From the Archives of the AFIP

Glioblastoma Multiforme: Radiologic-Pathologic Correlation

John H. Rees, MD • James G. Smirniotopoulos, MD • Robert V. Jones, COL, MC, USA • Kondi Wong, Maj, MC, USAFR

Astrocytic tumors are divided into two basic categories: circumscribed (grade I) or diffuse (grades II-IV). All diffuse astrocytomas tend to progress to grade IV astrocytoma, which is synonymous with glioblastoma multiforme (GBM). GBMs are characterized by marked neovascularity, increased mitosis, greater degree of cellularity and nuclear pleomorphism, and microscopic evidence of necrosis. Several genetic abnormalities have been associated with the development of GBM: In some cases, the abnormality is inherited (eg, Li-Fraumeni syndrome); in others, genetic alteration appears to result from mutation into an oncogene or deterioration of the tumor-suppressor gene p53. A common, distinctive histopathologic feature of GBM is pseudopalisading. The most common imaging appearance of GBM is a large heterogeneous mass in the supratentorial white matter that exerts considerable mass effect. Less frequently, GBM can occur near the dura mater or in the corpus callosum, posterior fossa, and spinal cord. GBM typically contains central areas of necrosis, has thick irregular walls, and is surrounded by extensive, vasogenic edema, but the tumor may also have thin round walls, scant edema, or a cystic appearance with a mural nodule. GBMs most commonly metastasize from their original location by direct extension along white matter tracts; however, cerebrospinal fluid, subependymal, and hematogenous spread also can occur. Given the rapidly growing body of knowledge about GBM, the radiologist’s role is more important than ever in accurate and timely diagnosis.

Abbreviations: AFIP = Armed Forces Institute of Pathology, GBM = glioblastoma multiforme, PET = positron emission tomography, WHO = World Health Organization

Index terms: Brain neoplasms, 10.3634 • Brain neoplasms, diagnosis, 10.365

Radiographics 1996; 16:1413-1438

1 From the Departments of Radiologic Pathology (J.H.R., J.G.S.) and Neuropathology (R.V.J., K.W.), Armed Forces Institute of Pathology, Washington, DC; the Division of Diagnostic and Interventional Neuroradiology, Department of Radiology, University of Maryland Medical System, 22 S Greene St, Baltimore, MD 21201 (J.H.R.); and the Department of Radiology, Uniformed Services University of Health Sciences, Bethesda, Md (J.G.S.). Received July 17, 1996; revision requested August 12 and received August 30; accepted September 3. Address reprint requests to J.H.R.

The opinions and assertions contained herein are the private views of the authors and are not to be construed as official nor as reflecting the views of the Departments of the Army or Air Force.

1 RSNA, 1996
INTRODUCTION
Primary tumors of the central nervous system are the fifth most common primary neoplasm, with an average incidence of five to 10 cases per 100,000 population per year (1). Approximately 50% of these tumors are astrocytomas, of which 50% are classified as glioblastoma multiforme (GBM) (2). Although it represents only 1%-2% of all malignancies, GBM is diagnosed in 15,000-20,000 patients per year, most of whom will die from their disease (3). Several recent studies have suggested that there is an increasing prevalence of primary brain neoplasms of all types, even allowing for such factors as earlier diagnosis because of advances in imaging technology (4), and this realization only serves to heighten interest in this devastating class of tumors. Quite often, the diagnosis of GBM is initially made or suggested on the basis of an imaging study, and it is therefore important for all radiologists to be aware of the many clinical and radiologic manifestations of this malignant tumor.

In this article, we demonstrate the wide spectrum of radiologic and pathologic findings in glioblastomas and discuss the latest information on the genetic basis of malignant gliomatous transformation and possible future therapeutic interventions. These observations are based on an extensive survey of the current literature and our own experience with more than 400 cases compiled over 40 years in the radiologic archives of the Armed Forces Institute of Pathology (AFIP).

CLINICAL PRESENTATION
Although GBM has been reported in patients of all age groups, it is most common in late adulthood, with a peak prevalence between 65 and 75 years of age (5). There is a very slight male predilection for GBM (1.6:1) (6), and it occurs more commonly in whites than in persons of African, Asian, or Latin American descent (7).

The clinical presentation of a patient with a GBM varies depending on the location of the tumor and the structures it affects, either directly, through destruction or invasion, or indirectly, due to mass effect and edema. Patients may present with localizing signs, such as focal neurologic deficits, seizures, or stroke-like symptoms, or nonlocalizing symptoms, such as severe headaches, if the areas of the brain that are affected are “noneloquent.” Temporal lobe tumors may manifest with non-motor seizure activity (eg, olfactory hallucinations) or headache, and frontal lobe tumors may manifest with subtle behavioral changes.

GBM can involve the motor cortex, resulting in generalized tonic-clonic seizures. Occasionally, Jacksonian seizures may occur. These are focal motor seizures that begin with localized tonic-clonic activity of a specific body part such as a finger or a lip, then progress to produce tonic-clonic movements of other muscle groups on the same side of the body. This progression is referred to as the Jacksonian march. There is substantial evidence that if a patient with a GBM presents with seizures, particularly with seizures for more than 18 months, the clinical prognosis is somewhat better than for patients with other presentations (8). The reason for this is not known, but these cases may represent the gradual development of a GBM in a more benign glioma (9).

Uncommonly, GBM is detected as an incidental finding, for example, on computed tomographic (CT) scans of the head obtained because of patient trauma. In this case, the question arises whether the tumor is truly incidental or perhaps precipitated the accidental or traumatic event.

Dissemination of GBM occurs most commonly by local extension, and spread through cerebrospinal fluid is seen in less than 2% of patients (10). Hematogenous metastases are even less common and usually occur in patients who have undergone surgery. The greatest morbidity and mortality from GBM is caused by local growth and direct extension from the site of origin within the brain.

HISTORICAL PERSPECTIVE
In a brief footnote to their classic work, The Classification of Tumours of the Glioma Group on a Histogenetic Basis with a Correlated Study of Prognosis (1926), Harvey Cushing and Percival Bailey suggested that the term glioblastoma multiforme should replace previous terms such as spongioblastoma unipolare.
and spongioblastoma multipolare, which had been used to describe the most common type of primary malignant brain tumor known at that time (11). The name GBM was initially intended by them to convey two basic facts about this malignancy: (a) It arose from the most primitive precursors of the supporting or stromal cell populations (glioblasts), and (b) its gross morphology was complex and highly variable (multiforme). Although their morphologic observations are still regarded as correct, current neuropathologic theory is that GBMs arise from the progressive dedifferentiation of mature cells, rather than from persistent embryonic cells or glioblasts. Frequently, this transformation occurs within a preexisting low-grade astrocytoma (12). Both genetic and histopathologic data support the concept of a stepwise increase in degree of malignancy from low-grade glioma to high-grade glioma, culminating in the GBM (13–15). Current research indicates that different genetic lesions are responsible for primary or de novo GBM, compared with secondary GBM that arises in a preexisting glioma (16).

Although the term glioblastoma multiforme is to some extent a misnomer, since the tumor does not arise from or contain glioblasts, its usage is too firmly rooted in modern clinical and neurosurgical practice to allow for correction. This usage may change if further advances in neuropathology give rise to more specific subcategories within this tumor group.

■ ETIOLOGY AND GENETICS

Major advances in the field of molecular biology have led to identification of a number of genetic abnormalities that predispose to the development of GBM. Although only a tiny fraction of primary central nervous system neoplasms occur in the setting of an inheritable disorder or syndrome, substantial evidence of genetic factors in their development has existed for some time. Two well-known examples are Turcot syndrome (colonic adenomatous polyposis, medulloblastoma, and malignant glioma) (17,18) and neurofibromatosis type 1 (increased prevalence of many tumors, including all grades of glioma and breast cancer) (19).

Another less well-known example is the Li-Fraumeni syndrome of familial neoplasms in various organs, including breast, bone, blood, soft tissues, and brain (20).

The term oncogene is used to describe genes that encode for proteins that directly promote neoplastic transformation and stimulate tumor growth. These abnormal genes may occur from a sporadic mutation or may be inherited as a germline mutation. Tumor-suppressor genes (also referred to as “wild type” genes), on the other hand, are normal genes present in most people. They encode for proteins that control the growth of normal tissues and prevent neoplastic growth and transformation. Either the absence of a tumor-suppressor gene or the mutation into an oncogene can lead to increased prevalence of neoplasms in various body tissues. Both oncogenes and malfunctioning tumor-suppressor genes have been identified in patients with GBMs.

Perhaps the best known tumor-suppressor gene is p53, which is located on the short arm of chromosome 17. An abnormal p53 gene has been implicated in a wide variety of tumors throughout the body, such as in the Li-Fraumeni syndrome, and studies have shown that at least 40% of GBMs have this mutation (21,22). Because an abnormal p53 gene seems to be more common in higher-grade astrocytomas, it is thought to contribute to the natural progression of low-grade to higher-grade astrocytomas (23). There is also evidence that it plays a role in the initial neoplastic transformation of a normal glial cell into an astrocytoma. In vitro studies have demonstrated partial growth stoppage in GBM after insertion of a normal p53 gene into GBM cells (24) and after direct administration of normal p53 protein to GBM cell colonies.

Many other tumor-suppressor gene mutations and oncogenes have been identified and are being actively studied. Because of the wide genotypic and phenotypic variation found in GBM, most researchers support a multistep
theory of tumorigenesis, in which many areas of genetic abnormality coexist simultaneously. These genetic lesions may be caused by inherited or acquired mutations and progressively disrupt the natural cellular balance between the positive and negative regulators of cellular growth and differentiation (25). It has been clearly documented that there is a direct relationship between the number and degree of detectable genetic abnormalities and the type and grade of the glioma. Simple astrocytomas (World Health Organization [WHO] grade II) may show no demonstrable karyotypic abnormalities, whereas anaplastic astrocytomas (WHO grade III) display variable genetic damage. GBMs (WHO grade IV) that have been karyotyped invariably show multiple loci of genetic abnormality and chromosomal derangement. One specific pathway for the development of GBM involves mutation of p53 at the astrocytoma stage; loss of tumor-suppressor genes on chromosomes 9, 13, or 19 to produce an anaplastic astrocytoma; and subsequent loss of tumor-suppressor genes on chromosome 10 in the transformation to a GBM (26). Although not as well studied as p53 mutation, allelic loss from chromosome 10 appears to be the most common genetic lesion in GBM and is found in up to 80% of specimens (27). Unlike p53 mutation, chromosome 10 damage does not appear to be common in other tumors in the body nor in lower grades of glioma, a finding that suggests chromosome 10 damage may be specific for GBM.

Current research suggests that primary GBM, which arises de novo, may have a genetic basis different from that of secondary GBM, which arises within a preexisting lower grade glioma (16). The overexpression of epidermal growth factor receptor appears to occur in the absence of p53 mutations in 90% of GBMs that are clinically considered likely to be primary. The possibility that these less common primary GBMs may arise through a mutation of the epidermal growth factor receptor represents an intriguing hypothesis but warrants further investigation.

How do these areas of genetic alteration occur? Some are inherited, such as in the Li-Fraumeni syndrome, in which abnormality in the p53 gene is inherited through a germline mutation. Others may be related to environmental mutagens such as radiation and certain chemical substances, such as vinyl chlorides. There is evidence suggesting that low-grade astrocytomas in children that were irradiated have a slightly higher prevalence of undergoing malignant transformation than nonirradiated tumors (28, 29). The increased prevalence of multifocal gliomas in patients who have previously been treated for acute lymphocytic leukemia suggests that chemotherapeutic agents, in particular intrathecal methotrexate, may have a synergistic effect with radiation in the generation of these tumors (30). Other potential environmental factors that have been suggested but not substantiated include proximity to electromagnetic fields generated by high-power lines.

The overwhelming majority of patients with GBMs have no history of irradiation or specific toxic exposure. Given the increased prevalence of GBM with age, it seems plausible that genetic injuries occur all the time for many reasons and that normal repair mechanisms may not be able to keep up with the ongoing deterioration of genes. Thus, genetic insults gradually accumulate, which in turn causes the progressive neoplastic transformation of normal glial cell lines into low-grade glioma and subsequently GBM.

**PATHOLOGIC CHARACTERISTICS**

Over the years, numerous attempts have been made to grade astrocytomas in a manner that correlates accurately and reproducibly with biologic behavior and aggressivity. Kernohan and
Sayre in the first series AFIP fascicle of 1952 (31) advocated a four-tiered grading system, which is still commonly referenced. Their scale was based simply on histologic features and unified many different descriptive names for astrocytic tumors into one continuum that correlated with patient outcome and survival time. Since then, numerous revisions have been made as more information about the clinical behavior of these tumors has been gathered and as neuropathologic techniques have increased in sophistication. In the modern era, widespread use of immunohistochemical staining—wherein antibodies to certain molecular components are attached to chromogenic (color-producing) materials—has allowed much greater uniformity and specificity in the diagnosis and classification of neoplasms.

The WHO has pioneered the effort to arrive at reproducible, uniform, international standards for classification and grading of these relatively common neoplasms. This effort culminated in the 1993 publication of the WHO II system (32). Within this all-inclusive classification scheme, WHO II incorporates a four-tiered grading system that applies to astrocytomas as well as other central nervous system neoplasms. This scale combines histopathologic criteria with clinical and prognostic information about biologic behavior and correlates only partially with purely histologic features of tumors (Table). The WHO II system recognizes distinct tumor subtypes, both within astrocytomas and within other tumor groups, which may exhibit distinct clinical and histopathologic features.

Astrocytic tumors are divided into two basic categories: circumscribed (grade I) or diffuse (grades II, III, and IV). Grade I tumors, such as pilocytic astrocytoma and subependymal giant cell astrocytoma, are generally well circumscribed and have low rates of recurrence after surgical excision. In addition, grade I tumors do not share the inherent tendencies of other gliomas to progress to tumors of higher grade. Within the diffuse astrocytomas, the specific
Figure 1. Typical GBM in the right frontotemporal region. (a) Axial contrast material-enhanced T1-weighted magnetic resonance (MR) image demonstrates a mass with irregular ring enhancement, a large area of central necrosis, perilesional edema, and early subfalcine herniation. (b) Photograph shows a gross pathologic specimen of a frontotemporal GBM. (c) Photomicrograph (original magnification, ×40; hematoxylin-eosin stain) of a typical GBM shows a ring of viable tumor cells (straight arrows) bordering on areas of necrosis (arrowheads), referred to as pseudopalisading. Note the extensive neovascularity (curved arrows).

criteria differentiate between the less biologically aggressive forms (grades II and III) and GBM (grade IV). Regardless of their grade at the time of diagnosis, all diffuse astrocytomas tend to progress to GBM (synonymous with grade IV). Criteria used to distinguish grade IV lesions include marked neovascularity, variable mitotic activity, increased cellularity, nuclear pleomorphism, and microscopic evidence of necrosis. One common and distinctive histopathologic feature of GBM is pseudopalisading (Fig 1), in which areas of viable neoplastic cells form an irregular border surrounding areas of necrotic debris. This feature is indicative of the uncontrolled growth within the tumor.

An important concept in understanding the pathologic characteristics of high-grade astrocytomas is that a single infiltrative astrocytoma (ie, grades II–IV) frequently contains multiple
Another important consequence of the histologic variations seen within infiltrative astrocytomas is the lack of correlation between the radiologic or even the gross pathologic margin of the tumor and the true margins of the area of neoplastic infiltration. An astrocytoma is seen on radiologic images because it produces significant mass effect, edema, necrosis, or hemorrhage. These imaging features correlate well with the histopathologic changes seen in higher-grade tumors, such as rapid cell growth leading to hypercellularity and neovascularity. Studies of tumor angiogenesis, which is another area of active research, have shown that the tumor cells secrete various substances, including vascular endothelial growth factor (33,34) and renin (35), which induce the rapid growth of new blood vessels. These new tumor-induced vascular channels are structurally abnormal and to varying degrees lack the normal blood-brain barrier. This characteristic leads to transudation of fluids and protein into the extracellular space that may be detected radiologically as vasogenic edema. MR imaging in particular is exquisitely sensitive to abnormal or disproportionate amounts of tissue water, both intra- or extracellular (Fig 2). Neither edema nor enhancement, however, truly demarcate the histologic margins of these tumors. Immediately adjacent to radiologically abnormal areas, there may be areas of low-grade astrocytoma and zones of infiltration by small numbers of high-grade tumor cells that do not cause significant mass effect and do not have abnormal vessels that can cause edema and thus are not detectable on MR images. Thus, even when all radiologically visible portions of the tumor have been excised, the surgical margins may not be “clean,” and further neoplastic growth can (and usually does) occur in the adjacent brain, leading from microscopic residual to gross recurrence (36).

Several distinct histologic variants within the grade IV astrocytomas or GBMs have been described, including the giant cell GBM, previously called the monstroucellular sarcoma, and
Figure 3. Four histologic variants of GBM. (a) Photomicrograph (original magnification, ×100; hematoxylin-eosin stain) of a giant cell GBM, previously known as monstrocellular sarcoma, demonstrates a single, large, multinucleated giant cell with abundant clear cytoplasm (arrows). (b) Photomicrograph (original magnification, ×40; hematoxylin-eosin stain) of a small cell GBM demonstrates large numbers of small uniform cells with scant cytoplasm. Note the pseudopalisading (curved arrows) and extensive neovascularity (straight arrows). (c) Photomicrograph (original magnification, ×40; hematoxylin-eosin stain) of a gliosarcoma shows a predominance of elongated spindle cells. (d) Photomicrograph (original magnification, ×40; hematoxylin-eosin stain) of a GBM with chondroid metaplasia (arrows).

the small cell GBM, which is relatively less common (Fig 3). Some GBMs contain a high proportion of malignant mesenchymal cells and are termed gliosarcomas or Feigin tumors. Certain histologic features of these tumors, such as the tendency for these sarcomatous areas to be perivascular, have given rise to the theory that the sarcoma component arises within areas of endothelial proliferation in the malignant glioma, perhaps directly from the walls of tumor vessels. Rarely, an intraaxial tumor is seen that consists almost entirely of these sarcomatous elements and is called a fibrosarcoma of the central nervous system. Although the histogenesis has not been proved, fibrosarcoma of the cen-
tral nervous system may represent an unusual outcome of gliosarcomatous degeneration. In addition, GBM may exhibit areas of chondroid or osseous metaplasia. Despite histologic variations, the prognosis and response to various treatment modalities are virtually the same for all grade IV tumors; therefore, these latter histologic features do not alter prognosis and are primarily for descriptive purposes. Whether these variations will come to be considered as distinct subtypes or possibly even distinct entities unto themselves remains to be seen.

- **RADIOLOGIC-PATHOLOGIC CORRELATION**

As the name implies, GBMs are notorious for a wide variety of appearances, both by location and by feature. However, the single most important unifying characteristic, recognized both at radiologic and gross pathologic examination, is the presence of hemorrhage or necrosis. The primary cellular component of the tumor is frequently of low attenuation on unenhanced CT scans and low signal intensity on T1-weighted MR images, primarily because of excess water in both the intra- and extracellular compartments. The presence of hemorrhage and necrosis bordering on areas of viable neoplastic tissue, however, frequently creates a mixed or heterogeneous pattern, which is clearly demonstrated on gadolinium-enhanced MR images (Fig 4). This heterogeneity may be caused by blood products in various stages of liquidity and oxidation or by complex fluid collections containing water with various concentrations of proteinaceous debris.

In the following subsections, we present many of the more classic appearances of these tumors and also some of their less common manifestations. Some of the variations depicted may also be seen in the lower grades of diffuse astrocytoma, and thus the only differentiating radiologic feature may be the presence of hemorrhage or necrosis.

- **Hemispheric GBM**

The most common imaging appearance of GBM is a large mass located in the supratentorial white matter, usually in the centrum semiovale. The GBM is typically heterogeneous, with central areas of necrosis surrounded by thick irregular walls of solid, living, neoplastic tissue (Fig 1). The gross tumor is surrounded by extensive, perilesional, vasogenic edema ("fingers of edema") and usually exerts considerable mass effect. The imaging appearance in these cases correlates well with the gross pathologic findings, and the correct diagnosis can usually be suggested on the basis of imaging features. Additional diagnostic considerations for this imaging appearance (although they are less likely) include solitary metastasis, tumefactive demyelinating lesion ("singular sclerosis"), and atypical abscess.

Before the availability of cross-sectional imaging, angiography and pneumoencephalography were more widely performed in the work-up of these patients. Nowadays, findings from angiograms can be correlated with those from MR images. On angiograms, prominent, wildly irregular neovascularity, often with early draining...
PET images of a patient with a left parietal GBM shows (clockwise from top left) increased cerebral blood flow, decreased oxygen extraction ratio, and increased cerebral blood volume in the region of the tumor.

Some helpful features that may suggest abscess are the presence of multiple lesions (particularly if centered at the border between gray and white matter) and a clinical history of altered...
immune status, pulmonary arteriovenous malformation or other right-to-left shunt, foreign travel, or high-risk behavior such as intravenous drug abuse. Differentiation from a low-grade cystic astrocytoma may be aided by considerations such as the patient’s age and location of the lesion. Usually, despite atypical imaging features, the pathologic analysis is very clear-cut, although in rare cases reactive gliosis surrounding an abscess has been mistaken for a low-grade glioma.
Figure 9. Peripheral GBM. (a) Coronal gadolinium-enhanced T1-weighted image shows a broad-based, densely enhancing mass with surrounding edema. (b, c) Coronal section (b) and enlarged view (c) of a gross pathologic specimen from a similar case.

Although most GBMs arise in the deep white matter, these tumors are by no means limited to these regions and may be seen in peripheral locations (Figs 9, 10), potentially resembling a dural-based process. Differential diagnosis in such a case could include atypical meningioma, hemangiopericytoma, dural metastasis, or another dural-based process.

Distinctly uncommon is a GBM that appears as a smooth-walled cyst with a mural nodule (Fig 11). This "cyst with a nodule" morphology is more suggestive of benign lesions, such as pilocytic astrocytoma, ganglioglioma, or pleomorphic xanthoastrocytoma. These largely circumscribed lesions usually occur in children (pilocytic astrocytoma) and tend to occur in specific locations such as the cerebellum or optic tracts, or they are superficially located in children and young adults (pleomorphic xanthoastrocytoma). Hemangioblastomas may also resemble a cyst with a mural nodule; however, these lesions are seen mainly in the posterior fossa and spinal cord.

A potential pitfall is the GBM that manifests primarily as a large intraparenchymal hemorrhage. Because vasogenic edema takes time to spread, any acute hemorrhage with evidence of extensive or distant edema should be suspected of being a neoplasm. In these cases, additional radiologic study with use of contrast material will usually demonstrate some areas of solid enhancing tissue, and biopsy would be recommended for definitive diagnosis. Differential diagnosis for a large intraparenchymal hemorrhage would include a hypertensive hemorrhage, vascular malformation, hemorrhagic metastasis, or hemorrhagic primary neoplasm (Fig 12). Other considerations such as amyloid angiopathy or traumatic hemorrhage are considered less likely on the basis of the imaging appearance.
Figure 10. Peripheral GBM. Intraoperative photograph shows a large fungating mass at the pial surface with evidence of focal hemorrhage.

Figure 11. GBM in the left temporal lobe in a 64-year-old woman. Axial gadolinium-enhanced T1-weighted MR image shows a cystic mass with a mural nodule, an extremely unusual appearance for a GBM. Differential diagnosis could include pilocytic astrocytoma, ganglioglioma, and pleomorphic xanthoastrocytoma, particularly if the patient were younger.

Figure 12. (a) Axial unenhanced CT scan shows a large intracerebral hematoma, consistent with a hypertensive hemorrhage originating in the left basal ganglia. Diagnosis at autopsy was GBM. (b) Sagittal T1-weighted image of a 12-year-old boy demonstrates a mass with an hematocrit effect, or fluid-fluid level, consistent with layering blood products. This case was another uncommon manifestation of bleeding within a GBM.
Patterns of Dissemination.—Three major patterns of dissemination are seen with GBM. Most frequently, they metastasize from their original location by direct extension, commonly along white matter tracts. One classic example is the spread from a primary lesion in the temporal lobe to the frontal lobe via the uncinate fasciculus (Fig 13).

Less commonly, GBM, like other central nervous system neoplasms, may spread via cerebrospinal fluid pathways (Fig 14). Less than 2% of GBMs exhibit cerebrospinal fluid seeding, either within the central nervous system or through ventriculoperitoneal or ventriculo-pleural shunts. Subependymal spread of GBM is another uncommon but characteristic pattern of dissemination (Fig 14) that correlates with a poor prognosis.
Hematogenous dissemination of GBM. Chest radiographs demonstrate osteoblastic bone lesions in the spine (a) and the scapula (arrow) (b).

Figure 15. Hematogenous dissemination of GBM. Chest radiographs demonstrate osteoblastic bone lesions in the spine (a) and the scapula (arrow) (b).

Multifocal GBM. —There are three pathways that can result in multifocal GBM. First, a primary GBM may spread, usually through cerebrospinal fluid pathways or through white matter, to other locations as discussed (Fig 14; see also Fig 24). Usually, when this occurs, the primary lesion is clearly seen or may have been previously known. Occasionally, it is necessary to image the entire neuraxis to locate the primary tumor.

Second, in a patient with a diffuse, low-grade astrocytoma, multiple areas of malignant degeneration may occur. All astrocytomas, other than grade I circumscribed astrocytomas, to some degree infiltrate through nearby white matter tracts, regardless of their apparent demarcation on radiologic images. Occasionally, within a large area of brain infiltrated by a diffuse but low-grade astrocytoma, multiple areas of malignant transformation occur, giving rise to multifocal GBM. In these cases, the presence of the underlying diffuse astrocytoma may be occult on images, but several distinct foci of ring-enhancing lesions will be seen, suggestive of high-grade tumor or metastases. One clue to the true nature of the abnormality is that the lesions of multifocal GBM tend to be largely within the deep white matter, whereas multiple metastases are usually centered at or near the gray matter-white matter junction (Fig 16).

Figure 16. Multifocal GBM. Axial contrast-enhanced CT scan reveals lesions in the splenium of the corpus callosum and near the cortical surface of the right parietal lobe.

Perhaps the least common mode of dissemination is hematogenous spread to extraneural sites. This pattern is so rare that Bailey and Cushing asserted that it did not occur (40). This pathway is a rare cause of dense, osteoblastic bone lesions (Fig 15) and is seen primarily in patients who have undergone surgical treatment of GBM.
Figure 17. Axial gadolinium-enhanced T2-weighted (a) and T1-weighted (b) MR images demonstrate gliomatosis cerebri with multifocal GBM.

Figure 18. Butterfly GBM. (a) Axial T2-weighted MR image shows a butterfly GBM arising from the splenium of the corpus callosum. (b) Photograph of an autopsy specimen from a different case shows a GBM of the same region.

If a diffuse astrocytoma is hemispheric, or even bihemispheric, the term gliomatosis cerebri is used. In the WHO II grading scale of biologic potential, gliomatosis cerebri is considered a grade III-IV lesion. Even without evidence of focal malignant change, such a diffuse
abnormality is presumed to have a high degree of biologic aggressivity, although this point has not been accepted universally. Occasionally, the underlying diffuse neoplasm is clinically occult and the patient comes to clinical attention because of focal or multifocal areas of degeneration to a more typical GBM (Fig 17).

Third, in a patient with a genetic abnormality, multiple areas of GBM may arise de novo, without the presence of an underlying low-grade lesion. These tumors may arise from cells that, although not neoplastic in themselves, are nevertheless “primed” by an inherited or acquired genetic defect.

GBM of the Corpus Callosum
One common and useful characteristic appearance for a diffuse astrocytoma is the so-called butterfly glioma. Because GBMs are thought to arise from preexisting low-grade diffuse astrocytomas, they too may extend through the commissural white matter tracts, crossing the midline in more than half the cases. Extension through the corpus callosum may occur in a relatively symmetric pattern, giving rise to a butterfly-like appearance (Figs 18, 19). Because the corpus callosum is relatively

Figure 19. Butterfly GBM. (a, b) Axial contrast-enhanced CT scan (a) and gadolinium-enhanced T1-weighted image (b) demonstrate a butterfly GBM arising from the genu of the corpus callosum in two different patients. (c) Photograph of a gross pathologic specimen from a different case shows the GBM diffusely involving the genu of the corpus callosum.
resistant to infiltration by edema or infection, any lesion seen extending across the midline in this way, whether symmetric or asymmetric, should always be suspected of being a diffuse astrocytoma. Other considerations in the differential diagnosis include primary central nervous system lymphoma, particularly if the patient has acquired immunodeficiency syndrome (AIDS). Cavitation and necrosis are relatively uncommon in central nervous system lymphoma; however, in the setting of AIDS, these atypical features are somewhat more common.

GBM may arise in any part of the corpus callosum and may grow exophytically into the lumen of the ventricle (Fig 20). This type of manifestation may lead, erroneously, into the differential diagnosis of masses of primary intraventricular origin, including choroid plexus papilloma, meningioma (both of which attach to the choroid plexus), central neurocytoma (which attaches to the pellucid septum), and subependymal giant cell astrocytoma (which attaches to the lateral ventricular surface in the region of the head of the caudate nucleus). Usually, careful analysis of imaging findings will prevent this mistake. The appearance of a

**Figure 20.** Photograph of a gross pathologic specimen shows a GBM arising in the body of the corpus callosum and projecting into the lateral ventricle.

**Figure 21.** GBM arising from the splenium of the corpus callosum mimicking the appearance of an intraventricular tumor. (a) On the axial T2-weighted MR image, the tumor is seen in the atrium of the right lateral ventricle and seems primarily intraventricular. (b) On the coronal T2-weighted view, however, one sees more clearly the broad base of attachment and the abnormal signal intensity in the splenium, which is where the tumor originated before growing exophytically into the ventricle.
Figure 23. Axial gadolinium-enhanced MR image of a 5-year-old girl shows a pontine GBM.

broad-based abnormality extending into a ventricle with evidence of extraventricular enhancement or mass effect should heighten the suspicion for an exophytic GBM (Fig 21).

- Posterior Fossa GBM
  The most common astrocytoma in the posterior fossa is the juvenile pilocytic astrocytoma, which occurs most often in the cerebellum, hypothalamus, and optic nerve and tracts. Juvenile pilocytic astrocytomas are distinct from diffuse astrocytomas and do not undergo progressive transformation from low-grade to high-grade gliomas.

  The prevalence of primary GBM of the cerebellum is extremely small, especially compared with the prevalence of this lesion in the supratentorial location. The imaging features of this tumor, when it does occur, are relatively similar to those of GBM in other locations (Fig 22). Differential diagnosis includes metastases, hemangioblastoma, or possibly an atypical medulloblastoma.

  Astrocytoma of the brain stem is classically seen in children and most commonly is a diffuse, fibrillary tumor of low histologic grade (Fig 23). This tumor does progress to GBM, however, and the tendency for this progression may be slightly increased after radiation therapy. GBM of the brain stem is also seen in the adults. These tumors represent a significant challenge for clinical management. Because even the initial surgical biopsy is associated with risk of injury to vital structures, some clinicians have advocated use of radiation therapy without biopsy in selected cases.
Figure 24. Primary leptomeningeal glioblastomatosis. (a) Axial gadolinium-enhanced T1-weighted image reveals diffuse leptomeningeal enhancement. (b) Sagittal gadolinium-enhanced T1-weighted image of the cervical spine shows a similar appearance. (c) Photograph of the corresponding pathologic specimen from the region of the pons shows diffuse leptomeningeal thickening. These findings are nonspecific and may be seen with metastatic disease, with granulomatous disease such as tuberculosis or sarcoidosis, or in cases of bacterial meningitis.

- Extraaxial GBM

Both benign and malignant glial neoplasms occasionally manifest as a diffuse leptomeningeal process, usually as a result of dissemination through the cerebrospinal fluid from a primary intraxial tumor. Primary leptomeningeal glioblastomatosis is a rare neoplastic condition that may originate from ectopic neuroglial cell rests within the pia mater and arachnoid (41). Radiologic features in cases of primary leptomeningeal glioblastomatosis consist of either a diffuse or focal thickening of the leptomeninges, usually with contrast material enhancement (Fig 24). The differential diagnosis for
pathologic conditions with this appearance is broad: Inflammatory disease, both infectious (tuberculosis) and noninfectious (Langerhans cell histiocytosis or sarcoidosis); metastatic deposits (especially from breast carcinoma and lymphoma); and cerebrospinal fluid spread of a primary central nervous system neoplasm such as medulloblastoma, germinoma, or pineoblastoma all may have this radiologic appearance. In addition, surgical scarring, as well as old subarachnoid hemorrhage or even a diagnostic lumbar puncture, can produce enhancing leptomeningeal tissue. Almost any of these other possibilities is more common than leptomeningeal gliomatosis (whether in the form of GBM or another tumor, such as oligodendroglioma), and a careful search for other causes is mandatory before the diagnosis is established. In fact, the diagnosis of leptomeningeal glioblastomatosis is generally made by the pathologist to the amazement of all others.

Even more uncommon is the occurrence of leptomeningeal gliosarcomatosis (Fig 25), whose imaging features are virtually indistinguishable from those of leptomeningeal glioblastomatosis. Theoretically, if leptomeningeal gliosarcomatosis contained enough of a nodular component, one might be able to see a slightly higher degree of attenuation on unenhanced CT scans, but in practical terms, it is very difficult to make this claim prospectively. Again, this diagnosis generally requires tissue examination by the neuropathologist.
Figure 26. Spinal GBM. (a) Sagittal T2-weighted MR image demonstrates a hyperintense mass that has greatly expanded the spinal cord. (b) Photograph of the corresponding pathologic specimen shows the expanded spinal cord with necrosis. (c) Axial gadolinium-enhanced T1-weighted image of the same patient shows an area of intramedullary enhancement. (d) Coronal gadolinium-enhanced T1-weighted image of the brain in the same patient shows diffuse leptomeningeal spread via cerebrospinal fluid pathways.

- Spinal GBM
The most common glioma of the spinal cord is the ependymoma; however, GBMs are also found to arise within the white matter tracts of the spinal cord. The most common location reported is the cervical region, which is also the most frequent location for lower-grade astrocytic neoplasms, including juvenile pilocytic astrocytoma. At radiologic examination, a spinal GBM is seen as an intramedullary mass enlarging the spinal cord; the mass demonstrates variable contrast enhancement and evidence of hemorrhage and necrosis (Fig 26).
Gliosarcoma and Fibrosarcoma

Gliosarcoma, which contains a substantial proportion of malignant mesenchymal cells, is very similar to other GBMs in most imaging characteristics with one important exception. On unenhanced CT scans, most GBMs are of low to intermediate attenuation except in areas of hemorrhage; in contrast, gliosarcoma may display high attenuation within the viable portion of the tumor (due to the presence of fibrous tissue) and low attenuation only within the necrotic center (Fig 27).

Gliosarcoma can occur in any location where GBM occurs, but it is usually found in the central white matter tracts or corpus callosum. One unusual and extreme example of this tumor type occurs if virtually the entire tumor bulk is composed of mesenchymal cells, with a minimal glial component. This tumor is referred to as a central nervous system fibrosarcoma (Fig 28), which represents an infrequent, highly specialized outcome of gliosarcomatous degeneration.
Pediatric and Congenital GBM

Although GBM occurs most frequently in patients aged 65-75 years, it has been reported in patients of every age, including newborns (Fig 16). The imaging and pathologic features of GBM in pediatric patients are similar to those of GBMs found in older patients.

The pathogenesis of congenital GBM is somewhat controversial in that one would expect that more time would be required for the maturation and subsequent dedifferentiation of these cells into GBM. More likely, a “congenital GBM” represents malignant glial differentiation within a primitive neuroectodermal tumor. Considered simply from an etymologic perspective, such a tumor may be the only true GBM. It is possible that future investigations will show that young patients with these tumors inherited a very active oncogene, or possibly an extremely potent spontaneous mutation will be found to be responsible. Happily, these cases are extremely rare.

THERAPY AND PROGNOSIS

Initial treatment of GBM involves surgical resection and debulking of the tumor to whatever extent possible, based on the location and extent of the tumor at the time of initial diagnosis. Surgery is usually followed by radiation therapy and, depending on clinical circumstances, various forms of chemotherapy. Radiation treatment may be administered as whole-brain irradiation, focused beam (with a gamma knife or particle bombardment where available) therapy, or brachytherapy. Chemotherapeutic response is optimized with use of multiple drug combinations, although some single-drug regimens are nearly as effective (39).

Despite the best efforts of neurosurgeons, neuro-oncologists, and radiation therapists, complete cure of GBM is rare, and the average life span of the patient who undergoes treatment with surgery, radiation, and chemotherapy from time of diagnosis is estimated at 16-18 months (42). Without therapy, average survival is 6 months, which is roughly comparable with estimates of survival for patients who underwent therapy 50 years ago.

Limited clinical trials of adjunctive gene therapy have been performed; in these trials, antigenic viral particles (primarily herpes simplex virus type 1) are inserted into neoplastic tissue in attempt to induce a host immune response against the tumor (43). These attempts have met with some limited success, as has the use of interleukin therapy to activate killer T cells and thereby increase the role of cell-mediated immunity in the host (44). As mentioned, various trials involving the p53 gene are under way, and further investigations of other tumor-suppressor agents are planned. Whether these
initial attempts are successful or not, the possibility of future uses of the information gained from the study of the genetic basis of neoplastic transformation represents an exciting area of scientific advancement.

**CONCLUSIONS**

GBM is a ubiquitous neoplasm that can affect any part of the central nervous system and has a wide variety of clinical symptoms and radiologic appearances. Usually, the diagnosis, both radiologic and pathologic, is straightforward and is made on the basis of key features of necrosis, hypervascularity, and hemorrhage. The pathologic examination of these tumors reveals several distinct variations, and it is possible that future pathologic investigations will demonstrate that these variations are in fact separate entities that enter into a final common pathway for highly malignant brain neoplasms. For the present, the great similarity in the biologic behavior of these tumors renders any distinctions between them relatively unimportant.

Major advances in the study of human genetics have contributed greatly to our current understanding of GBM and also to our increasing understanding of the normal genetic mechanisms for control of cellular growth and differentiation. The intense study of the pathologic aberrations of gene function carries with it the need to better understand normal genetic control, and our knowledge in both areas continues to expand rapidly. As the myriad of genetic defects that are found in these tumors is delineated, the exact nature of their specific contributions to the relentless, destructive nature of GBM will become clarified and lead to more specific modes of therapy. These exciting advances may yet alter the grim prognosis of these fatal brain neoplasms.

**REFERENCES**


This article meets the criteria for 1.0 credit hour in Category 1 of the AMA Physician's Recognition Award. To obtain credit, see the questionnaire on pp 1461-1465.