1.2 Adult-Type Diffuse Gliomas

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In the WHO CNS5, adult-type diffuse gliomas include a group of genetically defined tumors. The classification of this group of tumors is simplified and includes three tumor types: astrocytoma, IDH-mutant; oligodendroglioma, IDH-mutant and 1p/19q-codeleted; and glioblastoma, IDH-wildtype.

- 1.2.1 Astrocytoma, IDH-mutant
- 1.2.2 Oligodendroglioma, IDH-mutant and 1p/19q-codeleted
- 1.2.3 Glioblastoma, IDH-wildtype

1.2.1 Astrocytoma, IDH-mutant

Definition

“A diffusely infiltrating IDH1- or IDH2-mutant glioma with frequent ATRX and/or TP53 mutation and absence of 1p/19q codeletion.” (WHO CNS5)

Grade

- CNS WHO grade 2, 3, or 4.

Subtype(s)

- Astrocytoma, IDH-mutant, CNS WHO grade 2.
- Astrocytoma, IDH-mutant, CNS WHO grade 3.
- Astrocytoma, IDH-mutant, CNS WHO grade 4.

Age and Gender Distribution

- Median age at presentation is 38 years for grade 2 and grade 3 tumors.
- Grade 4 tumors occur in slightly older patients.
- Reported male:female ratio is 1.3:1.

Localization

- Predominantly cerebral hemispheric tumors.
- Most common location is the frontal lobe.
- Rarely occurs in infratentorial region and spinal cord.

Macroscopic Features

- Diffusely infiltrative tumor invading normal anatomical structures with blurring of the gray–white junction.
- Microcyst or macrocyst formation, sometimes filled with gelatinous material, may be observed.
- Tumor is most often soft to firm in consistency, and calcification is rare.
- Grade 4 tumors may have yellowish necrotic and hemorrhagic areas.

Histopathological Features

Astrocytoma, IDH-mutant, CNS WHO Grade 2

- Low-grade diffusely infiltrating astrocytic glioma that is mild to moderately cellular.
- Composed of well-differentiated fibrillary, protoplasmic or gemistocytic astrocytes.
- Lacks features of anaplasia.
- Nil or low mitosis.
- Stroma is fibrillary with or without a microcystic change.
- Absence of microvascular proliferation and necrosis.

Astrocytoma, IDH-mutant, CNS WHO Grade 3

- Increased cell density with features of anaplasia.
- Significant mitosis.
- Absence of microvascular proliferation and necrosis.

Astrocytoma, IDH-mutant, CNS WHO Grade 4

A diffusely infiltrating IDH-mutant astrocytoma WITH

- Microvascular proliferation and/or necrosis
- Or
- CDKN2A/2B homozygous deletion.
- Or
- Any combination of these features.

Immunophenotype

- Diffuse OLIG2 positivity with the majority expressing glial fibrillary acidic protein (GFAP).
- IDH1 p.R132H mutation can be detected by immunohistochemistry (IHC) with anti-IDH1 p.R132H antibody. The tumor cells exhibit cytoplasmic positivity for IDH1 p.R132H.
- Characterized by loss of alpha thalassemia mental retardation X-linked syndrome (ATRX) expression in the nuclei of the tumor cells, which is a surrogate for ATRX mutation.
- P53 expression is noted in the majority of astrocytomas, IDH-mutant, but it is neither a sensitive nor a specific marker for the diagnosis of astrocytoma, in view of false-positive and false-negative results.
- While grade 2 tumors have a low Ki-67 proliferation index of less than 4%, grade 3 tumors have a Ki-67 proliferation index between 4 and 10%.
Diagnostic Molecular Pathology

**IDH1 and 2 Mutations**
- These tumors are defined by IDH1 or IDH2 mutations.
- IDH1 mutation occurs at codon 132 and IDH2 mutation occurs at codon 172.
- IDH1 p.R132H (arginine to histidine) mutation is the most common, accounting for >90%.
- Other rare mutations at this position include R132C (arginine to cysteine), R132S (serine), R132L (leucine), R132G (glycine), and R132V (valine). All these mutations are missense and heterozygous mutations.
- Five other point mutations have been identified in IDH2, where arginine at 172 (R172) is replaced with glycine (R172G), methionine (R172M), lysine (R172K), serine (R172S), and tyrosine (R172Y).
- IHC for IDH1 p. R132H is very sensitive and specific for the IDH1 p.R132H mutation.
- While IHC serves as a surrogate for the IDH1 p.R132H mutation, the other uncommon IDH1 and IDH2 mutations are detected by DNA-sequencing methods.

**ATRX Mutation**
- Inactivating ATRX mutation is common.
- This usually co-occurs with TP53 mutation.
- ATRX mutation results in loss of ATRX protein expression.
- ATRX mutation is mutually exclusive with 1p/19q codeletion.
- Loss of ATRX is also seen in H3-altered diffuse gliomas and therefore is not a surrogate for IDH mutation exclusively.

**TP53 Mutation**
- TP53 mutation is one of the most common mutations in adult-type diffuse gliomas, particularly astrocytomas, IDH-mutant.
- A strong, diffuse p53 immunostaining along with ATRX loss of expression supports the diagnosis of astrocytoma, IDH-mutant.

**CDKN2A and/or CDKN2B Homozygous Deletion**
- Associated with poor prognosis in patients with astrocytoma, IDH-mutant irrespective of histological grade.
- Astrocytoma, IDH-mutant with CDKN2A and/or CDKN2B homozygous deletion corresponds to CNS WHO grade 4.
- Most often detected by the fluorescent in situ hybridization (FISH) technique.

**Prognosis**
- Patients with grade 2 tumors have a median overall survival (OS) of >10 years, while those with grade 3 tumors have a typical median OS in the range of 5 to 10 years.
- Grade 4 tumors are associated with a poorer outcome.

**Essential and Desirable Diagnostic Criteria**
Refer Table 1.2.
Fig. 1.2.1 Astrocytoma, IDH-mutant, grades 2 and 3.
(a, b) Gross specimen of a diffusely infiltrating astrocytoma, IDH-mutant, grade 2, in the left cerebral hemisphere, where histology shows neoplastic astrocytes dispersed over a fibrillated microcystic stroma and exhibiting mild nuclear atypia. (c) Astrocytoma, IDH-mutant grade 3, exhibiting significant nuclear atypia and increased mitosis. Tumor cells are (d) immunopositive for IDH1 p.R132H, and (e) show loss of ATRX expression and (f) diffuse p53 immunoreactivity.
Fig. 1.2.1 Astrocytoma, IDH-mutant, CNS WHO grade 4.

(g) High-grade astrocytoma showing microvascular proliferation and necrosis. (h) Tumor cells are diffusely immunopositive for IDH1 p.R132H. (i) In an IDH1 p.R132H immunonegative astrocytoma, DNA sequencing shows uncommon IDH1 p.R132G mutation compared to an IDH-wildtype control. (j) In a grade 3 astrocytoma, IDH-mutant, FISH shows two chromosome 9 centromere signals (green) and no 9p signal (orange), suggesting CDKN2A/2B homozygous deletion, thus conforming to astrocytoma, IDH-mutant, CNS WHO grade 4.
1.2.2 Oligodendroglioma, IDH-mutant and 1p/19q-codeleted

Definition

“A diffusely infiltrating glioma with IDH1 or IDH2 mutation and codeletion of chromosome arms 1p and 19q.” (WHO CNS5)

Grade

• CNS WHO grade 2 or 3.

Subtype(s)

• Oligodendroglioma, IDH-mutant and 1p/19q-codeleted, CNS WHO grade 2.
• Oligodendroglioma, IDH-mutant and 1p/19q-codeleted, CNS WHO grade 3.

Age and Gender Distribution

• Occurs mainly in adults, rare in children.
• Median age of grade 2 tumors is 41 years and of grade 3 tumors is 47 years.
• Slight male preponderance.

Localization

• Commonly localized to the cerebral hemispheres.
• Most frequent location is the frontal lobe, followed by the temporal and other lobes.
• Rarely involves the posterior fossa, basal ganglia, and brainstem.
• Occasionally, a gliomatosis cerebri-like spread or a diffuse leptomeningeal spread is seen.

Macroscopic Features

• Soft, gray-tan tumor, usually seen to arise in the white matter and infiltrate the gray matter resulting in blurring of the gray–white junction.
• Frequent calcification gives a gritty feeling on cut section of the tumor.
• Cystic degeneration, mucoid change, and hemorrhage can be seen.
• Local invasion into leptomeninges may be seen occasionally.

Microscopic Features

• Composed of tumor cells arranged in lobules separated by thin-walled, branching capillaries (chicken-wire vasculature).
• Cells have round uniform nuclei and a perinuclear halo, which gives a “fried-egg” appearance.
• Perinuclear halo is seen as a result of fixation artifact; hence not seen on the frozen sections.
• Microcalcification, mineralized blood vessels, hemorrhage, and microcystic change are frequently noted.
• Tumors may also have varying proportions of minigemistocytes, glio fibrillary oligodendrocytes, granular cells, signet ring cells, and mucocytes. These are more often seen in CNS WHO grade 3 tumors.
• Some tumors can be composed of cells with fibrillary astrocyte or gemistocyte-like morphology.
• Other characteristic features include perineuronal satellitosis and subpial carpeting.
• In grade 2 tumors, nuclear atypia and mitotic activity are minimal. Microvascular proliferation or necrosis is absent.
• Mitosis is prominent in grade 3 tumors, which may have microvascular proliferation or necrosis.

Immunophenotype

• Immunopositive for OLIG2, S100, MAP2, and other markers, but there is no specific immunohistochemical marker for the diagnosis since these markers are also positive in astrocytomas.
• GFAP labels minigemistocytes and glio fibrillary oligodendrocytes, whereas the classic oligodendroglioma cells exhibit minimal or negative expression.
• The underlying neuropil is usually positive for synaptophysin and does not indicate a neurocytic differentiation in the tumor.
• IDH1 p.R132H is uniformly positive in the majority of oligodendrogliomas.
• A proportion of oligodendrogliomas (<10%) that harbor rare IDH mutations are negative on IHC for IDH1 p.R132H.
• All tumors show retained nuclear expression of ATRX and are usually immunonegative for p53.
• Ki-67 proliferation index is less than 5% in grade 2 tumors and generally more than 10% in grade 3 tumors.

Diagnostic Molecular Pathology

• Characterized by IDH mutation and 1p/19q codeletion and hence the diagnosis is established only on demonstrating these two genetic alterations.
• IDH mutation is detected by IHC for IDH1 p.R132H, and when immunonegative, DNA sequencing of IDH1 or IDH2
genes is carried out to detect the other uncommon $IDH1$ or $IDH2$ mutations.

- Most common technique to test for 1p and 19q codeletion is FISH.
- Other techniques include chromogenic in situ hybridization, polymerase chain reaction (PCR) based loss of heterozygosity (LOH) studies, and other molecular genetic tests.
- A complete loss of whole chromosomal arms 1p and 19q is the diagnostic alteration.
- Lack $ATRX$ mutation and therefore show retained $ATRX$ expression.
- The majority of tumors harbor $TERT$ promoter mutations, whereas $TP53$ mutations are rare.
- A small proportion of grade 3 tumors harbor $CDKN2A/2B$ homozygous deletion, which is not seen in grade 2 tumors.

### Prognosis

- Associated with a favorable treatment response with a median survival of more than 10 years.
- Younger patients, presentation with seizures, tumor location in the frontal lobe, gross total tumor resection, and a high postoperative Karnofsky score have a better prognosis.
- Higher mitotic count and proliferation index are associated with shorter survival times.
- Presence of polysomy 1q and/or 19p or homozygous deletion of $CDKN2A/2B$ is associated with poor prognosis.

### Essential and Desirable Diagnostic Criteria

Refer Table 1.2.
Fig. 1.2.2 Oligodendroglioma, IDH-mutant and 1p/19q-codeleted, CNS WHO grade 2.
(a) The tumor shows neoplastic oligodendrocytes exhibiting mild nuclear atypia with thin-walled branching vessels in the background. (b) The tumor cells are immunopositive for IDH1 p.R132H, (c) show retained ATRX expression, and (d) negative for p53. (e) The FISH image shows one or nil orange (1p36) and two green (1q25-reference) signals in most interphase nuclei of tumor cells, depicting loss of 1p relative to 1q. (f) The FISH image shows one or nil orange (19q13) and two green (19p13-reference) signals in most interphase nuclei of tumor cells, depicting loss of 19q relative to 19p.
Fig. 1.2.2 Oligodendroglioma, IDH-mutant and 1p/19q-codeleted, CNS WHO grade 3.

(g) The tumor is highly cellular with increased mitosis and microvascular proliferation and (h) focus of necrosis. (i) Neoplastic oligodendrocytes are admixed with minigemistocytes. (j) The tumor is diffusely immunopositive for IDH1 p.R132H.
1.2.3 Glioblastoma, IDH-wildtype

**Definition**

“A diffuse astrocytic glioma that is IDH-wildtype and H3-wildtype and has one or more of the following histological or genetic features: microvascular proliferation, necrosis, TERT promoter mutation, EGFR gene amplification, +7/-10 chromosome copy-number changes.” (WHO CNS5)

**Grade**
- CNS WHO grade 4.

**Subtype(s)**
- Giant cell glioblastoma (GBM) accounts for <1% of GBM.
- Gliosarcoma accounts for 2% of GBM.
- Epithelioid GBM—rare subtype.

**Age and Gender Distribution**
- GBMs preferentially affect older adults.
- Peak incidence in patients between 55 and 85 years.
- Giant cell GBMs affect patients at a younger age (mean 51 years).
- Epithelioid GBMs usually occur in children and young adults.
- Men are more commonly affected than women.

**Localization**
- GBMs frequently involve the cerebral hemispheres with widespread involvement of multiple anatomical areas of the brain.
- Unique feature is the spread of the tumor across myelinated structures, corpus callosum, and commissures into the adjacent cortex and contralateral hemisphere (butterfly glioma).
- May also involve the basal ganglia, thalamus, and brainstem.
- Giant cell GBMs are circumscribed neoplasms, subcortically located, and commonly involve temporal and parietal lobes.
- Gliosarcomas are preferentially located in the temporal lobe followed by the frontal, parietal, and occipital lobes.
- Epithelioid GBM is most often a cerebral hemispheric tumor.

**Macroscopic Features**
- Highly variegated appearance.
- Areas of softening (necrosis) may be seen on the cut surface.
- Extensive hemorrhages and macroscopic cysts containing liquefied necrotic tissue can be seen.
- Giant cell GBM is well-circumscribed, with firm cut surface, and may mimic metastasis or meningioma (when dura based).

- In view of the rich collagenous stroma, gliosarcomas are usually well-circumscribed, firm masses on gross examination, often resembling a meningioma (when superficially located) or a metastatic lesion.

**Histopathological Features**
- A highly cellular diffusely infiltrating glioma, composed of pleomorphic and poorly differentiated astrocytic cells.
- Other cell types that may form minor or major proportions of the tumor are spindled, plump, round to polygonal cells with lipidized cytoplasm, gemistocytic astrocytes, bizarre multinucleated giant cells, and epithelioid and granular astrocytic cells.
- Tumor cells exhibit significant nuclear atypia and brisk mitosis.
- Cells are dispersed over a variably fibrillated stroma with or without a microcystic change.
- Prominent microvascular proliferation and/or confluent/palisading necrosis are essential for diagnosis.
- Microvascular proliferation typically appears as glomeruloid tufts of multilayered endothelial cells that are mitotically active along with smooth muscle cells or pericytes.
- Other common accompanying histologic features are sclerosed–thrombosed blood vessels with fresh and/or old bleed and tumor neovascularization (sprouts of newly formed vessels).
- Invasive nature of the tumor can be seen microscopically as secondary structures of Scherer—perineuronal/perivascular satellitosis and subpial/subependymal spread.

**Giant Cell Glioblastoma**
- Characterized by bizarre, multinucleated giant astrocytes, in a background of small fusiform or undifferentiated cells.
- This histology is also noted in “glioblastoma arising in the setting of constitutional mismatch repair deficiency syndrome (CMMRD).”
- Typical perivascular arrangement of tumor cells may be seen.
- Mitosis is brisk with atypical forms.
- Tumor-infiltrating lymphocytes may be present.

**Gliosarcoma**
- Biphasic tissue pattern with glial and sarcomatous components.
- Glial portion usually shows features of a GBM.
- Most commonly, the glial component has an astrocytic differentiation, with less common oligodendroglial, and ependymal differentiation.
- Sarcomatous component is composed of spindle cells in fascicles resembling fibrosarcoma or may show differentiation towards cartilage, bone, smooth/striated muscle, or lipomatous lineage.
- While the sarcomatous components are reticulin rich, the glial components are within reticulin-poor islands.
**Epithelioid Glioblastoma**
- Predominant population of monomorphic epithelioid cells with distinct cell membrane, abundant eosinophilic cytoplasm, and eccentric or central nuclei.
- Nuclear chromatin is vesicular with prominent nucleolus.
- Paucity of cytoplasmic processes and scant intervening neuropil.
- Highly proliferative with brisk mitotic activity.
- Focal rhabdoid morphology is often noted.
- Rare: lipidization, giant cell change, cytoplasmic vacuoles, and desmoplasia.
- Rosenthal fibers, eosinophilic granular bodies, are absent.
- Pleomorphic xanthoastrocytoma-like morphology may be seen at foci.
- Necrosis often zonal in nature.
- Palisading necrosis and microvascular proliferation are typically not evident, unlike in classic GBMs.

**Glioblastoma with Gemistocytic Astrocytes**
- Cells with abundant glassy cytoplasm with nucleus pushed to periphery.
- Perivascular lymphocytes are commonly seen.
- Gemistocytes may be present in IDH-mutant astrocytomas or IDH-wildtype GBMs.

**Glioblastoma with Epithelial Metaplasia**
- Squamous or adenomatous differentiation.
- Some tumors have abundant glandular/ribbon-like epithelial structures, referred to as adenoid GBMs or GBMs with epithelial metaplasia.
- More common in gliosarcomas than in classic GBMs.

**Glioblastoma with Oligodendrocyte-like Cells**
- Oligodendrocyte-like clear cells may include chicken-wire-like capillary network and microcalcifications.
- This pattern is seen in FGFR3::TACC3 fusion-positive GBM.

**Glioblastoma with Small Cells (Small Cell Glioblastoma)**
- Characterized by monomorphic small cells with a high nuclear:cytoplasmic ratio and scant cytoplasm, sometimes mimicking a dedifferentiated oligodendroglioma.

**Glioblastoma with Granular Cells (Granular Cell Glioblastoma)**
- Large cells with abundant eosinophilic to granular, periodic acid–Schiff (PAS) positive cytoplasm, sometimes resembling macrophages.
- GBMs comprising a significant proportion of such granular cells are known to have an aggressive behavior.

**Glioblastoma with Lipidized Cells (Heavily Lipidized Glioblastoma)**
- Lipidized cells are those that contain large vacuolated foamy cytoplasm.
- High-grade gliomas with large areas of lipidized cells are designated as “malignant gliomas with heavily lipidized tumor cells.”

**Glioblastoma with Primitive Neuronal Component**
- Characteristic biphasic pattern with a GBM component and demarcated nodule/s of highly cellular primitive neuronal component, composed of cells with a high nuclear-to-cytoplasmic ratio, brisk mitosis, and apoptosis.
- The primitive neuronal component is synaptophysin positive, whereas the glial component is positive for GFAP.
- The tumor may arise de novo or follow a primary GBM. Earlier termed as “GBM with PNET component.”
- MYC or MYCN amplification has been identified in the primitive neuronal component of the tumor.
- Diagnosis of this tumor is critical as they disseminate through the cerebrospinal fluid.
- Primitive neuronal component may also be seen in IDH-mutant high-grade astrocytic glioma, H3G34-mutant diffuse hemispheric glioma, and H3K27M-mutant diffuse midline glioma.

**Immunophenotype**
- Retained ATRX expression.
- Diffuse p53 immunopositivity seen in 25 to 30% of tumors, frequent in giant cell GBMs (>80%).
- GFAP expression is variable, strong in gemistocytes, whereas negative in primitive cellular components including small cells.
- S100 and OLIG2 are commonly positive.
- Adenoid GBMs retain glial immunophenotype, whereas GBMs with epithelial metaplasia show immunopositivity with epithelial markers only.
- Sarcomatous components of gliosarcomas are vimentin immunopositive and lack GFAP expression.
- Stem cell markers such as CD133, CD44, SOX2, OCT4, and nestin may be positive in tumor cells.
- Epithelioid GBM:
  - Variable patchy staining for GFAP, OLIG2, CK (AE1/AE3), EMA, p53, and synaptophysin.
  - About 50% cases are immunopositive for BRAF p.V600E.
  - IN1 shows uniform retained expression in tumor cells, thus excluding AT/RT.
  - HMB45 is negative excluding a melanoma.
- In pediatric patients with multinucleate tumor giant cells, workup for defect in mismatch repair genes is recommended.
**Diagnostic Molecular Pathology**

- Lacks IDH1(R132), IDH2(R172), H3 p.K28(K27) and H3 p.G35(G34) mutations.
- Absence of immunopositivity for IDH1 p.R132H is sufficient in patients aged ≥55 years for the diagnosis of IDH-wildtype GBM provided the tumor is not located in midline and there is no preexisting lower-grade glioma.
- In patients <55 years or with a history of preexisting lower-grade glioma and/or tumors showing loss of nuclear ATRX expression and negative for IDH1 p.R132H, DNA sequencing for other IDH1 and IDH2 mutations is recommended.
- Diagnostic molecular alterations include TERT promoter mutations, EGFR gene amplification, and +7/−10 genotype: presence of any one of these molecular alterations is diagnostic of IDH-wildtype GBM even in the absence of microvascular proliferation and/or necrosis.
- DNA methylation profiling may be useful in the cases without diagnostic histopathological and molecular alterations.
- BRAF p.V600E mutation is seen in about 50% of epithelioid GBM and in 35% of adult-type IDH-wildtype GBM.
- TP53 mutations is seen in 25% of all IDH-wildtype GBMs and >80% of giant cell GBMs.
- EGFR amplification is most common in small cell GBM.
- MYC or MYCN amplification is noted in GBM with primitive neuronal components.
- Small cell GBMs frequently have EGFR amplifications (70%) and chromosomal 10 losses (>95%), with the absence of IDH mutations and 1p/19q codeletion.
- O6-methylguanine-DNA methyltransferase (MGMT) gene promoter methylation:
  - MGMT promoter methylation is present in 40 to 50% of IDH-wildtype GBMs.
  - Both a prognostic and a predictive marker.
  - Predictive of benefit from alkylating agent/s therapy (temozolomide), particularly in older adults with GBM
  - Useful in the recurrent setting.
  - Frequently associated with pseudoprogression.

- GBM gene expression:
  - Can differentiate IDH-wildtype GBMs from other gliomas.
  - Gene expression classifier has identified three subtypes: proneural, classic, and mesenchymal.
- Three molecular subclasses of epithelioid GBM have been identified:
  - Conventional IDH-wildtype GBM-like.
  - Pleomorphic xanthoastrocytoma-like (with BRAF p.V600E mutations and homozygous CDKN2A deletions).
  - RTK1-type pediatric high-grade glioma-like (with PDGFRA amplification).

**Prognosis**

- Younger patients (<50 years of age) have a better prognosis.
- The prognostic role of EGFR amplification and PTEN mutation is debatable.
- MGMT promoter methylated tumors respond better to chemotherapy (temozolomide) than their unmethylated counterparts.
- MGMT promoter methylation is an independent prognostic marker for longer OS.
- TERT promoter mutation is associated with aggressive behavior.
- Giant cell GBM patients have been reported to have a better prognosis than classic GBMs.
- Gliosarcoma patients have a poor prognosis similar to that of IDH-wildtype GBM.
- Epithelioid GBMs are generally associated with poor prognosis, although the clinical outcome is variable in the three molecular subclasses.

**Essential and Desirable Diagnostic Criteria**

Refer Table 1.2.
Fig. 1.2.3 Glioblastoma, IDH-wildtype.
(a) Gross specimen shows a large tumor diffusely infiltrating the parenchyma and causing midline shift. (b) The tumor is composed of spindled and pleomorphic astrocytes and shows prominent microvascular proliferation, (c) confluent necrosis and sclerosed–thrombosed vessels with (d) areas of palisading necrosis. Two diagnostic molecular alterations include (e) EGFR amplification and (f) TERT promoter mutation. (C228T)
Fig. 1.2.3 Giant cell glioblastoma and gliosarcoma.

(g) Giant cell glioblastoma showing several bizarre multinucleate tumor giant cells, which show (h) diffuse, strong nuclear p53 immunopositivity.
(i) Gliosarcoma showing biphasic pattern of arrangement of neoplastic glial and sarcomatous elements. (j) The silver stain highlights the reticulin-rich sarcomatous areas, whereas (k) GFAP highlights the glial component and (l) vimentin highlights both glial and sarcomatous components.
Fig. 1.2.3 Epithelioid glioblastoma. (m) The tumor is composed of plump epithelioid cells arranged in sheets and around vessels. (n) BRAF p.V600E is diffusely positive.

Table 1.2 Essential and desirable diagnostic criteria (WHO CNS5)

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Essential criteria</th>
<th>Desirable criteria</th>
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<tbody>
<tr>
<td>Astrocytoma, IDH-mutant</td>
<td>• A diffusely infiltrating glioma AND • IDH1 codon 132 or IDH2 codon 172 missense mutation AND • Loss of nuclear ATRX expression or ATRX mutation OR • Exclusion of combined whole-arm deletions of 1p and 19q</td>
<td>• TP53 mutation or strong nuclear expression of p53 in &gt;10% of tumor cells • Methylation profile of astrocytoma, IDH-mutant • Astrocytic differentiation by morphology</td>
</tr>
<tr>
<td>Oligodendroglioma, IDH-mutant and 1p/19q-codeleted</td>
<td>• A diffusely infiltrating glioma AND • IDH1 codon 132 or IDH2 codon 172 missense mutation AND • Combined whole-arm deletions of 1p and 19q</td>
<td>• DNA methylome profile of oligodendroglioma, IDH-mutant and 1p/19q-codeleted • Retained nuclear expression of ATRX • TERT promoter mutation</td>
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<tr>
<td>Glioblastoma, IDH-wildtype</td>
<td>• An IDH-wildtype, H3-wildtype, diffuse astrocytic glioma AND • One or more of the following: o Microvascular proliferation o Necrosis o TERT promoter mutation o EGFR gene amplification o +7/+−10 chromosome copy-number alterations</td>
<td>• DNA methylation profile of glioblastoma, IDH-wildtype</td>
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