involving chromosome 9p21, resulting in hemizygous deletion of the *CDKN2A* tumor suppressor gene, are also common; you will recall that this unusual locus encodes two tumor suppressors, p16/INK4a and p14ARF, which function by augmenting the activity of RB and p53, respectively.

- The *proneural type*, which is the most common type associated with secondary glioblastoma, is characterized by mutations of *TP53*, and point mutations in the isocitrate dehydrogenase genes, *IDH1* and *IDH2*. The proneural glioblastoma also often shows an overexpression of the receptor for platelet-derived growth factor receptor α (PDGFRA). Low grade gliomas (grades II and III astrocytomas) also tend to have mutations in *TP53* and in the *IDH* genes, a molecular signature that is carried forward as the neoplasm evolves to the higher grade, secondary glioblastoma.
- The *neural type* is characterized by higher levels of expression of neuronal markers, including NEFL, GABRA1, SYT1, and SLC12A5.
- The *mesenchymal type* is characterized by deletions of the *NF1* gene on chromosome 17, and lower expression of the NF1 protein. Genes involved in the TNF pathway and the NF-κB pathway are highly expressed in the mesenchymal glioblastoma.

The common theme of these diverse genotypic changes is that most affect two cancer hallmarks, sustained proliferative signaling and evasion of growth suppressors. For example, overexpression of PDGFRA in proneural glioblastomas, and mutation and amplification of *EGFR* genes in classic glioblastomas, both lead to increased receptor tyrosine kinase signaling. You will recall from Chapter 7 that tyrosine kinases stimulate RAS and PI3K/AKT signaling, which act together to drive cells from the G1 to S phase of the cell cycle and to deregulate cellular metabolism so as to promote growth. Other common events directly or indirectly inhibit RB and p53 function. Based on whole genome sequencing, it is estimated that mutations that activate RAS and PI-3 kinase and inactivate p53 and RB are present in 80% to 90% of primary glioblastomas.

Additionally, among the higher grade astrocytomas (WHO grades III and IV), the presence of the mutant form of *IDH1* (predominantly the R132H mutation) is associated with a significantly better outcome than in tumors with wild type *IDH1*. You will recall that *IDH1* mutations create a neomorphic enzyme activity that generates 2-hydroxyglutarate, which appears to contribute to oncogenesis by inhibiting enzymes that regulate DNA methylation, an example of oncogenesis by epigenetic dysregulation (Chapter 7).

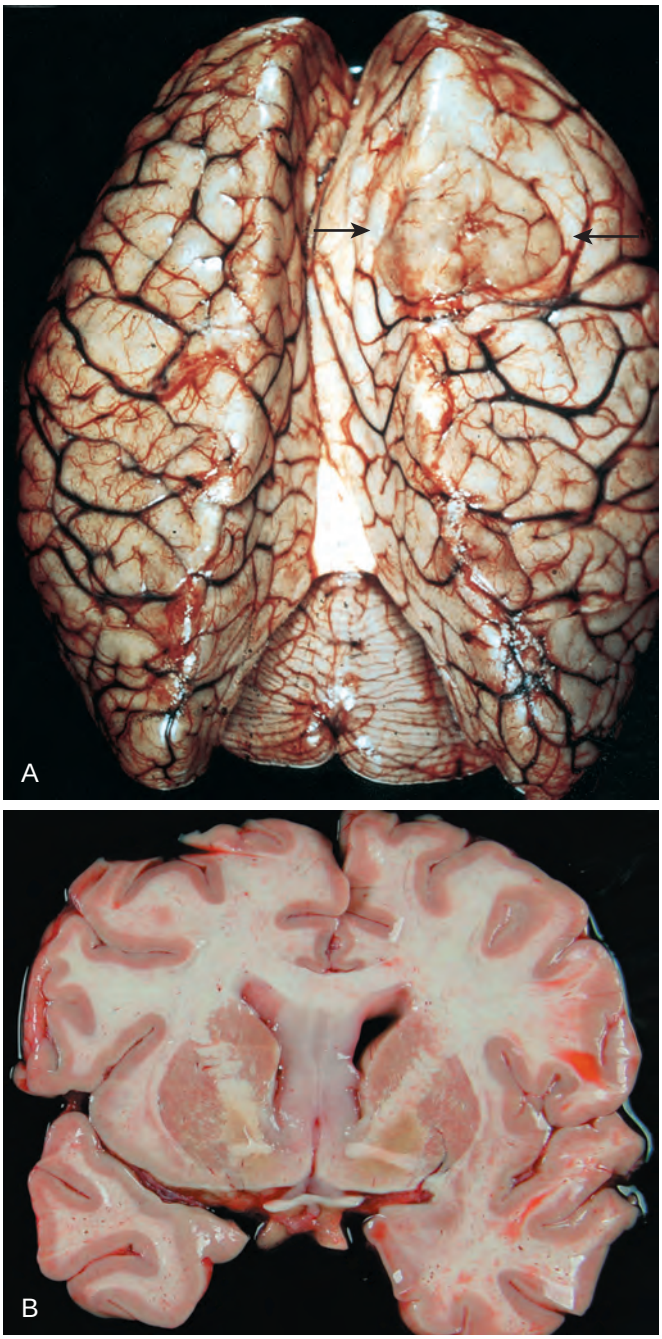

Figure 28-46 Diffuse astrocytoma. **A,** The right frontal tumor has expanded gyri, which led to flattening *(arrows)*. **B,** There is bilateral expansion of the septum pellucidum by gray, glassy tumor.

MORPHOLOGY

Diffuse astrocytomas are poorly defined, gray, infiltrative tumors that expand and distort the invaded brain (Fig. 28-46). These tumors range in size from a few centimeters to enormous lesions that replace an entire hemisphere. The cut surface of the tumor may be either firm or soft and gelatinous; cystic degeneration may be seen. The tumor may appear well demarcated from the surrounding brain tissue, but infiltration beyond the outer margins is always present.

Microscopically, diffuse astrocytomas have a cellular density that is greater than normal white matter. Between the tumor cell nuclei there is an extensive feltwork of fine, GFAP-positive astrocytic processes that create a fibrillary background appearance. There are variable degrees of nuclear pleomorphism. The transition between neoplastic and normal tissue is indistinct, and tumor cells infiltrate normal tissue some distance away from the main lesion.

Anaplastic astrocytomas are more densely cellular and have greater nuclear pleomorphism; mitotic figures are often observed. The term **gemistocytic astrocytoma** is used for

www.PTools.ir