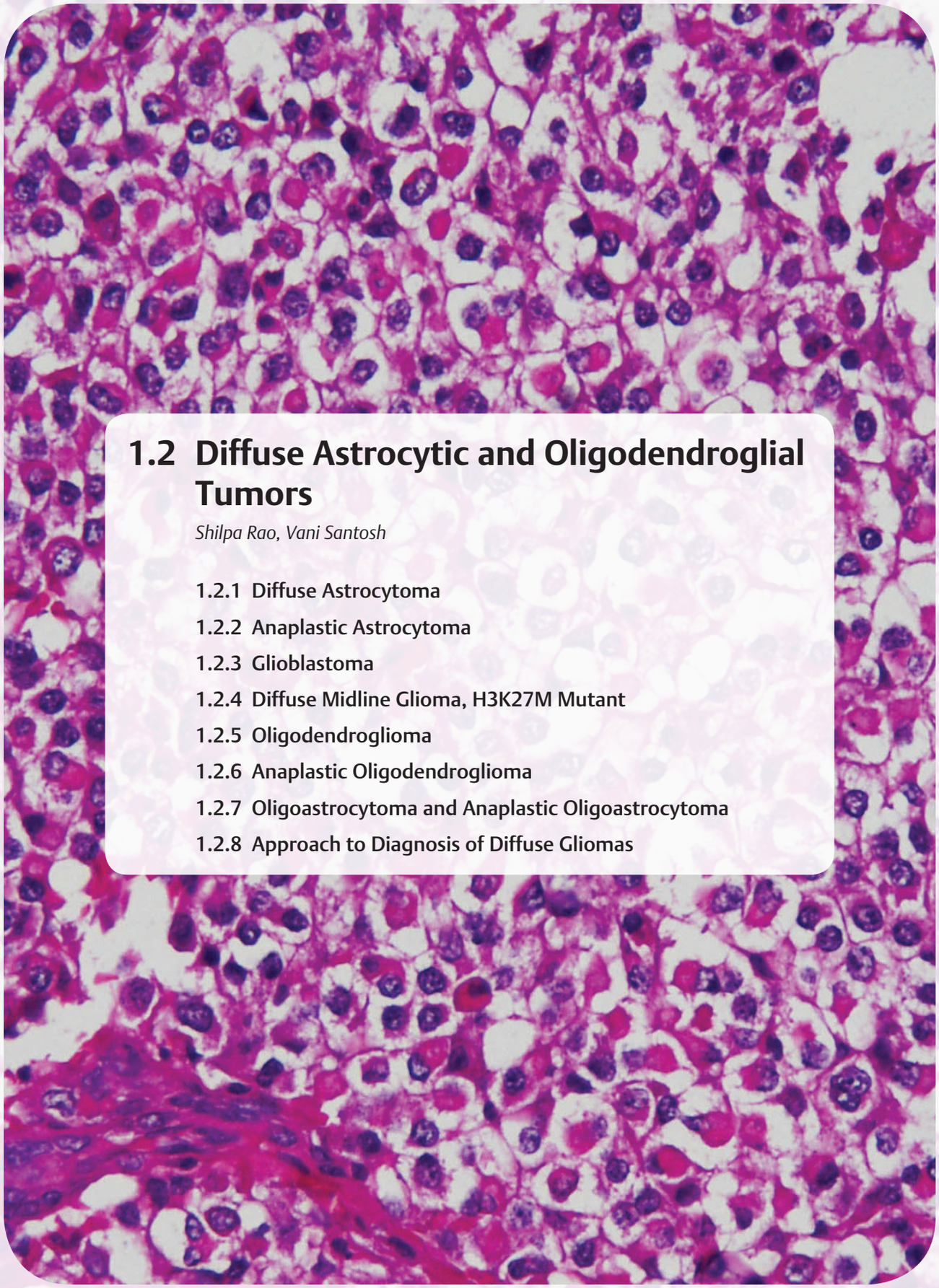
1 Tumors of the Nervous System



1.2 Diffuse Astrocytic and Oligodendroglial Tumors

Shilpa Rao, Vani Santosh

1.2.1 Diffuse Astrocytoma

Definition

- "*A diffusely infiltrating astrocytoma composed of moderately pleomorphic cells with a high degree of cellular differentiation and slow growth*" (WHO 2016).

Diffuse astrocytomas are further classified into
- Diffuse astrocytoma, isocitrate dehydrogenase (IDH) mutant
  - Gemistocytic astrocytoma, IDH mutant
- Diffuse astrocytoma, IDH wild type
- Diffuse astrocytoma, not otherwise specified (NOS)

WHO Grade

- A low-grade glioma corresponding to the WHO grade II.
- May progress to anaplastic astrocytoma (grade III) and later to glioblastoma (grade IV).

Incidence

- Accounts for 11 to 15% of all the astrocytomas (WHO 2016).
- Annual incidence of 0.55 and 0.75 new cases per 100,000.

Age and Gender Distribution

- Median age at presentation is 38 years (IDH mutant astrocytoma).
- Reported male:female ratio is 1.3:1.

Localization

- Cerebral hemispheric tumors.
- The most common location is the frontal lobe.

Macroscopy

- Diffusely infiltrative lesion invading normal anatomical structures and blurring of the gray-white junction.
- Secondary changes such as microcyst or macrocyst formation, sometimes filled with gelatinous material, may be observed.
- Occasionally, present as local mass lesions, but with indistinct boundaries.
- Calcification is rare.

Microscopy

Diffuse Astrocytoma, IDH mutant

This tumor is defined as a "*Diffusely infiltrating astrocytoma with a mutation in IDH1 or IDH2 gene*" (WHO 2016). The majority of diffuse astrocytomas are IDH mutant.

- A low-grade glioma that is moderately cellular
- Composed of fibrillary, protoplasmic, and gemistocytic astrocytes in varying combination/proportion.
- The background is fibrillary with or without microcystic change.
- Nuclear atypia and mitotic activity are minimal.
- Absence of microvascular proliferation and necrosis.

Immunophenotype

- The majority of the Diffuse astrocytomas express glial fibrillary acidic protein (GFAP).
- About 90% of the IDH-mutant astrocytomas can be detected by immunohistochemistry (IHC) with anti-IDH1 (R132H) antibody. The tumor cells exhibit cytoplasmic positivity for IDH1 (R132H).
- Diffuse astrocytomas are characterized by loss of alpha thalassemia mental retardation X-linked syndrome (ATRX) expression in the nuclei of the tumor cells.
- ATRX loss of expression indicates ATRX mutant status, which is a diagnostic feature of diffuse astrocytoma.
- Endothelial cells, microglia, lymphocytes, native glial cells, and overrun neurons express ATRX normally, thus serving as internal control.
- P53 expression is noted in the majority of astrocytomas with ATRX loss of expression, but it is neither a sensitive nor a specific marker for the diagnosis of astrocytoma, in view of false-positive and false-negative results.
- Diffuse astrocytomas have a low proliferation index of less than 4%.

Genetic Profile

IDH1 and 2 Mutations in Diffuse Gliomas

- IDH catalyzes the oxidative carboxylation of isocitrate to α-ketoglutarate (α-KG), resulting in the production of nicotinamide adenine dinucleotide phosphate (NADPH), thus protecting the glial cells from oxidative stress.
- In humans, three isoforms of IDH exist, and IDH 1 is localized to the peroxisomes and the cytoplasm.
- IDH1 and IDH2 are mutated in high proportions of diffuse low-grade gliomas of any phenotype (astrocytoma, oligodendroglioma, oligoastrocytoma) and progressive gliomas including secondary glioblastoma but not in primary de novo glioblastoma.
- Patients with IDH1/IDH2-mutant gliomas are known to have a better clinical outcome.
- Heterozygous mutations in IDH1 dominantly inhibit wild-type IDH1, resulting in reduced α-KG and increased accumulation of 2-hydroxyglutarate (2HG), which acts as an oncometabolite, thereby inhibiting dioxygenases, demethylases affecting DNA repair mechanisms, and chromatin modification.
- IDH1 mutation results in DNA hypermethylation of CpG islands in the promoters of various genes (G-CIMP) and histone hypermethylation, which further arrest cellular differentiation by transcriptional silencing of target genes.
- IDH1 mutations observed in gliomas are most often point mutations at position 132 (R132H), where wild-type

arginine is replaced by histidine. This mutation is also called canonical IDH1 mutation. The nucleotide change causing this mutation is G395A, that is, change of nucleotide from G to A at the position 395.
- Other rarer 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 point mutations have been identified in IDH2, where arginine at 172 (R172) is replaced with glycine (R172G), methionine (R172 M), lysine (R172 K), serine (R172S), and tyrosine (R172Y).
- While IHC serves as a surrogate for the IDH1(R132H) mutations, the other uncommon IDH1 and 2 mutations are detected by DNA-sequencing methods.

ATRX Mutation

- The *ATRX* gene is located at Xq21 and is a DNA helicase and chromatin remodeling gene. Germline mutations in ATRX are associated with alpha thalassemia mental retardation X-linked syndrome (ATRX), hence the name.
- ATRX mutation results in loss of ATRX protein expression.
- Loss of ATRX and death-domain–associated protein (DAXX) play an important role in telomere maintenance mechanism.
- Loss of ATRX expression is commonly seen in the majority of grades II and III astrocytomas and secondary glioblastoma.
- ATRX mutations are mutually exclusive with 1p/19q co-deleted oligodendrogliomas that often show retained ATRX expression by IHC.
- Molecular testing for ATRX is now routinely done using IHC in which mutant phenotype is evidenced by the loss of expression of the protein.

TP53 Mutation

- TP53 mutation is one of the common mutations in diffuse gliomas, particularly astrocytomas.
- Commonly tested through immunohistochemical staining for p53 protein accumulation in the cell nuclei. However, this nuclear accumulation is only an indicator, and not concrete proof of mutation in the *TP53* gene.
- Although ATRX loss has taken over as a defining molecule for astrocytoma, P53 IHC can complement ATRX, and hence these two markers are often used together to define diffuse astrocytomas.

Gemistocytic Astrocytoma, IDH Mutant

- Gemistocytic astrocytoma, IDH mutant, is a variant of IDH-mutant diffuse astrocytoma, characterized by the presence of a conspicuous (> 20%) proportion of gemistocytic neoplastic astrocytes.
- Gemistocytes are plump astrocytes with glassy eosinophilic cytoplasm and stout cytoplasmic processes.
- They have an eccentric nucleus and small nucleoli.
- The stroma is coarse and fibrillary.
- Being an IDH-mutant tumor, the cells diffusely express IDH1(R132H).
- P53 mutations are seen in more than 80% of the cases.

Diffuse Astrocytoma, IDH Wild Type

- Definition: "*A diffusely infiltrating astrocytoma without mutations in IDH genes*" (WHO 2016).
- NOTE: For the diagnosis of diffuse astrocytoma, IDH wild type, the tumor needs to be negative for all the mutations by sequence analysis for IDH1 codon 132 and IDH2 codon 172.

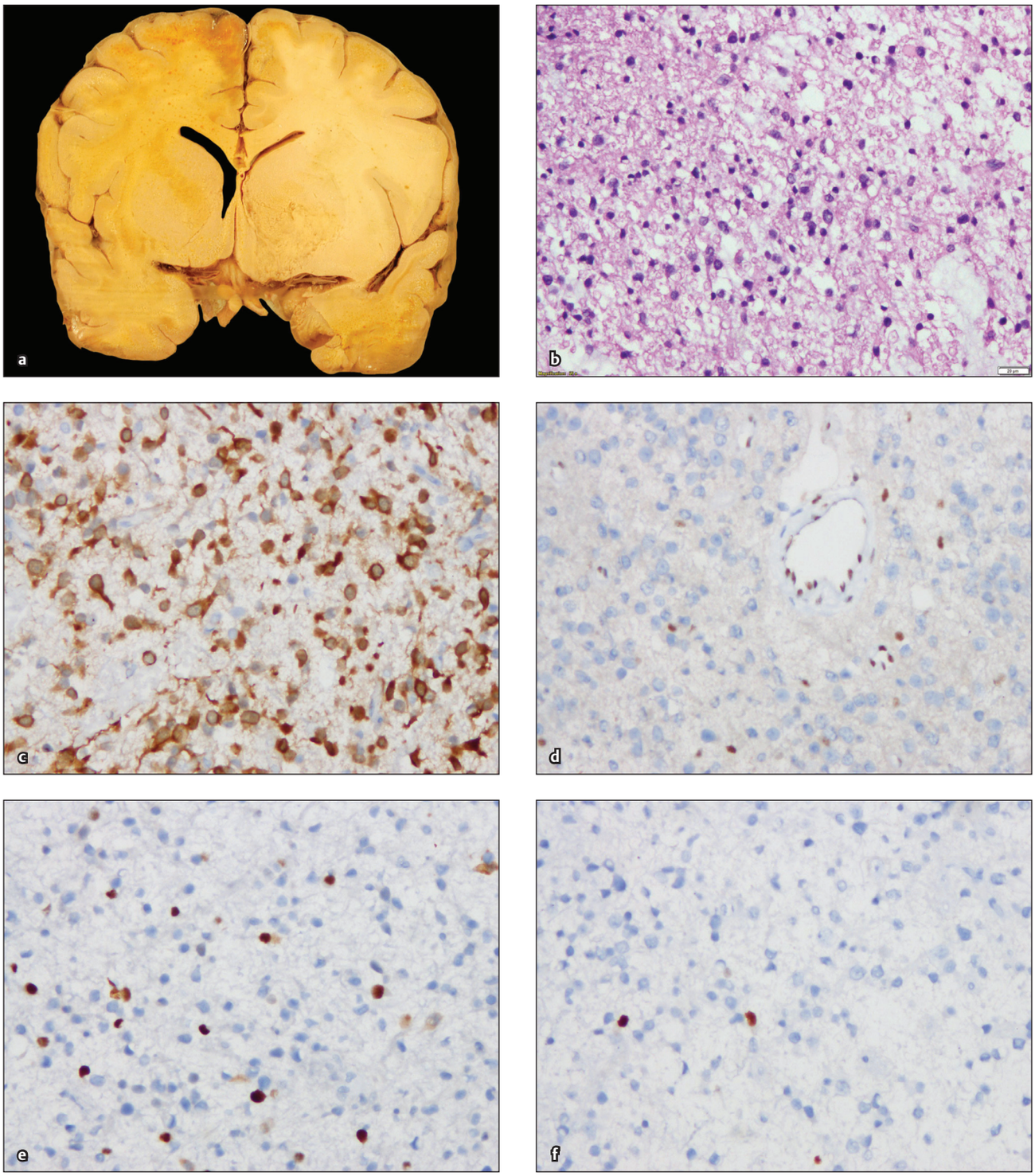
Diffuse Astrocytoma, NOS

- Definition: "*A tumor with morphological features of diffuse astrocytomas but in which IDH mutation status has not been fully assessed*" (WHO 2016).

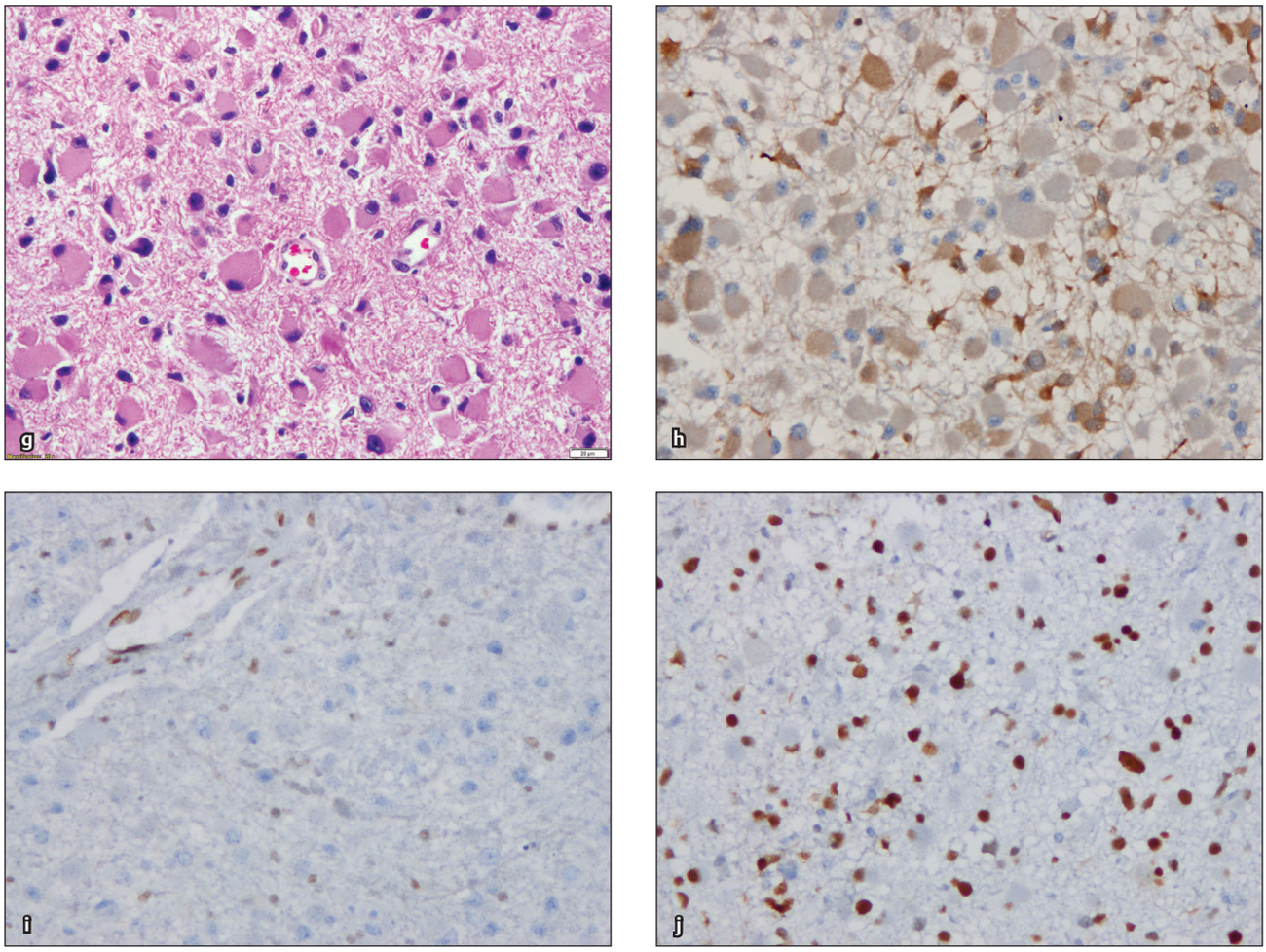
The earlier entities of fibrillary and protoplasmic astrocytomas are now no longer considered as variants of diffuse astrocytoma according to the WHO 2016 classification.

Prognosis

- Gemistocytic astrocytoma has been associated with early malignant progression and poor outcome.
- IDH-mutant astrocytomas have a favorable outcome compared to IDH–wild-type tumors.
- ATRX loss defines a subgroup of astrocytomas with a favorable prognosis.
- Among the IDH–wild-type tumors, those with TERT promoter mutation, EGFR amplification/mutation, H3F3A mutations are known to be associated with poor outcome.



1.2.1 Gemistocytic astrocytoma, IDH mutant WHO grade II
(a) Gross specimen of a diffusely infiltrating astrocytoma in the left cerebral hemisphere. **(b)** Fibrillary and protoplasmic astrocytes exhibiting mild nuclear atypia dispersed over a fibrillated microcystic stroma (H&E ×100). **(c)** Immunostain shows IDH1(R132H) positivity in the cytoplasm of tumor cells (×200). **(d)** Immunostain for ATRX shows loss of expression in the tumor cell nuclei. The endothelial cells and some overrun native glial cells are stained positively, thus serving as an internal control (×200). **(e)** Immunostain. for P53 shows variable nuclear positivity (×200). **(f)** The tumor shows low MIB-1 labeling (×200).



1.2.1 Diffuse astrocytoma, IDH mutant WHO grade II
(g) Sheets of gemistocytic astrocytes exhibiting mild nuclear atypia (H&E ×200). **(h)** Immunostain shows IDH1(R132H) positivity in the cytoplasm of several gemistocytic cells (×200). **(i)** Immunostain for ATRX shows loss of expression in the tumor cell nuclei. The endothelial cells and some overrun native glial cells are stained positively, thus serving as an internal control (×200). **(j)** Immunostain shows diffuse P53 positivity (×200).