

# From the Archives of the AFIP

## Oligodendroglioma and Its Variants: Radiologic-Pathologic Correlation<sup>1</sup>

Kelly K. Koeller, CAPT, MC, USN • Elisabeth J. Rushing, COL, MC, USA

### CME FEATURE

See accompanying test at [http://www.rsna.org/education/rg\\_cme.html](http://www.rsna.org/education/rg_cme.html)

### LEARNING OBJECTIVES FOR TEST 6

After reading this article and taking the test, the reader will be able to:

- Identify the distinguishing imaging features of oligodendroglioma and its variant forms.
- Describe the gross pathologic and histologic appearances of oligodendroglioma and its variants and the direct correlation with the imaging appearances.
- Discuss the importance of genotyping in establishing the diagnosis of these tumors and the correlation with imaging features.

Oligodendroglioma is the third most common glial neoplasm and most commonly arises in the frontal lobe. It occurs in males more frequently, and the peak manifestation is during the 5th and 6th decades. Children are affected much less commonly. The clinical presentation is often of several years duration with most patients presenting with seizures, reflecting the strong predilection of this tumor to involve the cortical gray matter. Current histopathologic classification schemes recognize two main types of tumors: well-differentiated oligodendroglioma and its anaplastic variant. Less commonly, neoplastic mixtures of both oligodendroglial and astrocytic components occur and are termed *oligoastrocytomas*, with both well-differentiated and anaplastic forms. Surgical resection is the mainstay of initial treatment, and many patients experience a long progression-free period. Recent genotyping has revealed chromosomal loss of 1p and 19q as a genetic signature in most oligodendrogliomas, and these tumors respond favorably to chemotherapy. Hence, radiation therapy is now generally reserved for partially resected tumors and cases that failed to benefit from chemotherapy. At cross-sectional imaging, the tumor characteristically involves the cortical gray matter and frequently contains calcification. Robust enhancement is not a common feature and suggests transformation to a higher histologic grade. Advanced magnetic resonance imaging techniques and metabolic imaging play increasingly important roles in both pre- and postoperative assessment of these complex neoplasms.

**Abbreviations:** ADC = apparent diffusion coefficient, PCV = procarbazine, lomustine, and vincristine, WHO = World Health Organization

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<sup>1</sup>From the Departments of Radiologic Pathology (K.K.K.) and Neuropathology (E.J.R.), Armed Forces Institute of Pathology, Washington, DC; the Department of Radiology and Radiological Sciences, Uniformed Services University of the Health Sciences, Bethesda, Md (K.K.K.); and the Department of Pathology, George Washington University, Washington, DC (E.J.R.). Received June 30, 2005; accepted August 30. Both authors have no financial relationships to disclose. **Address correspondence to** K.K.K., Department of Radiology, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (e-mail: [koeller.kelly@mayo.edu](mailto:koeller.kelly@mayo.edu)).

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## Historical Perspective and Nomenclature

The oligodendrocyte, as recognized by Robertson in 1900, is part of the neuroglial family of cells and is found predominantly in the white matter of the central nervous system (1). This is not a surprise as its primary function is the production and replenishment of myelin, which it spins off to form a bilaminar layer around axons. As with other glial cells, neoplastic transformation of the oligodendrocyte may occur, eventually resulting in a true neoplasm known as an oligodendroglioma. As described in their famous treatise on brain tumors, Bailey and Cushing (2) were the first to recognize this tumor as a distinct entity in 1926. Three years later, Bailey and Bucy (3) provided the classic description of 13 cases of the tumor and, through the early and middle portion of the 20th century, other reports accumulated of this fairly uncommon brain neoplasm (1,4).

These early investigators noted that this tumor had unusual characteristics compared to other glial tumors, particularly concerning its quite variable biologic behavior. In general, it was not as biologically aggressive as astrocytic gliomas of similar histologic grade. Yet, occasionally, it could show clinical and pathologic features much more consistent with the most highly malignant glial neoplasms (1,4).

As one might surmise, these seemingly unpredictable tumors have defied mutually agreeable histologic classification among neuropathologists despite many schemes being implemented over the years, from four-tiered systems originally employed by Kernohan, St Anne–Mayo, and the Armed Forces Institute of Pathology (AFIP) (4–6), to three-tiered schemes such as that used by Ringertz (7), and finally to today's two-tiered systems such as the World Health Organization (WHO) system and others (8–10). In this classification scheme, oligodendrogliomas are divided into two forms: the well-differentiated oligodendroglioma and the less common anaplastic oligodendroglioma. In addition, oligodendrogliomas may occasionally contain clear evidence of neo-

plastic astrocytes and may then be considered "mixed gliomas," most commonly as oligoastrocytomas (11). These tumors are also divided into two groups: the better differentiated oligoastrocytoma and the anaplastic oligoastrocytoma.

Using case material from the Thompson Archives of the Department of Radiologic Pathology at the AFIP, this review highlights the epidemiologic, clinical, neuropathologic, and neuroimaging manifestations of these four tumor types and presents information that facilitates the recognition of these tumors at neuroimaging. Therapy, recurrence and metastasis, and prognosis and survival rates are also discussed.

## Epidemiology

Oligodendroglioma is the third most common glioma overall, accounting for 2%–5% of primary brain tumors and 5%–18% of all glial neoplasms (8,12–14). The tumor accounts for less than 1% of pediatric central nervous system neoplasms (15). According to the Central Brain Tumor Registry of the United States, oligodendrogliomas have an annual incidence of 0.3 per 100,000 people, while the tumor composed 4.2% of all primary brain tumors over a 25-year period in the Norwegian Cancer Registry (14,16).

The actual prevalence of the other oligodendroglial tumors is difficult to determine, primarily because of a lack of uniformity regarding the morphologic criteria at histopathologic analysis and the lack of a defining immunohistochemical or molecular marker that would facilitate the diagnosis. The prevalence of anaplastic oligodendrogliomas varies from 3.5% of all malignant gliomas to 20%–54% of all oligodendroglial tumors in reported series (16–20). Mixed oligoastrocytomas accounted for about 9% of all glial tumors in the Norwegian Cancer Registry, while they composed only 1.8% of all brain tumors in the Central Brain Tumor Registry of the United States (21,22).

In recent years, the number of reported oligodendrogliomas has substantially increased, in part because of implementation of superior cross-sectional imaging techniques (23). Most important, recognition of the significant differences in prognosis between oligodendrogliomas and astrocytomas of similar histologic grade has influenced recent changes in accepted histopathologic criteria

and is believed to have contributed to a dramatic increase in the number of oligodendrogliomas being diagnosed by neuropathologists. With use of these criteria modifications, up to 25% of gliomas may be considered oligodendrogliomas (24).

Most oligodendrogliomas manifest in the adult age groups with a peak incidence in the fourth and fifth decades (5,14,25). Patients with anaplastic tumors are usually slightly older (peak age, sixth and seventh decades) than those with well-differentiated oligodendrogliomas (17,25). Patients with oligoastrocytomas have a median age of 35–45 years (11,22). A small percentage (about 6%) arise in children, accounting for a second smaller age peak at 6–12 years (13,14,26–28). The tumor may rarely manifest as a fetal tumor (29).

Males are more commonly affected, up to 2:1 in some series, among patients with oligodendrogliomas (1,5,13). This male gender predilection is also noted in the other oligodendroglial tumors (11,17,22). While no definite inheritance pattern or known genetic risk factors have been documented, occasional familial groupings of oligodendroglioma and oligoastrocytoma have been reported (30–32).

The vast majority of all oligodendroglial tumors occur in the supratentorial brain with the frontal lobe the most common site overall (50%–65%) (5,11–14,18,33–35). The temporal lobe (47%) is the second most common location, with the parietal lobe (7%–20%) and occipital lobe (1%–4%) being less frequent sites of involvement (34,35). Multiple lobar involvement is possible (34). Other sites for primary tumors include the cerebellum (3%), brainstem, spinal cord (1%), leptomeninges (so-called “oligodendrogliomatosis”), cerebellopontine angle, cerebral ventricles, retina, and optic nerve (1,8,12,15,35–41). Primary leptomeningeal tumors are speculated to arise from glial heterotopias in this location (42).

Interesting observations of oligodendrogliomas coexisting with other intracranial neoplasms and diseases have been noted. Meningioma, sarcoma, lymphoma, pilocytic astrocytoma, and pleomorphic xanthoastrocytoma in association with oligodendrogliomas have been reported in the literature (43–49). Several reports of oligodendroglioma with arteriovenous malformation, some presenting with subarachnoid hemorrhage, and with multiple sclerosis have also been added (50–56).

## Clinical Features

In accordance with its slow growth, oligodendroglioma typically demonstrates a long clinical presentation, frequently 5 years or more (6,13,14,18,57). Patients with anaplastic oligoastrocytomas typically have a shorter clinical presentation (11). Seizure activity (35%–85%) is the most common symptom overall (5,13,14,19,34,35,58–60). It is believed that the high incidence of seizure activity is likely related to the tendency of the tumor to involve the cortical gray matter (8). Headache is the second most common symptom, followed by mental status changes, vertigo or nausea, visual complaints, and weakness (13,14,57). Patients with intraventricular oligodendrogliomas tend to present with headaches as a consequence of increased intracranial pressure and usually have a shorter duration of symptoms without focal neurologic deficits compared to those whose tumors arise within the brain parenchyma (61). Among 323 patients from an AFIP series, the most common clinical signs were paralysis (50%), visual loss (49%), papilledema (47%), ataxia (39%), abnormal reflexes (37%), and meningismus (10%) (6).

## Pathologic Features

At gross inspection, oligodendrogliomas are usually soft, fleshy, grayish-pink masses, frequently extending to the pial margin of the cerebral hemispheres, most commonly in the frontal lobe (8,38,62). Occasionally, mucoid degeneration and leptomeningeal infiltration are seen (8). Calcification is a common feature and may be detected at surgical resection by a hard “gritty” sensation (8).

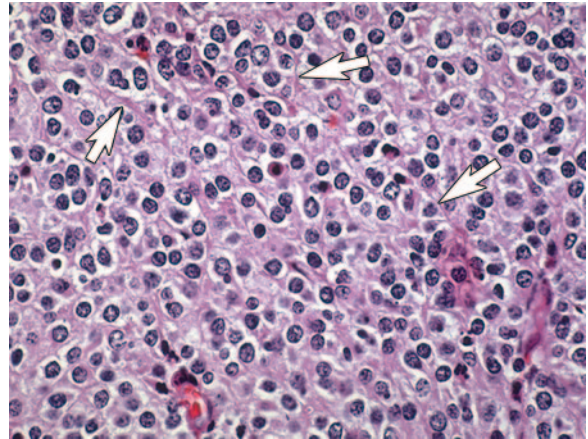
Histopathologic evaluation of oligodendroglioma reveals a moderately cellular neoplasm with a typically monotonous pattern of uniformly rounded hyperchromatic nuclei surrounded by prominent clear cytoplasm (“perinuclear halo”). This frequently results in a classic “fried-egg” appearance at hematoxylin-eosin staining (8). This manifestation is actually an artifact of delayed fixation of the tissue and will not be seen in frozen section specimens (8). A delicate branching network of capillaries is characteristic, often producing a “honeycomb” or “chicken-wire” pattern (Fig 1) (8).

Microcalcifications are seen in 90% of tumors, making oligodendroglioma the most common glial tumor to have this feature (63). Mucoïd or cystic degeneration is also frequently noted (8). In accordance with its low-level proliferative ability, little or no mitotic activity is noted. Reactive gemistocytic astrocytes are seen occasionally (8). Rarely, an oligodendroglioma may be predominantly composed of signet-ring cells (“signet-cell oligodendroglioma”) or in combination with giant cells (“polymorphous oligodendroglioma”) (30,64).

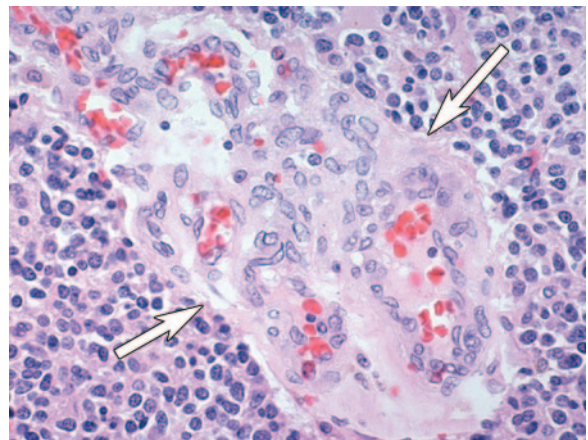
While low levels of angiogenesis-promoting epidermal growth factor and vascular endothelial growth factor have been noted in most oligodendrogliomas, endothelial proliferation and necrosis are not characteristic features (8,65). Accordingly, the WHO classifies well-differentiated oligodendroglioma as a WHO grade II lesion (8).

Involvement of the cortical gray matter is a highly distinctive feature of this tumor (63). In this area, perineuronal satellitosis, perivascular aggregations of tumor cells, and subpial accumulations may be noted and provide valuable ancillary clues to the diagnosis (8,63). Normal neuronal cells of the cortex are often “overrun” by the infiltrating neoplastic oligodendroglial cells (63). This infiltration also gives rise to the typical “diffuse” appearance seen both histologically and at neuroimaging (63). Occasionally, the tumor may have an abrupt and well-defined margin (63).

Unfortunately, there is no specific immunohistochemical marker to substantiate the diagnosis of an oligodendroglioma (8). However, recent molecular investigations have revealed a propensity for loss of heterozygosity on the long arm of chromosome 19 (19q) in 50%–80% of oligodendrogliomas and on the short arm of chromosome 1 (1p) in 40%–92%, and virtually all oligodendrogliomas with loss of heterozygosity on 1p also have loss on 19q (8). This consistent finding is now being recognized as a signature genetic feature of an oligodendroglioma and is strongly affiliated with the classic histopathologic findings seen in well-differentiated (WHO grade II) oligodendrogliomas (66–68). In contrast, those oligodendroglial tumors that do not possess these chromosomal losses are associated with more variable and atypical histopathologic features (68). Losses of genetic material from other chromosomes (4, 6, 9, 10, 11p, 14, and 22q) have also been identified (8). It is becoming clear that genotyping of



**Figure 1.** Well-differentiated oligodendroglioma. Photomicrograph (original magnification,  $\times 40$ ; hematoxylin-eosin stain) shows uniform round cells that are interrupted by a dense network of branching capillaries, a few of which are indicated by arrows.

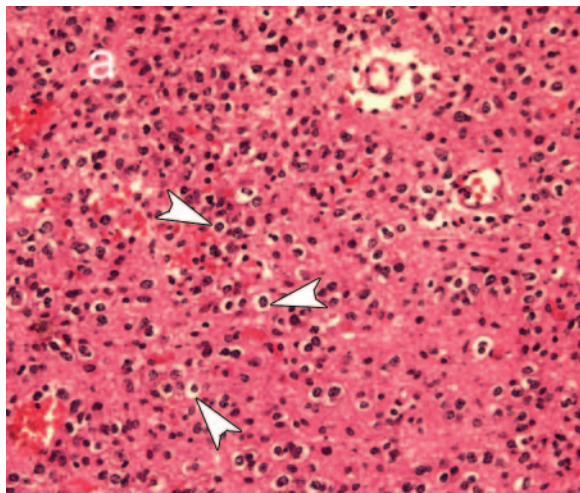


**Figure 2.** Anaplastic oligodendroglioma. Photomicrograph (original magnification,  $\times 40$ ; hematoxylin-eosin stain) shows florid microvascular proliferation (arrows) within a typical oligodendroglial morphology.

oligodendroglial tumors is important to the diagnosis of these tumors, perhaps even surpassing the importance of the histopathologic features (68).

The anaplastic oligodendroglioma, arising either *de novo* or from an existing well-differentiated oligodendroglioma, is noted for its increased cellularity, marked atypia, and increased mitotic activity. Endothelial proliferation, resulting from amplification of epidermal growth factor, and necrosis are also common (Fig 2) (69–71). Not surprisingly, these tumors are regarded as grade III neoplasms in the WHO classification scheme (17).

While similar to oligodendrogliomas with common deletions of 1p and 19q alleles, anaplastic oligodendrogliomas also show even more chro-



**Figure 3.** Oligoastrocytoma. Photomicrograph (original magnification,  $\times 40$ ; hematoxylin-eosin stain) shows unequivocal neoplastic astrocytic (*a*) and oligodendroglial components combined in this field. Arrowheads = representative oligodendrocytes with the typical “fried-egg” appearance.

mosomal deletions overall and an increased rate of deletions involving 9p and on chromosome 10 (17). In addition, a subgroup of anaplastic oligodendrogliomas is suspected because loss of chromosome 10 and gain of chromosome 7 is usually linked with absence of 1p and 19q deletions (17). Such tumors show more aggressive biologic behavior and may be genetically related to glioblastoma multiforme (17). About 25% of anaplastic oligodendrogliomas have deletion of a tumor suppressor gene, *CDKN2A*, located on the short arm of chromosome 9 (69).

As its name implies, the diagnosis of oligoastrocytoma rests on the detection of two different but definitely neoplastic glial components, one oligodendroglial and the other astrocytic (Fig 3) (22). Similar to oligodendroglioma, the tumor is moderately cellular, may contain microcalcifications or cystic degeneration, and demonstrates little or no mitotic activity and no necrosis or endothelial proliferation (22). The tumor may be either biphasic, with the two components clearly adjacent to each other, or intermingled, with the components diffusely intertwined. Many oligoastrocytomas (30%–50%) contain deletions of 1p and 19q alleles, while about 30% carry genetic changes (ie, mutation of the TP53 tumor suppressor gene and loss of heterozygosity of chromosome 10) typically seen in astrocytomas, supporting the hypothesis that oligoastrocytomas may be composed of two different subsets (72, 73). The tumor is considered a WHO grade II lesion (22).

While the terminology is simple, it has been difficult to establish a uniform criterion regarding exactly what percentage of astrocytic component—recommendations have ranged from 1% to 50%—is required before one labels the tumor an oligoastrocytoma instead of an oligodendroglioma (22,63,68). Hence, the tumor remains a nosologically controversial entity. The distinction between an oligoastrocytoma and astrocytoma is of more than simply academic interest, as there is a marked difference in response to chemotherapy with procarbazine, lomustine, and vincristine (PCV) and hence in prognosis for patients with the anaplastic forms of these tumors (74–76).

The anaplastic oligoastrocytoma is an even more heterogeneous tumor histopathologically and contains the additional features of nuclear atypia, pleomorphism, increased cellularity, and high mitotic activity. Therefore, it is considered a WHO grade III tumor (11). Many chromosomal alterations similar to those found in the other oligodendroglial neoplasms have been reported (11).

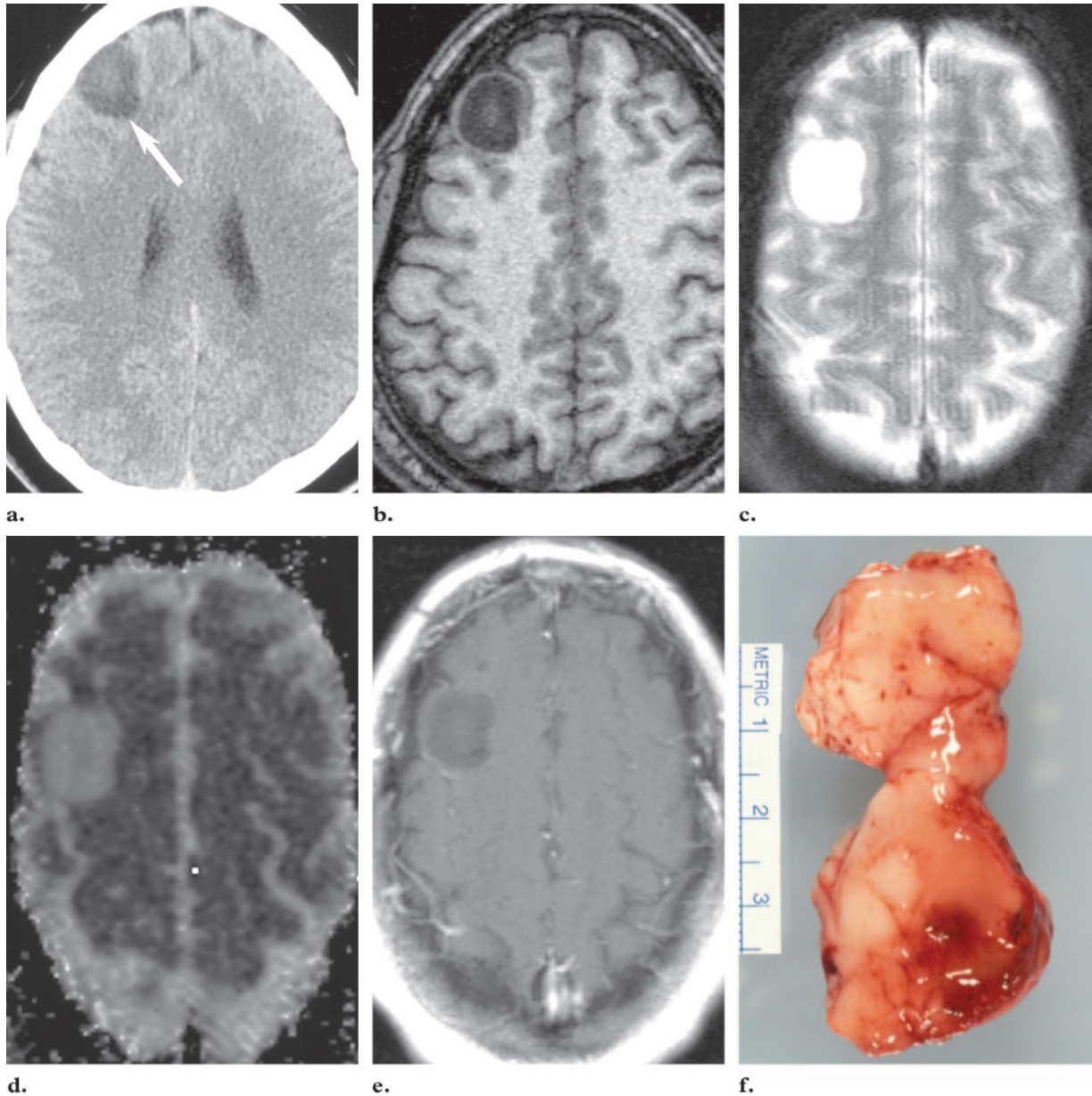
### Histogenesis

To date, definitive proof that oligodendrogliomas arise from oligodendroglial cells is lacking. The perception that these tumors are oligodendroglial in nature rests primarily on the morphologic similarities of the tumor cells to normal oligodendrocytes at histopathologic analysis. On the basis of animal models, it may be that the cell of origin is a bipotential progenitor cell that can differentiate into either oligodendrocytes or astrocytes (8). This may also explain the origin of the mixed oligoastrocytoma, which is suspected to arise from a single precursor cell (22,77). The recent finding of neuron-related genes being expressed in oligodendrogliomas with the 1p loss raises the intriguing possibility that perhaps some of these tumors may have a neuronal heritage (78).

### Imaging Features

Oligodendrogliomas typically manifest as a round or oval sharply marginated mass involving the cortex or subcortical white matter at cross-sectional neuroimaging (79). Occasionally, the tumor margins are not well-defined, as it appears to blend imperceptibly into the normal adjacent brain parenchyma. At computed tomography (CT), about 60% are hypoattenuating while 23% are isoattenuating and about 6% are hyperattenuating (Fig 4) (79). Calcification, usually coarse in

**Figure 4.** Oligodendroglioma. (a) Axial CT image shows a hypoattenuating mass (arrow) in the cortex and subcortical white matter of the right frontal lobe. (b) Axial T1-weighted magnetic resonance (MR) image shows low signal intensity of the mass, which spares the extreme perimeter of the cortical gray matter. (c) Axial T2-weighted MR image shows high signal intensity of the mass. (d) Axial apparent diffusion coefficient (ADC) MR image shows mild high signal intensity of the mass, a finding that indicates absence of restricted water diffusion. (e) Axial contrast-enhanced T1-weighted MR image shows no enhancement of the mass, a finding typical of this tumor. (f) Photograph of the gross specimen shows expanded gyri, which are a result of neoplastic involvement. Scale is in centimeters.



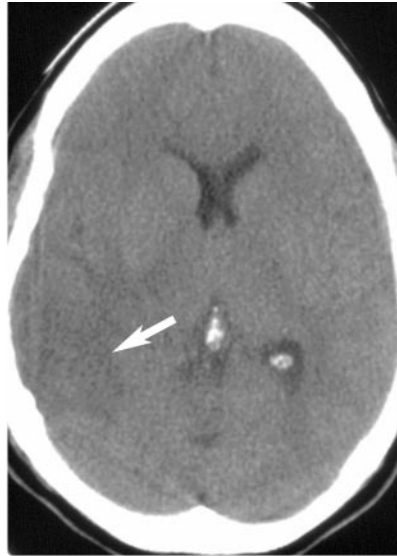
morphology, is noted in 20%–91% of cases (Fig 5) (34,79,80). Occasionally, cystic degeneration and hemorrhage may be seen (79). When the mass is sufficiently exophytic, calvarial erosion may be noted (Fig 6) (79). Subtle ill-defined en-

hancement following intravenous contrast material administration is seen in 15%–20% of oligodendrogliomas and is associated with higher-grade tumors (34,79,80). Calcification, vasogenic edema, and enhancement are less commonly noted in children with oligodendrogliomas than in adults (26). The tumor may not be visualized on CT images (34).

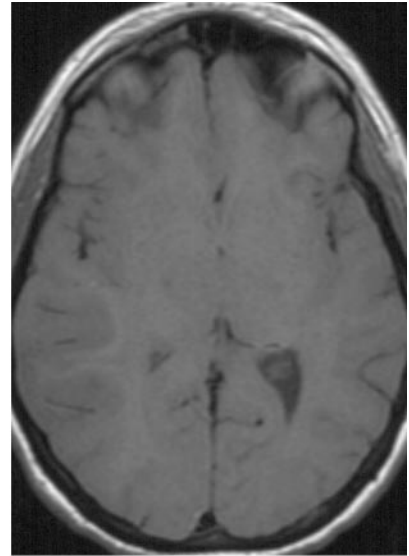
**Figures 5, 6.** (5) Oligodendroglioma. Axial CT image shows a heavily calcified mass (arrows) in the right frontal lobe without surrounding vasogenic edema. (6) Oligodendroglioma. (a) Axial CT image shows a peripheral, ill-defined, hypoattenuating mass (arrow) in the posterior portion of the right temporal lobe. (b) Axial T1-weighted MR image shows low signal intensity of the mass. (c) Axial T2-weighted MR image shows heterogeneous high signal intensity of the mass. (d) Coronal contrast-enhanced T1-weighted MR image shows no enhancement of the mass.



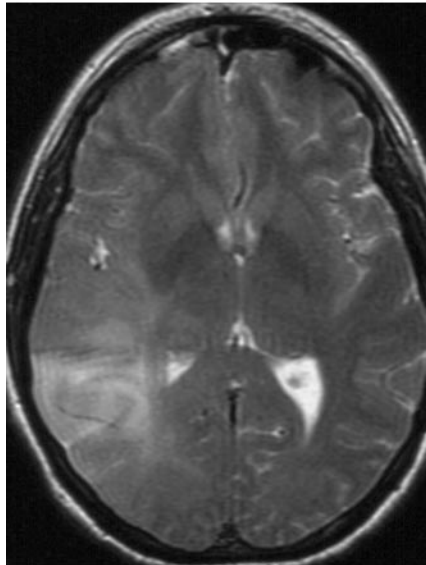
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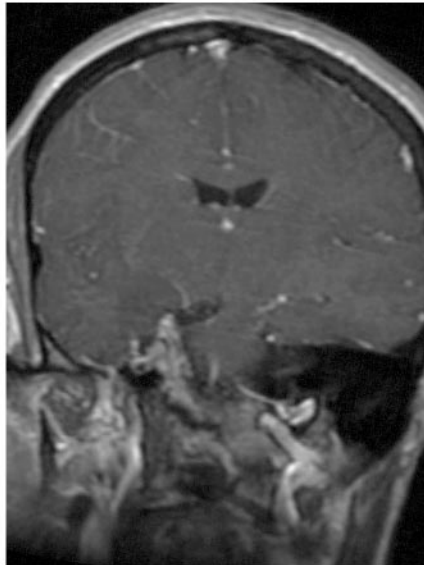
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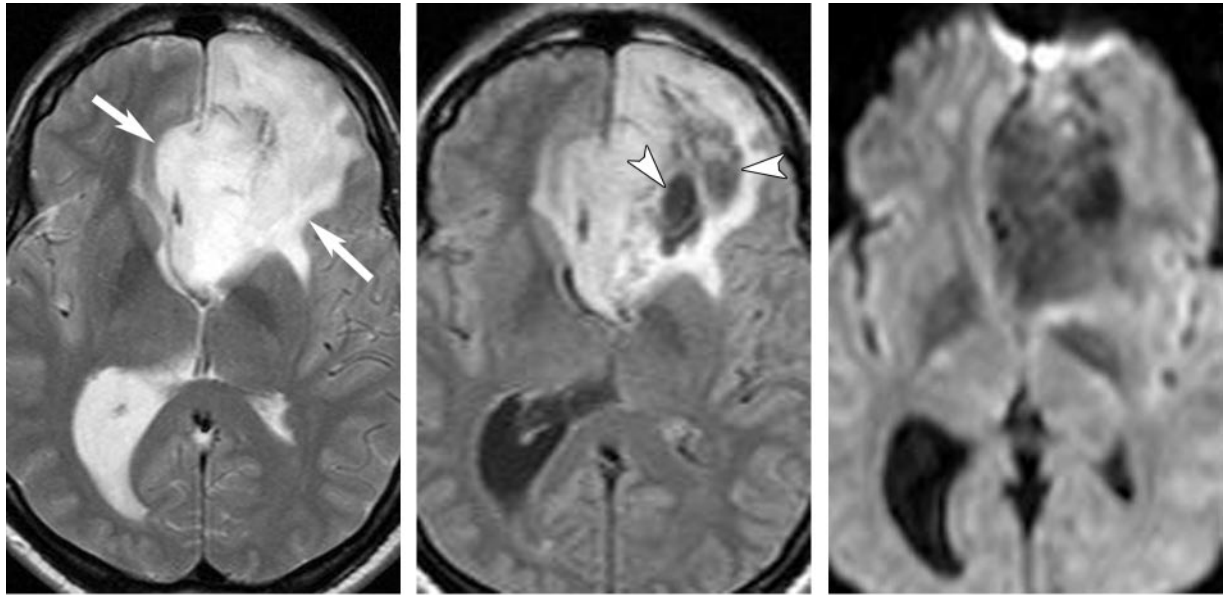
6c.



6d.

MR imaging is superior to CT in defining the full extent of tumor involvement (81). The tumor is usually hypointense compared to gray matter on T1-weighted images and hyperintense compared to gray matter on T2-weighted images (Figs 4, 6, 7) (79). Heterogeneity of this signal intensity is the rule. Less commonly, a large cyst-like pattern may be seen (82). Surrounding vasogenic edema is not common (79). On occasion,

frontal lobe tumors may extend through the corpus callosum to produce a “butterfly glioma” pattern. Advanced MR imaging with the apparent diffusion coefficient (ADC) shows a characteristic but not pathognomonic difference between low-grade and high-grade glial neoplasms. Lower ADC values, indicative of water restriction and



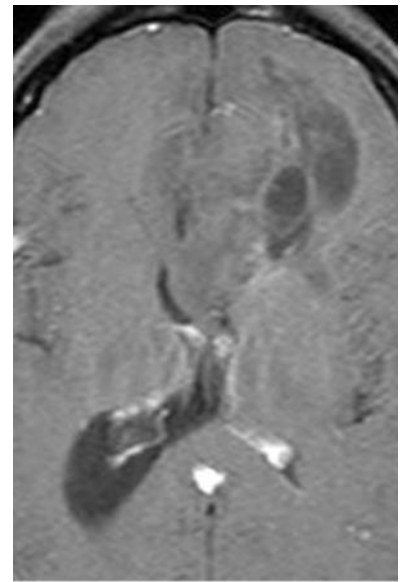
**Figure 7.** Oligodendroglioma. **(a)** Axial T2-weighted MR image shows a heterogeneous hyperintense mass (arrows) in the left frontal lobe with extension to the cortex and through the genu of the corpus callosum into the right frontal lobe. **(b)** Axial fluid-attenuated inversion-recovery MR image shows low signal intensity in more cystlike regions (arrowheads) of the mass. **(c)** Axial diffusion-weighted MR image shows low signal intensity of the mass, a finding that indicates absence of restricted water diffusion. **(d)** Axial contrast-enhanced T1-weighted MR image shows minimal enhancement of the mass.

likely reflective of lowered extracellular hyaluronic acid, are noted in high-grade tumors compared to the higher ADC values seen in low-grade tumors (Figs 4, 7) (83).

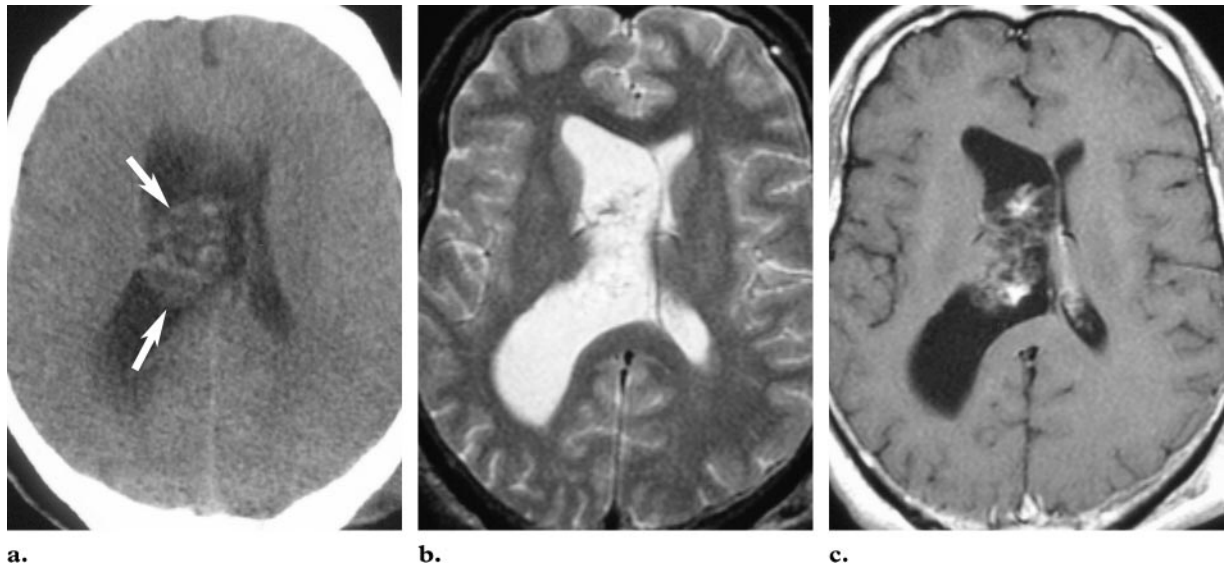
The pattern of contrast enhancement seen at CT is also noted at MR imaging. “Dot-like” lacy enhancement is commonly seen, but many tumors may not enhance at all (82). The presence or absence of enhancement has even been utilized to some extent in the grading of these neoplasms by Daumas-Duport and colleagues (10). While the presence of enhancement tends to be noted more commonly in more aggressive oligodendrogliomas, the reader is cautioned that this feature is not a fail-safe finding for that diagnosis. Con-

versely, the absence of enhancement does not inherently indicate a low-grade tumor. Histologic confirmation is always desired (84,85).

Evaluation with thallium 201 single photon emission CT (SPECT) reveals that the overall metabolic rate of oligodendrogliomas and mixed oligoastrocytomas correlates with the histologic



**d.**



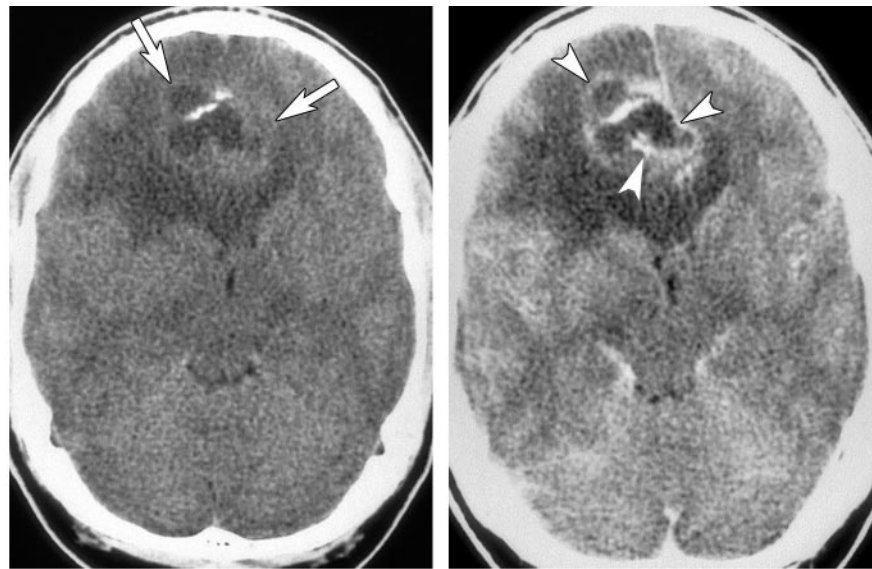
**Figure 8.** Intraventricular oligodendroglioma. (a) Axial CT image shows a heterogeneous mass (arrows) within the right lateral ventricle. (b) Axial T2-weighted MR image shows heterogeneous high signal intensity of the mass. (c) Axial contrast-enhanced T1-weighted MR image shows focal areas of enhancement in the mass. Findings at electron microscopy confirmed that the mass was an oligodendroglioma and not a central neurocytoma.

grade and the presence of contrast enhancement. In their study using the amino acid tracer carbon 11 L-methylmethionine for positron emission tomography (PET), Derlon et al (86) reported that all oligodendrogliomas were hypermetabolic compared to the more variable activity seen in low-grade astrocytomas. A follow-up study that used the same tracer showed highly significant differences between low-grade and high-grade oligodendrogliomas (87). They also noted that PET studies with fluorine 18 fluorodeoxyglucose recorded less variance between these types of tumors (87). Another study showed that many low-grade oligodendrogliomas, including those with allelic loss of 1p and 19q, contain hypermetabolic regions (88). Metabolic imaging is useful in identifying tissue regions of potentially greater interest based on their hypermetabolism, helping establish the need for open surgical resection instead of biopsy, and determining the presence of residual disease (87).

Tumors with 1p and 19q deletions have noteworthy imaging features. They are also more likely to have ill-defined margins on T1-weighted MR images and to have calcification (89). They

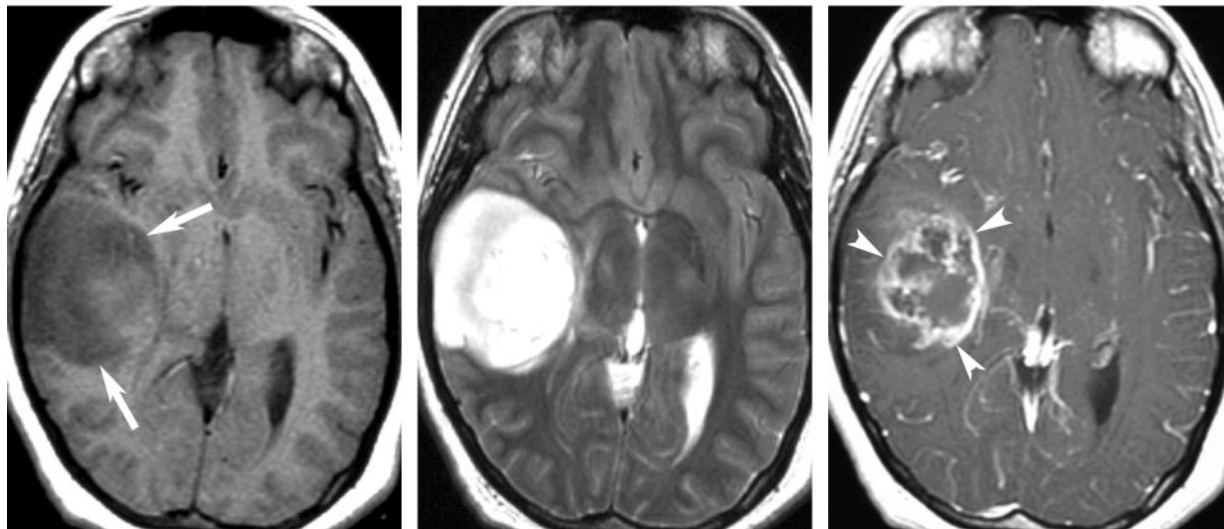
are more likely to be found in the frontal lobe and extend across the midline more often compared to tumors that lack these deletions, which are more common in the temporal lobe, insula, and midbrain (90).

Intraventricular oligodendrogliomas are rare (Fig 8). Only six (3%) of 208 oligodendrogliomas from the Norwegian Cancer Registry were located within the ventricular system (14), while up to 14 (8%) of 165 oligodendrogliomas involved the ventricular system in the series of Earnest et al (1). Reports in the literature from the 1980s and early 1990s of such lesions note that many of these tumors have different imaging characteristics compared to those oligodendrogliomas arising in the brain parenchyma (91–96). The lesions were usually hyperattenuating at CT compared to normal brain parenchyma. Almost all of the tumors enhanced on postcontrast images, and a tumor blush was seen at angiography in a higher percentage compared to the parenchymal oligodendrogliomas. Attachment to the ventricular



9a.

9b.



10a.

10b.

10c.

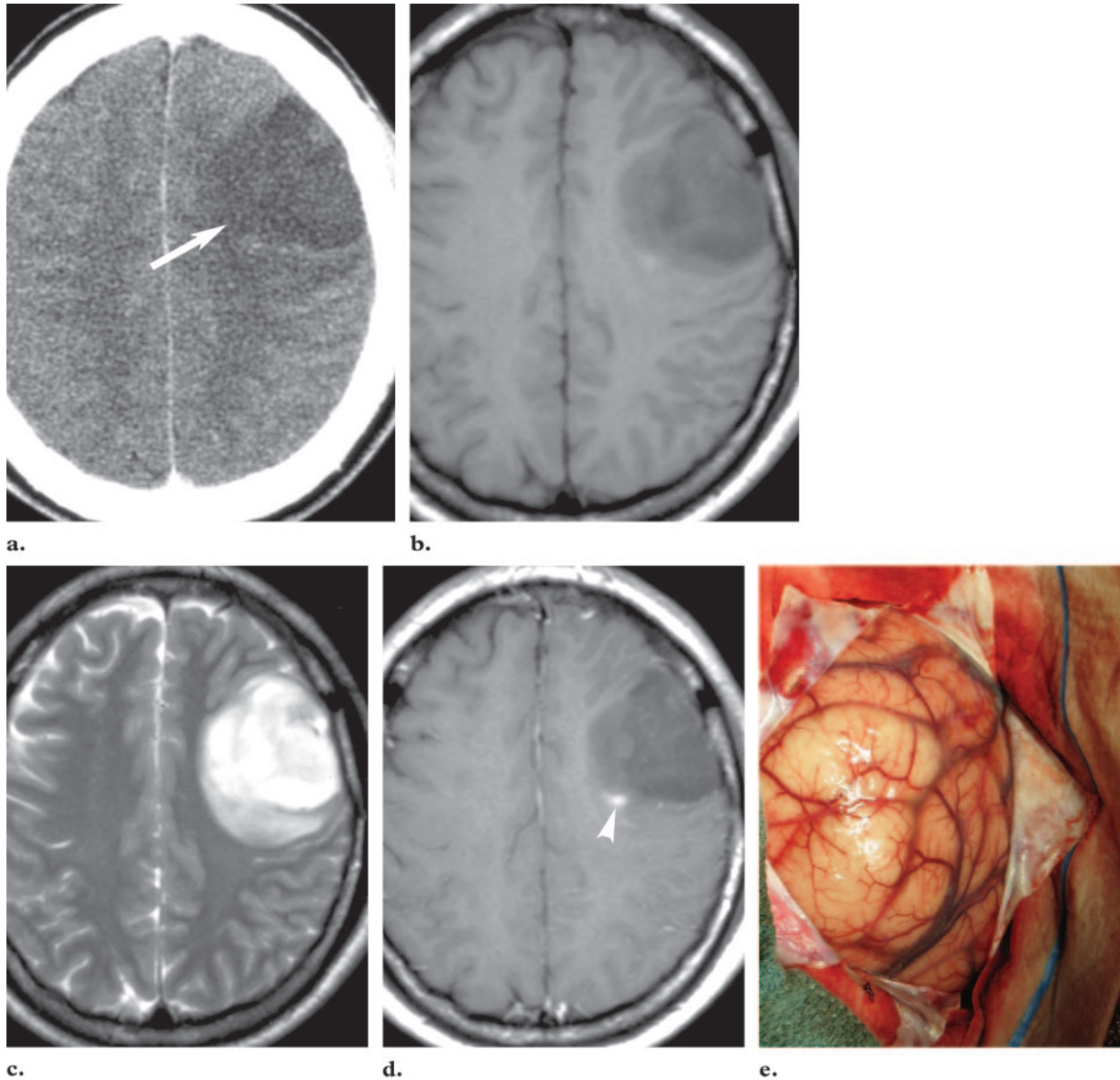
**Figures 9, 10.** (9) Anaplastic oligodendroglioma. (a) Axial CT image shows a heterogeneous mass with both cystlike and calcified components (arrows). Extension through the corpus callosum with involvement of both frontal lobes is seen. (b) Axial contrast-enhanced CT image shows ringlike enhancement of the cystlike portion (arrowheads). (10) Anaplastic oligodendroglioma. (a) Axial T1-weighted MR image shows a mass in the right temporal lobe (arrows) with both soft-tissue and cystlike components. (b) Axial T2-weighted MR image shows heterogeneity of the mass and minimal surrounding vasogenic edema. (c) Axial contrast-enhanced MR image shows irregular ringlike enhancement of the mass (arrowheads). This appearance mimics that of a glioblastoma multiforme.

wall, a site not known to harbor any oligodendroglial cells, was noted in many cases. Together, these findings raise the distinct possibility that some of these tumors were actually central neurocytomas, a tumor that bears a striking resemblance to oligodendrogliomas not only at cross-sectional imaging but also at histopathologic examination with its “fried-egg” appearance (97). Interestingly, Lee et al (82) reported just such an

occurrence in four tumors originally believed to be “intraventricular oligodendrogliomas” that were later reclassified as central neurocytomas following further analysis.

Diffuse involvement of the cisternal and subarachnoid spaces characterizes the imaging appearance of diffuse leptomeningeal oligodendroglioma (39,42,98). Meningeal calcification has been noted at CT in one case of primary leptomeningeal oligodendroglioma (39).

Reflecting the presence of necrosis, cystic degeneration, and hemorrhage at histopathologic



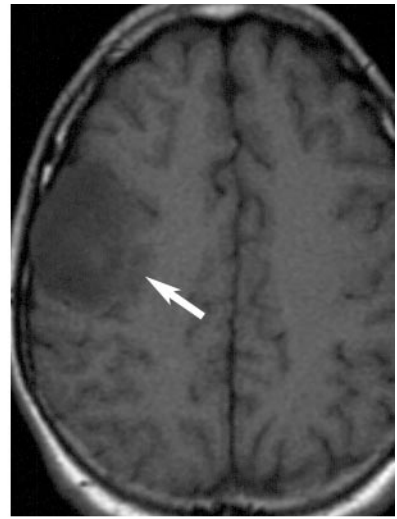
**Figure 11.** Oligoastrocytoma. (a) Axial CT image shows a hypoattenuating mass (arrow) in the left frontal lobe. (b) Axial T1-weighted MR image shows low signal intensity of the mass with mild exophytic extension beyond the normal cortical margin. (c) Axial T2-weighted MR image shows heterogeneous high signal intensity of the mass. (d) Axial contrast-enhanced MR image shows only a small focal region of enhancement (arrowhead) in the mass. (e) Intraoperative photograph shows the mass protruding beyond the normal cortical margin of the brain.

analysis, the usual imaging appearance of an anaplastic oligodendroglioma is more variable compared to that of an oligodendroglioma (69). On occasion, a ringlike contrast enhancement pattern may be seen and the overall appearance may mimic that classically associated with glioblastoma multiforme (Figs 9, 10) (17,69). While tumors with high mitochondrial activity accumulate technetium 99m methoxyisobutyl-isonitrile (MIBI), there is at least one report of a recurrent high-grade oligodendroglioma that was not detected in a SPECT study with this radiopharmaceutical (99). Perfusion imaging commonly shows

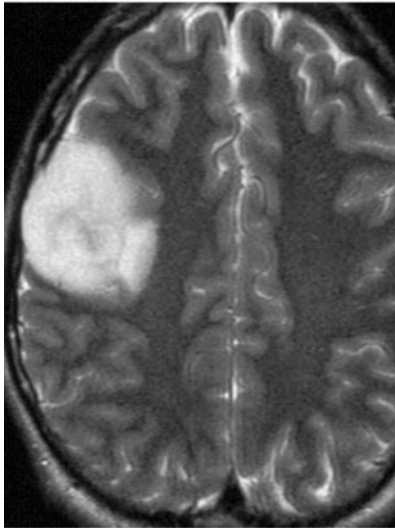
increased relative cerebral blood volume (rCBV) in high-grade glial tumors and is useful to assess their response to therapy (100).

There are no unique features at cross-sectional neuroimaging that allow distinction of a mixed oligoastrocytoma from an oligodendroglioma (Figs 11–14) (82). While calcification is not as common (14%) as seen in pure oligodendrogliomas, enhancement following intravenous contrast material administration (50%) is more common (58,79).

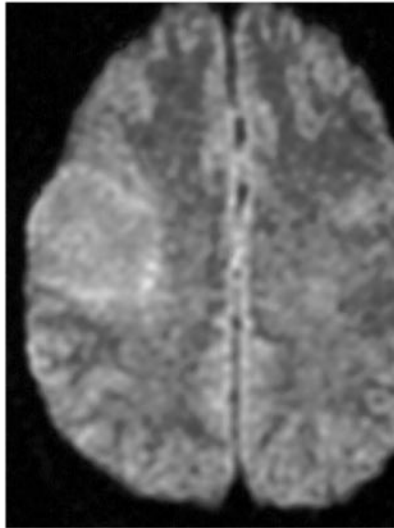
**Figure 12.** Oligoastrocytoma. **(a)** Axial T1-weighted MR image shows a hypointense mass (arrow) in the right frontal lobe. **(b)** Axial T2-weighted MR image shows heterogeneity of the mass with exophytic extension. **(c)** Axial diffusion-weighted MR image shows that the mass is predominantly isointense relative to the adjacent gray matter. **(d)** Axial contrast-enhanced T1-weighted MR image shows no enhancement of the mass.



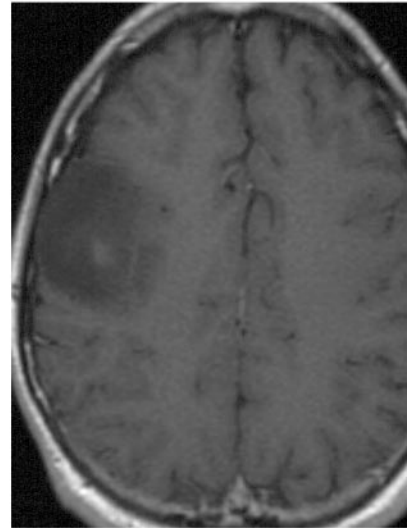
**a.**



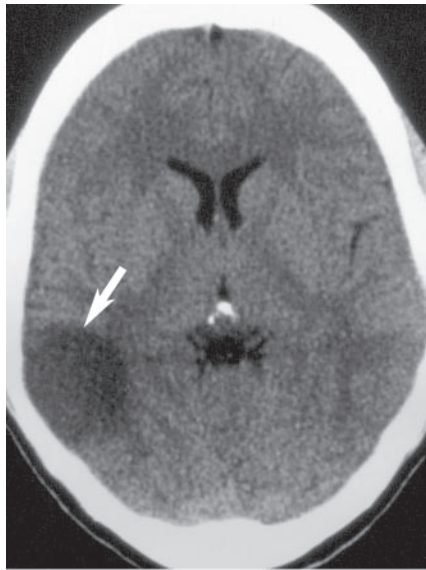
**b.**



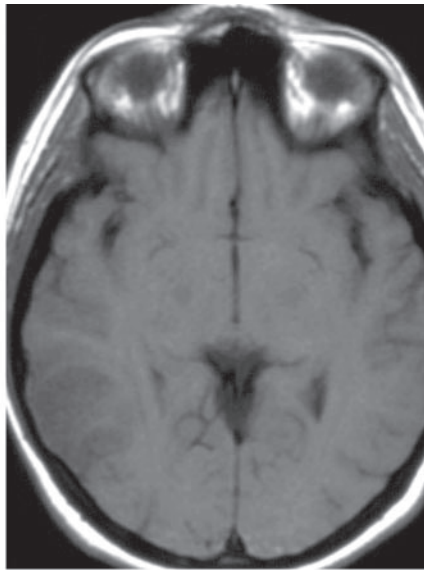
**c.**



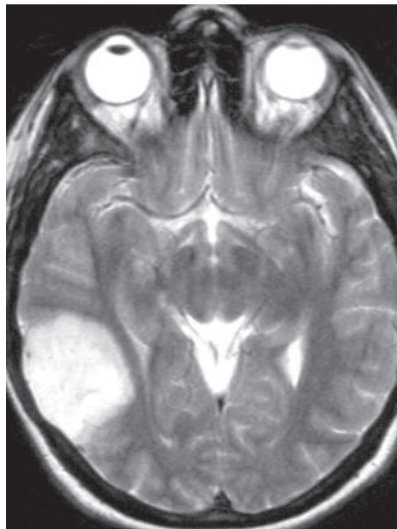
**d.**



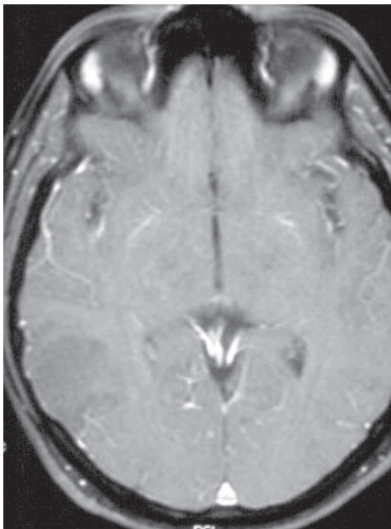
a.



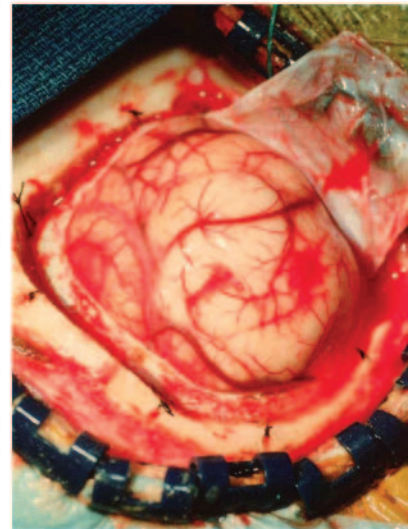
b.



c.

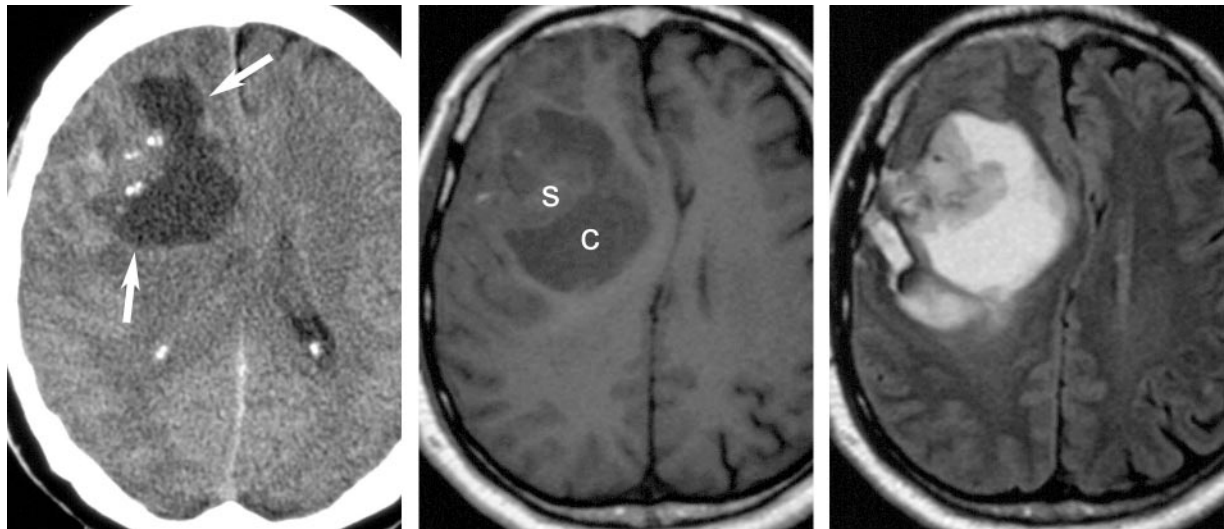


d.



e.

**Figure 13.** Anaplastic oligoastrocytoma. **(a)** Axial CT image shows a hypoattenuating mass (arrow) in the posterior portion of the right temporal lobe. The mass produces mild calvarial erosion. **(b)** Axial T1-weighted MR image shows low signal intensity of the mass. **(c)** Axial T2-weighted MR image shows mild heterogeneity of the mass. **(d)** Axial contrast-enhanced T1-weighted MR image shows no enhancement of the mass. **(e)** Intraoperative photograph shows exophytic extension of the mass beyond the normal cortical margin.



**Figure 14.** Anaplastic oligoastrocytoma. **(a)** Axial CT image shows a heterogeneous mass (arrows) with calcifications in the right frontal lobe. **(b)** Axial T1-weighted MR image shows heterogeneous low signal intensity of the mass, which has both soft-tissue (*s*) and cystlike (*c*) components. **(c)** Axial fluid-attenuated inversion-recovery MR image shows similar heterogeneity of the mass. **(d)** Axial contrast-enhanced T1-weighted MR image shows irregular ringlike enhancement of the mass and abnormal leptomeningeal enhancement.

### Therapy

Surgical resection is the main form of therapy for most patients with an oligodendroglial tumor, and gross total resection, provided it can be performed safely, is the goal (12,101,102). While reducing mass effect, this procedure also allows a reduction in the portal for radiation therapy, improves diagnostic accuracy by limiting sampling error, and is associated with increased survival (5,19,25,33,34,103–105). Patients who undergo gross total resection of their tumors have better survival compared to those who undergo only partial resection (25). However, because of its infiltrative nature, the tumor may frequently be poorly delineated from the normal brain parenchyma, making complete resection impossible (105).

Especially in younger patients who have undergone complete or near complete total resection of the tumor, most authorities recommend no further therapy until there is evidence of recurrence (63,106). This is primarily for two reasons. First, many patients with a WHO grade II oligodendroglioma will be disease-free for several years after surgery. Second, the postoperative use of radiation therapy has been shown to be only modestly

beneficial at best in sustaining a long progression-free duration and permanent deleterious side effects are common (5,18,25,33,35,68,105). While immediate postoperative radiation therapy is indicated for incompletely resected higher-grade oligodendrogliomas (68), its use for partially resected low-grade tumors is controversial (107).

Chemotherapy was not believed to be useful in the treatment of oligodendroglial tumors until 1988, when Cairncross and Macdonald (108) reported the astounding (and entirely unexpected) favorable chemotherapeutic responses of patients with recurrent anaplastic oligodendrogliomas following the use of a combination of procarbazine, lomustine, and vincristine (PCV). Numerous studies have since documented similar results with PCV therapy, with favorable responses seen in about 70% of patients and a median response duration being about 12–18

months (74,101,109–112). Other studies have also shown a favorable response in patients with both low-grade and recurrent oligodendrogliomas as well as oligoastrocytomas (74,109,111,113). More recently, another alkylating agent, temozolomide, has shown promise, although at a lower response rate compared to PCV, as an effective chemotherapeutic alternative (102,114). On the basis of these encouraging results, other chemotherapeutic agents are being investigated (12, 115). Most authorities now advocate giving chemotherapy as the preferred therapy of choice when recurrent disease is detected and reserving radiation therapy for disease that does not respond to chemotherapy (12,109,110,116). Speculative reasons explaining why oligodendroglial tumors but not astrocytic tumors respond to alkylating chemotherapeutic agents include presumed relative lack of reparative function in oligodendroglial tumors to correct DNA damage and activation of p53-mediated apoptosis caused by the chemotherapy (117).

The use of chemotherapy is especially remarkable when administered to patients whose tumors contain the 1p and 19q chromosomal deletions (69). Virtually all tumors with this genetic alteration respond to PCV chemotherapy, and its detection is now considered crucial in the complete evaluation of these tumors (12,68). It is likely that the 1p and 19q deletion is not the sole molecular pathway, as many other routes may be involved in the production of these tumors (70). On diffusion-weighted and perfusion images, tumors with these deletions demonstrate better chemosensitivity in focal areas of lower apparent diffusion coefficient (ADC) and higher relative cerebral blood volume (rCBV) (118).

### Recurrence and Metastasis

Despite the achievement of gross total resection, practically every patient ultimately develops recurrence of their disease, usually several years following resection and at the surgical site (18,63, 119,120). Malignant transformation of the recurrence to an anaplastic oligoastrocytoma or glioblastoma multiforme may occur (18,121).

Leptomeningeal seeding is variably reported in 1%–14% of cases, and the tendency of oligodendrogliomas to disseminate was noteworthy even to the earliest neurosurgeons and pathologists who encountered the disease (1,6,12,14,122). Diffuse spread throughout the subarachnoid and cisternal spaces (“oligodendrogliomatosis”) is rarely reported in patients with either oligodendroglioma or its anaplastic variant (123). Delayed

cerebrospinal fluid seeding many years after the original surgical resection has been reported (124). The detection of such spread is important as it may impact therapeutic options in a given patient (68). Metastatic involvement of the spinal cord itself has been reported (125–127).

Distant extraneural spread is rare, although it appears to be more common than is seen in other central nervous system tumors (14,128). Recently, the number of reports substantially increased, a trend suspected to be related to more aggressive chemotherapy directly leading to longer survival times (129). The skeletal system, lymph nodes, lung and pleura, and liver are the most commonly reported extraneural sites (14,128,130,131). Local recurrence and spread of anaplastic oligodendroglioma is more commonly noted in patients who have undergone multiple craniotomies, whereas distant metastasis is more commonly seen in patients who have received early radiation therapy and chemotherapy (128).

### Prognosis and Survival Rates

Although, as a general rule, the biologic behavior of oligodendrogliomas is less aggressive compared to that of astrocytomas of similar histologic grade, the overall prognosis for patients with a WHO grade II oligodendroglioma is still guarded (63). The median postoperative survival period for patients with oligodendrogliomas ranges from 3 to 17 years (6,19,25,34,35). Five-year survival rates have ranged from 39% to 75%, while 10-year survival rates range from 19% to 59% (8). Occasional long-term survivors, up to 40 years and following only surgical resection, have been reported (132–134). However, practically all patients ultimately die from their disease (18,68).

Oligodendrogliomas with 1p and 19q deletions appear to have a better biologic behavior and are more likely to respond to PCV chemotherapy. Patients with these tumors have a more favorable clinical course (68). Better prognosis and a more favorable response to chemotherapy are associated with an initial presentation of seizures, younger age at time of surgical resection, frontal lobe location, higher postoperative performance score, absence of enhancement at CT or MR imaging, gross total resection, and use of radiation therapy after partial resection (8,10,33,104,105, 111,135).

Older age at the time of diagnosis is associated with more aggressive biologic behavior and worsened prognosis (5,6,19,33,34,104,105,136,137). In one illustrative study, when patients received a diagnosis before the age of 30 years, the overall 5-year survival rate was 75%, while it was only 21% for those older than 50 years when the diagnosis was made (136). In addition, the presence of a neurologic deficit has been reported to correlate with a worsened prognosis (10,19,137). More centrally located tumors of the brain are affiliated with significantly poorer prognosis in children compared to those that arise in the cerebral hemispheres (138). One report claimed a worsened prognosis for patients who had type A blood (14).

For patients with anaplastic oligodendroglioma, studies of patients treated with surgery alone or with postoperative radiation therapy reported a median survival time varying from 10 months to 3.9 years with a 5-year survival rate of 23%–41% and a 10-year survival rate of 20% (5,25). More recent studies have shown improved response to PCV chemotherapy in tumors that lack contrast enhancement at cross-sectional neuroimaging and when these tumors contain the allelic loss of 1p and 19q (69). In contrast, tumors that contain *CDKN2A* deletions, demonstrate amplification of epidermal growth factor, and have chromosome 10q deletions respond poorly to chemotherapy and carry a worsened prognosis with shorter survival times (69,70). Although these molecular markers are helpful, it is difficult to predict how an individual patient will respond to therapy, as oligodendrogliomas still have the capacity to undergo malignant transformation (12). Regardless, the current lengths of survival for patients with these tumors are substantially higher (5-year survival rates of 57%–73% and 10-year survival rates of 38%–63%) compared to those of just 10 years earlier (12,136,139,140).

For patients with mixed oligoastrocytoma, the median survival time is about 6 years with a 5-year survival rate of 58% and 10-year survival rate of 32% (58). As with oligodendroglioma, longer survival times are noted when the tumor is resected in younger patients (<37 years), when a gross total resection is achieved, and with the use of postoperative radiation therapy (58).

For patients with anaplastic oligoastrocytoma, the median survival time is about 3 years with a 5-year survival rate of 36% and 10-year survival rate of 9% (58). In general, the prognosis is worse

for patients with these tumors compared to those with anaplastic oligodendroglioma but better than for those with anaplastic astrocytoma (76).

## Conclusions

Although considered a rare brain tumor in the past, oligodendroglioma may be much more common than previously believed on the basis of new genotyping studies, which have diagnostic implications for those who perform neuroimaging and therapeutic consequences for patients with the disease. Tumors that contain deletions of genetic material on 1p and 19q are found more commonly in the frontal lobe, frequently with bilateral extension, are more likely to have calcification, and are more likely to have ill-defined margins. Such tumors are also more likely to respond to chemotherapy. Postoperative neuroimaging assessment performed with the full spectrum of advanced imaging modalities is expected to play an even more crucial role in the future as more is learned about these intriguing tumors.

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