely gliomas for MIB1, GFAP, MAP2, WT1 and IDH1 R132H. Expression of GFAP is usually absent in tumor cytoplasm of oligodendroglia, however in our daily practice sometime there is ample overlapping of GFAP-positive fibrillary neuropil background. In addition minigemistocytes and gliofibrillar oligodendrocytes are usually positive for GFAP. MAP2 is constantly expressed in oligodendrogliomas, but also found in 92% of astrocytomas and glioblastomas (Blümcke et al., 2004). A perinuclear "capped" expression pattern is more typical for oligodendrogliomas, while in astrocytomas the elongated cell processes are also immunoreactive for MAP2. WT1 in oligodendrogliomas is usually restricted to single WT1-positive tumour cells or completely absent while WT1 is strongly expressed in 83-92% of high grade astrocytic lesions (Schittenhelm et al., 2009). Therefore, in our experience, expression of WT1 in more than 50% of tumor cells indicates either astrocytoma or oligoastrocytoma rather than oligodendroglioma. Nogo-A is found in 71% oligodendrogliomas and 24% glioblastomas but is absent in astrocytomas (Kuhlmann et al., 2008). While Olig2 immunoreactivity is slightly stronger in oligodendrogliomas is also constantly seen in other glial neoplasms (Ligon et al., 2004). Alpha internexin is found in 45-59% of oligodendrogliomas ans seems to be associated with an 1p19q codeletion (Ducray et al., 2011). Positive IDH1-R132H immunoreactivity is so frequent in oligodendroglial tumors (up to 91% in grade II and 94% in grade III lesions) that this marker is very useful to discriminate oligodendrogliomas from other brain tumors with oligodendroglial morphology (Capper et al., 2011). Diffuse immunoreactivity of p53 is uncommon in oligodendroglial tumors but when present indicates an intact chromosomal 1p arm (Hirose et al., 2010). Oligodendrogliomas with neurocytic differentiation may show synaptophysin-positive neuropil islands and rosettes but usually lack the NeuN nuclear immunoreactivity of neurocytomas. In addition presence of IDH1 or IDH2 mutation strongly favors diagnosis of oligodendroglioma over neurocytoma (Capper et al., 2011).

5.4 Electron microscopy

The short tumor cell processes contain microtubuli and ocassionally pericellular spiral laminations but usually lack the abundant intermediate filament of astrocytic tumor cells (Min et al., 1994). Electron microscopy is not used in regular routine practice as combined data from histology, immunistochemistry and molecular pathology is usually sufficient enough do diagnose an oligodendroglioma or mixed glioma.

6. Oligoastrocytoma

Criteria for mixed astrocytomas / oligodendrogliomas are weakly defined. Not surprisingly interobserver variaibility is great ranging from 9-80% as seen in a study on 155 tumors that were initially classified as oligoastrocytomas (Fuller et al., 2003). Macoscopically these tumors are similar to other diffuse grade II or grade III lesions. Histological diagnosis of oligoastrocytoma requires that both astrocytic and oligodendrogial neoplastic tumor cells are present in the same tumor. These may appear biphasic as two distinct tumor areas or more commonly as intermingled tumor. The minimal amount to which one tumor component has to be present is unfortunately not properly defined. Some authors are satisfied when one single high power field has either astrocytic or oligodendroglial tumor cells, other authors request at least a minimum of 50% neoplastic astrocytes. Separation of astrocytes and oligodendrocytes is not always possible. Every pathologist has seen tumor cells that have features of both lineages. It is important however to distinguish minigemistocytes and gliofibrillar oligodendrocytes in oligodendrogliomas from astrocytes, as they do not warrant the diagnosis of oligoastrocytoma. Single mitoses are compatible with a grade II oligoastrocytoma, however in our institution we have an relaxed approach, when mitoses are increased in a distinct oligodendroglial compartment only. Anaplastic oligoastrocytomas show increased nuclear atypia, elevated cellularity and abundant mitoses. Microvascular proliferations are frequent in grade III oligoastrocytomas. Discrimination of anaplastic oligoastrocytoma from glioblastomas with oligodendroglial differentiation is especially difficult, as WHO criteria allows pseudopalisading necroses to be present in oligoastrocytic tumors. In our institution decision is based on whether necroses are present in astrocytic tumor parts indicating a glioblastoma or is limited to oligodendroglial tumor parts indicating anaplastic oligoastrocytoma. Like histology, immunhistochemistry results are very mixed and represent the immunophenotype of neoplastic astrocytes or oligodendrogytes as discussed in their sections. Grade II tumors have a MIB-1 proliferation index usually less than 6% (Deckert et al., 1989).

7. Molecular biology

Because of their favourable prognostic value 1p19q codeletion, MGMT promoter methylation and isocitrate dehydrogenase mutations are considered important clinical biomarkers for diffuse gliomas. In addition p53 is useful for diagnostic purposes. These markers are requested with increasing frequency and are discussed in detail below. Even when the diagnosis of a specific glioma type is readily apparent in histological stains, pathologist need to take care, that sufficient tissue is available for future molecular analysis.

7.1 Tumor protein 53 mutations

Since Tp53 mutations are broadly distributed, exons 5-8 need to be screened by single-strand conformational polymorphism analysis followed by direct sanger sequencing of samples exhibiting mobility shifts. In unremarkable cases, sequencing analysis is usually extended to exons 4, 9 and 10. Because of these efforts, Tp53 molecular analysis is not part of routine diagnosis unlike p53 immunostaining. A Tp53 mutation in diffuse astrocytomas grade II WHO is observed in 52-60% of the tumors, while Tp53 mutations are present in 35-44% of oligoastrocytomas and in 10% oligodendrogliomas (Okamoto et al., 2004, Kim et al., 2010). Especially astrocytomas with gemistocytic tumor cell morphology may contain Tp53 mutations in up to 82% of tumors (Watanabe et al., 1998). Since Tp53 mutations are acquired early, their frequency does not increase much further during tumor progression (Watanabe 1997). In pediatric glioblastomas, Tp53 mutations were found in 60% of tumors examined (Srivastava et al., 2010). Grade II WHO diffuse astrocytomas may show in 49% a combined TP53 mutation and IDH1 or IDH2 mutation (Kim et al., 2010). A Tp53 mutation without associated IDH1/2 mutation is rare (3%), thus indicating that IDH mutations occur at an earlier stage of tumorgenesis.

7.2 Isocitrate dehydrogenase mutations

The NADP-dependent enzymes IDH1 and IDH2 catalyze the conversion from isocitrate in alpha-ketoglutarate. Mutations of the catalytic center in gliomas result in accumulation of the oncogenic metabolite D-2-hydroxyglutarate (Dang et al., 2009). It is thought that the reduced NADPH levels in IDH mutated gliomas could sensitize tumors to radiation and chemotherapy (Bleeker et al., 2010). The frequency of IDH mutations is high in diffuse astrocytomas, anaplastic astrocytomas and secondary glioblastomas evolving from these precursor lesions, while presence of IDH mutations is seen in only 3-7% primary glioblastomas (Hartmann et al., 2009). The vast majority of IDH1 mutations are point mutations leading to a distinct amino acid substitution on codon 132 (Arg132His) for which an specific antibody has been developed (Capper et al., 2010). The other amino exchange mutations can be detected either by direct sanger sequencing or restriction-endonuclease based PCR (Meyer et al., 2010).

IDH1 mutations are found in 59-88% diffuse astrocytomas, 50-78% anaplastic astrocytomas and 50-88% secondary glioblastomas, IDH2 mutations are present in 1-7% diffuse astrocytomas, 1-4% anaplastic astrocytomas and seem to be absent in secondary glioblastomas (Bourne et al., 2010). The rate of IDH2 mutations in oligodendrogliomas is higher as in astrocytomas (4-8% in oligodendrogliomas grade II and grade III, 1-6% of oligoastrocytomas grade II and grade III) but still lower than number of IDH1 mutations (68-82% oligoadendrogliomas grade II, 49-75% anaplastic oligodendrogliomas grade III, 50-100% oligoastrocytomas, 63-100% anaplastic oligoastrocytomas grade III) (Bourne et al., 2010). In addition the IDH1 R132C mutation is strongly associated with an astrocytoma phenotype (Hartmann et al., 2009).

7.3 MGMT methylation status

The DNA repair enzyme O-methylguanine-DNA methyltransferase (MGMT) removes alkyl groups from the O^6 position resulting in an increased tumor resistance to alkylating agents therapy. Methylation of the MGMT promotor region results in decreased MGMT activity which in turn increases glioblastoma tumor cell sensivity to therapy with temozolomide and

is therefore a predictive molecular marker (Hegi et al., 2005). MGMT expression in tumor cells of astrocytomas and glioblastomas can be determined by nuclear immunoreactivity of tumor cells (Capper et al., 2008). Together with other sophisticated methods such as realtime RT-PCR or methylation-specific pyrosequencing, they lack a valid definition for clinically relevant cut-off values (von Deimling et al., 2010). Usually MGMT is determined in formalin-fixated paraffin-embedded specimens through methylation-specific PCR, yet reliability and reproducibility are still limited in the current standard method (Preusser, et al., 2008b, Elezi et al., 2008). Not only is MGMT protein expression within tumors heterogenous, but also highly dependent on the method used and changes during therapy (Jung et al., 2010, Preusser et al., 2008a, Janzer et al., 2008). Thus reports on MGMT methylation range from 93% in frozen tissue sections in diffuse astrocytoma grade II (Everhard et al., 2006) to 30-35% in glioblastoma paraffin blocks (Tabatabai et al., 2010). In pediatric glioblastomas approximately half of the tumors are methylated (Srivastava et al., 2010). Despite these shortcomings MGMT analysis is essential for almost all clinical studies and one of the most requested molecular analysis in neuropathology routine practice.

7.4 Loss of 1p/19q

A loss of heterozygosity is usually assessed though use of microsatellite marker PCR. This method requires corresponding blood samples to determine allele status. Therefore use of fluorescent in situ hybridisation is preferred by some laboratories but carries the risk of misdiagnosing cases with only partial loss. This risk can be covered by additional PCR that contains several loci along the chromosomal arms (Riemenschneider et al. 2010).
Loss of heterozygosity in 1p and 19q are found in 78% of oligodendrogliomas grade II, 44% of oligoastrocytomas and 17% of diffuse astrocytomas grade II WHO. Therefore 1p19q codeletion is strongly associated with a oligodendroglial tumor morphology and often used as a diagnostic marker. In addition in oligodendrogliomas up to 73% of codeleted tumors also show either additional IDH1 or IDH2 mutations (Kim et al., 2010). Not surprisingly journal reviewers often require 1p19q deletions in oligodendrogliomas for sample homogeneity.

8. Prognostic implications

8.1 Immunohistochemistry

Generally, tumor grade increases with age and younger age of onset is one of the strongest predictive factor of prolonged survival (Kita et al., 2009) and thus heavily influences all other markers found. Despite this fact, many publications do not take patients age into account when analyzing biomarkers on patient survival. In astrocytomas, MIB-1 proliferation values above 5% are considered to be associated with a shorter survival (Jaros et al., 1992). Because of study population heterogeneity, predictive data on Tp53 mutations are limited. Some authors see p53 immunoreactivity to be associated with a shorter survival or shorter time to malignant progression (Jaros et al., 1992, Ständer et al., 2004). It is noteworthy, that not all p53 immunoreactive tumors contain mutations in the TP53 gene (Kösel et al., 2001). Further contrasting to immunohistochemistry data, a molecular study on 159 grade II astrocytomas and oligoastrocytomas did not found an influence on overall survival, but reported a significant shorter progression-free survival (Peraud et al., 2002). In glioblastomas p53 mutation status does not correlate with patients outome (Weller et al., 2009). Thus, p53 is only useful as a diagnostic marker but not prognostic.

8.2 Molecular biology

Patients with IDH1/2 mutations in anaplastic astrocytomas and glioblastomas are usually younger than those lacking a IDH mutation (Nobusawa et al., 2009, Hartmann et al., 2009). In addition IDH1 mutations are a prognostic marker of favorable outcome in grade III and IV tumors (Yan et al., 2009, Nobusawa et al., 2009, Sanson et al., 2009). There is even a study demonstrating that IDH1-positive glioblastomas WHO grade IV have a better prognosis than IDH1-negative anaplastic astrocytomas WHO grade III (Hartmann et al., 2010). In contrast patients with IDH1 mutations in diffuse astrocytomas grade II WHO are older (Kim et al., 2010) or show at least a similar age distribution (Balss et al., 2008). The prognostic role of IDH1 in grade II diffuse astrocytomas is still to be determined. Sanson and colleagues found IDH1 to be an independent prognostic factor for longer survival in 100 samples (Sanson et al., 2009), while Kim et al. in 174 grade II tumors did not observe a more favorable outcome (Kim et al., 2010). So far IDH tumor status has not been incorporated into any current therapeutic trials but is likely to be included in the future.

Analysis of low-grade astrocytomas did not found any association with MGMT promoter methylation and overall survival (Komine et al., 2003). In anaplastic gliomas, MGMT promoter hypermethylation is associated with longer progression free survival (Wick et al., 2009). In glioblastomas, MGMT methylation status in addition as a marker of prolonged survival is a predictor to therapy response (Hegi et al., 2005). In oligodendroglial tumors there is a strong association between MGMT promoter methylation and 1p19q codeletion the latter also contributing to the improved survival of patients with MGMT methylation (Levin et al., 2006; Kesari et al., 2009). MGMT alone is useful as a prognostic marker but not useful to predict outcome of adjuvant treatment in oligodendrogliomas (van den Bent et al., 2009).

In oligodendrogliomas 1p19q codeletion is associated with improved survival (Jeon et al., 2007, McLendon et al., 2005). Presence of oligodendroglial histopathology and 1p19q deletetion shows a better overall survival for anaplastic oligodendrogliomas treated with radiation and PCV chemotherapeutic regimen (Giannini et al., 2008). The same study also demonstrated that 1p19q deletion alone is associated with a longer progression-free survival but that this effect is independent of initial treatment of oligodendrogliomas and mixed oligoastrocytomas (van den Bent et al., 2006). There is an inverse correlation with p53 mutation and codeletion of chromosomal arms 1p and 19q in oligodendrogliomas implicating that oligodendrogliomas harbouring a Tp53 mutation have a reduced overall survival (Jeon et al., 2006, McLendon et al., 2005).

In 9% of astrocytomas grade II WHO no common genetic alterations are detected (Kim et al., 2010). In small biopsy specimen these tumors may enter the differential diagnosis of pilocytic astrocytoma. The latter often show BRAF abnormalities, wich drive MAPK pathway activation (Cin et al., 2011) but are absent in diffuse astrocytoma (Korshunov et al., 2009). Another possible differential diagnosis to low-grade diffuse astrocytoma is ganglioglioma and pleomorphic xanthoastrocytoma which in addition to their unique histological properties also exhibit BRAF V600E mutations, at present not known to be in diffuse astrocytomas (Schindler et al., 2011).

9. Conclusion

Histological classification of diffuse gliomas based on the WHO grading scheme is a prerequisite to optimal patient treatment decisions. Clinicians need to be aware that

diffuse gliomas form a histological continuum and that the four-tiered scores introduces a somewhat artificial separation. Tumors on the edge between grade II and III lesions behave different than tumors showing beginning endothelial proliferations indicating close progression to grade IV. A panel of different antibodies is very helpful to secure the diagnosis and avoids potential differential diagnosis pitfalls. Immunohistochemistry has also shown that several antibodies show divergent expression patterns. Researchers therefore should strive to clearly delineate between astrocytomas, oligodendrogliomas and oligoastrocytomas, when examining new biomarkers. Primary and secondary glioblastomas are another example of "convergent evolution showing a similar phenotype of genotypically different tumor cells" (Basanta et al., 2011). The distinction of primary and secondary glioblastomas does not immediately influence management decisions, but because of their different genetic profile, it is expected that they may also differ in response to experimental therapies. Recent years have seen a progress in supplementing histological diagnosis of diffuse gliomas with an increasing spectrum of molecular markers. The utility of MGMT and 1p/19q in predicting response to therapy has led to their inclusion in current clinical trials. Implementation of these markers into routine diagnostic setting is expected after further successful results. Especially in oligoastrocytomas they complement histological results and provide a more objective classification. However clear cut-off levels for each assay is needed to guarantee interlaboratory compatibility. Histological control of the tissue used for molecular neuroonclogy through (neuro)pathologists is indispensable to avoid false-negative test results. Determining IDH1 status in diffuse gliomas is of diagnostic and clinical relevance. Not only indicates equal presence of IDH mutations a likely common origin of astrocytomas and oligodendrogliomas, but also the strong prognostic role in high-grade gliomas is likely to be included in future revisions of the current WHO classification.

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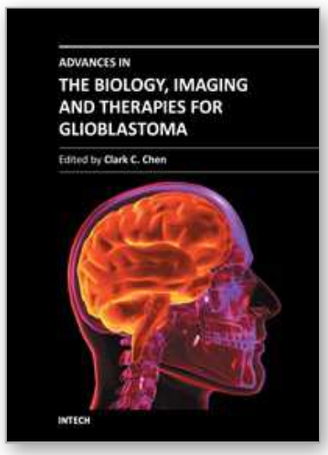

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