Glioblastoma

Morphologic and Molecular Genetic Diversity

C. Ryan Miller, MD, PhD; Arie Perry, MD

● Context.—Glioblastoma (GBM), the most common primary intracranial malignancy, is a morphologically diverse neoplasm with dismal prognosis despite multimodality therapy. Only 3 distinct morphologic variants of GBM are currently recognized by the current World Health Organization (WHO) classification scheme, including GBM, giant cell GBM, and gliosarcoma. Additional variants, some of which have significant morphologic overlap with tumors that have more favorable prognosis and treatment response rates, particularly anaplastic oligodendroglioma, have been described since its publication in 2000 and may be included in the next classification.

Objective.—To summarize the morphologic and molecular genetic diversity of both well-established and novel GBM variants and outline our approach to these heterogeneous neoplasms and their distinction from other diffuse, high-grade gliomas.

Data Sources.—Published literature and our own experience in an active academic diagnostic surgical neuropathology practice were reviewed.

Conclusions.—Precise subclassification of GBM is required for accurate prognostication and appropriate treatment planning.

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Diffuse, infiltrative gliomas are the most common primary intracranial neoplasms, accounting for 40% of all primary and 78% of all malignant central nervous system tumors.1 More than 80% of these tumors are considered high-grade (grades III and IV) when diagnosed according to the current World Health Organization (WHO) classification, a system based on morphologic evidence of differentiation along astrocytic, oligodendrogial, or mixed lineages. Classification and grading criteria for astrocytic neoplasms are well established, having been refined periodically during the last 80 years from the classification schemes of Bailey and Cushing,2 Kernohan,3 Ringertz,4 Nelson,5 St. Anne-Mayo,6,7 and WHO.8–9

The WHO 2000 criteria are currently the most widely accepted scheme and are based largely on the St. Anne-Mayo classification. For example, it uses mitotic activity to distinguish anaplastic astrocytoma (AA), WHO grade III, from its low-grade counterpart, diffuse astrocytoma, WHO grade II. Median overall survival (OS) for patients with AA is typically 3 to 5 years.10 Microvascular proliferation (MVP), loosely defined to include endothelial hyperplasia, endothelial hyperplasia, and glomeruloid vessels, and/or necrosis are distinguishing features of WHO grade IV astrocytoma, the latter being synonymous with the commonly used term glioblastoma multiforme or simply glioblastoma (GBM) in the current WHO scheme.10

Despite advances in microsurgical techniques, radiation, and chemotherapy, GBM is still associated with a median OS of approximately 1 year.4 In its most mature and prognostically significant manifestation, MVP is recognized as multilayered tufts of hyperplastic and mitotically active endothelial cells, accompanied by smooth muscle cells and pericytes. The presence of MVP in GBM has been correlated with hypoxia-induced neoangiogenic and infiltrative phenotypes, the former of which is characterized by expression of cytokines such as vascular endothelial growth factor.11,12 Microvascular proliferation is both temporally and spatially linked to the presence of necrosis, particularly pseudopalisading necrosis.11,12 These morphologic criteria are highly reproducible and serve as useful prognostic factors for OS.13–15

Glioblastoma may arise through 2 distinct pathways of neoplastic progression. Tumors that progress from lower-grade (II or III) astrocytic tumors, termed secondary or type 1 GBMs, typically display both well-differentiated and poorly differentiated foci. Secondary GBMs develop in younger patients (fifth to sixth decade), with time to progression from lower-grade lesions ranging from months to decades. In contrast, primary, type 2 GBMs develop in older individuals (sixth to seventh decade), have short clinical histories (less than 3 months), and arise de novo without any evidence of a lower-grade precursor. Primary and secondary GBMs also harbor distinct molecular genetic abnormalities: Primary GBMs are characterized by relatively high frequencies of EGFR amplification, PTEN deletion, and CDKN2A (p16) loss, whereas secondary GBMs often contain TP53 mutations, especially those involving codons 248 and 273 or G:C→A:T mutations at CpG sites.16 The clinicopathologic and molecular genetic features of primary and secondary GBM have been recently reviewed in detail by Ohgaki and colleagues.16

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variants of GBM

The term GBM was coined by Mallory in 1914 and solidified in the lexicon of surgical neuropathology by Bailey and Cushing in 1926. As the original designation multiforme implies, GBMs comprise a morphologically highly heterogeneous neoplasm. In other words, the cellular composition, even within a single tumor, may vary widely and mixed histologic features are typical. Three GBM variants are recognized as distinct clinicopathologic entities in the current WHO classification: conventional GBM, giant cell GBM (GC-GBM), and gliosarcoma (GS). In addition, other variants of GBM with distinct clinicopathologic and genetic features have been described (Table 1). In the present review, we discuss the cytologic heterogeneity that may be encountered in the variants of GBM and outline our approach to their subclassification.

Conventional GBM

Even within the conventional GBM category, the cellular composition is heterogeneous and may include fibrillary, gemistocytic, and/or occasional giant cells (GCs). Neoplastic fibrillary astrocytoses contain enlarged, elongated to irregularly shaped, hyperchromatic nuclei; short cytoplasmic processes; and variable glial fibrillary acidic protein (GFAP)-immunoreactive processes that form a loose, fibrillary matrix (Figure 1). Such tumors may also harbor mucin-rich microcystic spaces. Because of cross sectioning of spindled neuroglia, occasional giant nuclei, neoplastic fibrillary astrocytomas may also appear to have occasional rounded nuclear profiles, raising the differential diagnosis of high-grade oligodendrogial (HOG) neoplasms (WHO grade III anaplastic oligodendroglioma [AO, O3] and WHO grade III anaplastic mixed oligoastrocytoma [AOA, MOA3]). Nevertheless, a significant fraction of cells should have classic cytology (eg, round uniform cells with sharp nuclear membranes and bland chromatin) before one invokes an oligodendrogial component in the diagnosis.

Gemistocytes were first described by Franz Nissl as glia (gemaestete glia) with voluminous cytoplasm. Gemistocytic astrocytoses contain plump, glassy, eosinophilic GFAP-immunoreactive cytoplasm; eccentric, irregularly shaped, hyperchromatic nuclei; and short cytoplasmic processes. Because of cross sectioning of spindled neuroglia, occasional giant nuclei, neoplastic fibrillary astrocytomas may also appear to have occasional rounded nuclear profiles, raising the differential diagnosis of high-grade oligodendrogial (HOG) neoplasms (WHO grade III anaplastic oligodendroglioma [AO, O3] and WHO grade III anaplastic mixed oligoastrocytoma [AOA, MOA3]). Nevertheless, a significant fraction of cells should have classic cytology (eg, round uniform cells with sharp nuclear membranes and bland chromatin) before one invokes an oligodendrogial component in the diagnosis.

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**Table 1. Clinicopathologic and Molecular Genetic Features of Glioblastoma Multiforme (GBM) Variants**

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* Fib indicates fibrillary; Gem, gemistocytic; GCA, granular cell astrocytoma; GC, giant cell; GS, gliosarcoma; SCA, small cell astrocytoma; GBM-O, GBM with oligodendroglial features; ... , no data available; --, absent; +/-, infrequent; + to ++, increasing frequency; PVI, perivascular inflammation; del, deletion; codel, codeletion; amp, amplification; and mut, mutation. Sources of molecular genetic frequencies are referenced by column except PTEN mutation (row).

**GBM—Miller & Perry**

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GBM Variants—Miller & Perry

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cytoplasmic epithelial membrane antigen but no cytokeratin immunoreactivity. Similar to astrocytomas with nongranular cytology, these tumors may also harbor TP53 mutations, high-frequency loss of heterozygosity at 9p, 10q, and 17p, and less frequent loss of heterozygosity at 1p and 19q. Ultrastructural studies have shown that the cytoplasmic granularity correlates with increased lysosomes, evident as either dense or multivesicular bodies. Brat and colleagues reported the largest series of such tumors to date (22 cases, including 4 grade II, 7 grade III, and 11 grade IV tumors) and found that these tumors were more aggressive than non-granular cell astrocytomas of the same grade. Given their average survival of 7.6 months, it may indeed be appropriate to consider them variants of GBM.

**Giant Cell GBM**

Giant cell GBM constitutes approximately 5% of GBMs and is recognized as a distinct clinicopathologic entity in the WHO 2000 classification. Although occasional neoplastic GCs may be found in conventional GBM, these cells are a dominant cytologic component in GC-GBM. As the name implies, the tumor cells are markedly enlarged and bizarre, often appearing multinucleated (Figure 4, A). Giant cell GBMs are typically well-circumscribed masses that occur in younger patients (fifth decade). Their molecular genetic features include relatively high frequencies of TP53 mutations (75%–90%) and PTEN deletion (5%–30%), whereas EGFR amplification and CDKN2A deletion are rare in comparison to conventional GBMs; therefore, GC-GBMs contain clinical and molecular genetic features of both primary and secondary GBMs and as such occupy an intermediate position between these two.

Several reports have demonstrated a slightly better prognosis for GC-GBM than for conventional GBM. Nevertheless, the prognosis remains poor overall. As shown in Table 2, this has similarly been our experience at Washington University School of Medicine. Among 453 supratentorial GBMs newly diagnosed between 1990 and 2005, only 7 (1.5%) were GC-GBMs. These patients were approximately 10 years younger than those with non–GC-GBMs. Median OS was 11.4 months for GC-GBM, compared with 9.3 months for non–GC-GBM. However, this difference was not statistically significant (log-rank P = .48) after adjusting for patient age and surgery type (resection vs stereotactic needle biopsy).

A potential molecular mechanism for GC formation has recently been described. The process of endoreduplication results in multiple cycles of DNA replication associated with a failure of cell division, thus causing markedly enlarged polyploid nuclei with extensive chromosomal gains (Figure 4, B). Using antibodies to specific phosphorylation sites on vimentin and GFAP catalyzed by various kinases, including cdc2, CF, Rho, protein kinase C,
Table 2. Prognostic Impact of Morphologic Variants in 453 Newly Diagnosed, Adult (>20 y) Supratentorial Glioblastoma Multiformes (GBMs) at Washington University School of Medicine (1990–2005)*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>GBM</th>
<th>GC-GBM</th>
<th>GS</th>
<th>SC-GBM</th>
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<td>n</td>
<td>388</td>
<td>7</td>
<td>10</td>
<td>21</td>
<td>27</td>
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<td>%</td>
<td>85.7</td>
<td>1.5</td>
<td>2.2</td>
<td>4.6</td>
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<td>Mean age, y</td>
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<td>52.1</td>
<td>59.1</td>
<td>57.6</td>
<td>47.9</td>
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<td>Resection, %</td>
<td>64</td>
<td>57</td>
<td>90</td>
<td>91</td>
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<td>Median OS, mo</td>
<td>9.3</td>
<td>11.4</td>
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<td>Log-rank P (vs GBM)</td>
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<td>.48</td>
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* P adjusted for patient age and surgery type. GC-GBM indicates giant cell GBM; GS, gliosarcoma; SC-GBM, small cell GBM; GBM-O, GBM with oligodendroglial features; and . . . , no data available.

and aurora-B, investigators have shown that the molecular alteration that causes failure of cytoplasmic cleavage in cultured multinucleated GCs is loss of aurora-B kinase function. Importantly, loss of aurora-B kinase–mediated phosphorylation was confirmed in human GC-GBM samples. However, aurora-B kinase has been shown to be overexpressed in astrocytomas in general, with both mRNA and protein levels correlating with WHO grade. Therefore, the molecular basis for aurora-B kinase dysfunction (mutation, gene deletion, methylation) in GCs and its overexpression in non-GC-GBM remains to be established.

Gliosarcoma and “Adenoid” GBM

Gliosarcoma constitutes approximately 2% of GBMs and is likewise recognized as a distinct clinicopathologic entity in the WHO 2000 classification. These tumors are characterized by their well-circumscribed, biphasic growth pattern with clearly identifiable glial and metaplastic mesenchymal components (Figure 5, A and B). The glial component of GS may show any of the aforementioned cytologic features and is typically immunoreactive for GFAP (Figure 5, D). The mesenchymal component may also show a wide variety of morphologic appearances, with evidence of differentiation along fibroblastic, cartilaginous (Figure 5, E and F), osseous, smooth and striated muscle, and adipose lines. These areas are generally characterized by dense extracellular matrix deposition, the latter evident on reticulin-stained sections (Figure 5, C, upper) and contrasting with the typically reticulin-poor glial component (Figure 5, C, lower). In addition to sarcomatous differentiation, epithelial metaplasia may also occur in either GS or conventional GBM, including areas of keratinizing squamous or glandular differentiation. Such cases often invoke a differential diagnosis of metastatic carcinoma. The latter is illustrated in Figure 6, A, an “adenoid glioma” that was immunoreactive for both GFAP (Figure 6, B) and low-molecular-weight cytokeratins (CK7;

Figure 5. Gliosarcoma. A, These tumors show a well-circumscribed, biphasic growth pattern with clearly identifiable glial (right) and metaplastic, nonglial components (left) (hematoxylin-eosin, original magnification ×200). B, These components are often intermingled (hematoxylin-eosin, original magnification ×100). C, A reticulin stain is helpful in identifying the 2 distinct components: The glial component is reticulin poor (center), whereas the sarcomatous component is reticulin rich (top and bottom) (original magnification ×100). D, The glial element expresses glial fibrillary acidic protein (immunoperoxidase, original magnification ×100). E and F, The sarcomatous component may also show evidence of other mesenchymal elements, such as cartilaginous differentiation (hematoxylin-eosin, original magnifications ×400 [E] and ×200 [F]).
Adenoid glioblastoma multiforme. This tumor is an extremely rare variant with epithelial (glandular) metaplasia (A). The glial component (B) is intermingled with the epithelial component, which was immunoreactive for a variety of cytokeratins, including CK7 (C) (hematoxylin-eosin, original magnification \( \times 200 \) [A]; immunoperoxidase, original magnifications \( \times 200 \) [B] and \( \times 400 \) [C]).

Overall, these tumors are exceedingly rare and are thus far not recognized as a distinct clinicopathologic entity by the WHO.

Several reports have demonstrated a slightly better prognosis for GS than for conventional GBM.\(^{10,38}\) However, the differences in OS have been statistically insignificant in most series. This too has been our experience at Washington University School of Medicine (Table 2). Among the 453 newly diagnosed, adult supratentorial GBMs, only 10 (2.2%) were GSs. These patients were of similar age to those with no sarcomatous component. Median OS was 7.6 months for GS, compared with 9.3 months for conventional GBM. This difference was not statistically significant (log-rank \( P = .33 \)) after adjusting for patient age and surgery type.

Metaplasia in non–central nervous system epithelial tumors is not infrequently encountered in general surgical pathology. Extensive work in developmental and tumor molecular cell biology has elucidated potential molecular mechanisms responsible for epithelial-mesenchymal transition, a phenomenon postulated to be essential for systemic metastasis in non–central nervous system epithelial tumors. The existence of epithelial-mesenchymal transition is an area of intense debate within the cancer research community and has been extensively reviewed elsewhere.\(^{39-42}\) The possibility of an analogous role of epithelial-mesenchymal transition in GS is currently unexplored. Regardless, it is clear that the metaplastic component in GS is neoplastic and frequently harbors cytogenetic and molecular abnormalities similar to those found in the glial component. In this regard, GSs are genetically similar to primary GBMs: 20% to 40% of tumors harbor \( TP53 \) mutations, \( PTEN \) deletions, and \( CDKN2A \) deletions. The only exception to this generalization is the relative infrequency of \( EGFR \) amplification in these tumors.\(^{10,43}\) The notion that the sarcomatous element represents mesenchymal metaplasia analogous to that seen in carcinosarcomas elsewhere in the body comes from data demonstrating the presence of 1 or more identical genetic aberrations in both elements from individual tumors; the latter supports a monoclonal process rather than a collision tumor.\(^{43-45}\) Similarly, identical genetic alterations have been described in microdissected portions from the glial and epithelial elements of adenoid GBMs and GSs, suggesting that this too represents metaplasia.\(^{46,47}\)

**OTHER VARIANTS OF GBM**

Additional variants of GBM have been described beyond those published in the 2000 WHO classification scheme. These include small cell astrocytomas (SCAs), glioblastoma with oligodendrogial features (GBM-O), and GBM with primitive neuronal (primitive neuroectodermal tumor [PNET]–like) features. In contrast to granular cell astrocytoma, GC-GBM, and GS, all of which pose little diagnostic difficulty for the experienced neuropathologist on routine histopathologic examination, these variants have significant morphologic overlap with other recognized clinicopathologic entities, particularly HGO neoplasms. Identification of signature molecular genetic alterations, specifically codeletion of material on chromosomes 1p and 19q, and its association with responsiveness to adjuvant therapy and improved prognosis, has made accurate histopathologic and molecular genetic characterization of these neoplasms of paramount importance for proper treatment planning and precise prognostication.\(^{48-51}\) Codeletion of 1p/19q has been shown to occur most frequently (50%–80%) in morphologically classical AO.\(^{52,53}\) A subset (~20%) of AOA also harbor 1p/19q codeletion,\(^{50}\) although its prognostic utility remains less well defined for these neoplasms. Even when histopathologic
Small Cell Astrocytoma

Small cell astrocytoma is a variant of GBM with considerable morphologic overlap with AO on routine hematoxylin-eosin–stained sections. The histopathologic hallmarks of this tumor are its bland nuclear cytology and striking mitotic activity (Figure 7, A and B). It is composed of a large (>80%) monotonous collection of astrocytes with small, uniformly oval nuclei with mild hyperchromasia and minimal discernible cytoplasm. Like other diffuse gliomas, SCA can show cortical infiltration and secondary structuring, including perineuronal satellitosis (Figure 7, C). The tumor vasculature is sometimes composed of a delicate, chicken-wire capillary network (Figure 7, D). Immunohistochemical studies are a useful adjunct in diagnosing SCA: Tumor cells typically contain long, thin, GFAP-positive cytoplasmic processes (Figure 8, A) and a markedly elevated MIB-1 (Ki-67) labeling index (Figure 8, B).

In contrast to AO, in which median OS ranges from 5 to 10 years, the clinical behavior of SCA is much more aggressive, with median OS virtually indistinguishable from conventional GBM. It is for this reason that accurate diagnosis of SCA is imperative for accurate prognostication and proper treatment planning. Our experience with 21 SCAs (4.6% of 453 newly diagnosed, adult supratentorial GBMs) at Washington University School of Medicine is listed in Table 2. These patients were of similar age to those with conventional GBMs. Their median OS was 14.3 months and was not statistically significantly different (log-rank ț = .95) from that of conventional GBM after adjusting for patient age and surgery type.

Identification of characteristic molecular genetic alterations in SCA has provided an additional diagnostic aid in challenging cases. In contrast to AO, SCAs rarely harbor deletion of either 1p or 19q and we have never encountered codeletion of these chromosomes (Table 1). Rather, SCAs show chromosome EGFR amplification and chromosome 10q (PTEN) deletion, with frequencies even higher than conventional GBMs (Table 1). Combined EGFR amplification and 10q deletion is likewise more prevalent in SCA compared with conventional GBM. We have recently...
Figure 8. Immunohistochemical and genetic features of small cell astrocytoma. A, Tumor cells typically contain long, thin glial fibrillary acidic protein–positive cytoplasmic processes (immunoperoxidase, original magnification ×400). B, Mitotic activity and MIB-1 (Ki-67) labeling index is markedly elevated (immunoperoxidase, original magnification ×200). C and D, Fluorescence in situ hybridization analyses for chromosomes 7 (EGFR region in red, centromere for chromosome 7 in green) and 10q (PTEN in green and DMBT1 in red) typically reveal evidence of EGFR gene amplification (C) and 10q deletion (D, single red and green signals), respectively (original magnifications ×400 [C] and ×1000 [D]).

analyzed the diagnostic utility of molecular genetic analysis in the diagnosis of SCA. Among 239 diffuse, high-grade gliomas (HGGs, including AAs, GBMs, AOs, and AOAs) analyzed by fluorescence in situ hybridization (FISH) for EGFR amplification, including 108 SCAs, the sensitivity and specificity for the diagnosis of GBM were 54% and 94%, respectively. EGFR amplification was equally sensitive (92%) and slightly more specific (64%) for SCA (Figure 8, C). Among 222 HGGs with 106 SCAs that were analyzed for 10q abnormalities by FISH, the sensitivity and specificity of 10q deletion for the diagnosis of GBM were 81% and 71%, respectively. 10q deletion was slightly more sensitive (90%) but slightly less specific (64%) for the diagnosis of SCA (Figure 8, D). Because these molecular genetic abnormalities may occasionally be found in other HGGs, FISH analysis does not serve as a replacement for routine histopathologic examination but only as an objective adjunct to confirm the initial morphologic impression of SCA or GBM in general.

GBM With Oligodendrogial Features

The current WHO classification of HGO neoplasms contains significant ambiguities. The 2 forms of HGO neoplasms, AO and AOA, are distinguished from their low-grade counterparts, oligodendroglioma and oligoastrocytoma, by the presence of any one or more of the following histologic features: brisk mitotic activity, microvascular proliferation, and necrosis. No significant weight is given to any of these features, which has given rise to the following debate within the neuro-oncology community: Do grade IV variants of HGO neoplasms exist and, if so, what diagnostic features constitute such entities?

We recently performed a retrospective analysis of prognostic factors in 1093 newly diagnosed, adult supratentorial HGGs specifically to address this issue. This study included 81 AAs, 581 GBMs (including 120 SCAs, 13 GSs, and 2 GC-GBMs), 215 AOAs, and 216 AOs diagnosed according to current WHO 2000 criteria. We considered the diagnosis of an AOA only if distinct astrocytic (Figure 9,
of Medicine is presented in Table 2. In this cohort of 27 these GBM-O cases seen at Washington University School to AOA without necrosis. Survival data for a subset of AOA with necrosis was closer to GBM (9.8 months) than pure AO (log-rank evidence interval 1.5–3.7, Cox

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GLIOMA MULTIFORME WITH OLIGODENDROGLIAL FEATURES

We therefore consider WHO grade III AOA with necrosis to constitute a distinct grade IV variant of AOA and routinely designate such neoplasms as GBM-O. An alternative, equally valid designation would be highly anaplastic oligoastrocytoma, grade IV (MOA4). These tumors portend a significantly better prognosis than other variants of GBM, in line with the relatively better prognosis for oligodendrogial neoplasms in general.

In contrast to the finding of codeletions in roughly 85% of our AOs, deletion of either 1p (24%), 19q (43%), or combined 1p/19q (22%) is relatively infrequent in GBM-O (Table 1). Nonetheless, these frequencies are nearly identical to those we have encountered in mixed oligoastrocytomas overall. Interestingly, these tumors more frequently show solitary 19q deletion (21% of 58 analyzed tumors). Among 586 diffuse HGGs analyzed by FISH for 1p/19q abnormalities, the sensitivity and specificity of solitary 19q deletion for the diagnosis of AOA and GBM-O were 25% and 93%, respectively. Thus, the presence of solitary 19q deletion may be a useful molecular genetic feature to confirm the impression of a GBM-O after routine histopathologic examination, but its infrequent occurrence in these tumors precludes reliance on this feature in establishing the diagnosis.

GBM WITH PRIMITIVE NEURONAL (PNET-LIKE) FEATURES

Rare examples of high-grade glioneuronal tumors or GBMs combined with cerebral neuroblastoma/supratentorial PNET have been previously published but remain relatively poorly characterized.6 Similarly, we have encountered a number of such cases, often as consults with the differential diagnosis including an unusual GBM versus a supratentorial PNET with extensive glial differentiation (Figure 10, A). In support of the former interpretation, the majority of our cases have occurred in adults and had foci resembling conventional GBM, sometimes with foci of low-grade glioma in either the same or a prior biopsy. The primitive neuronal (PNET-like) element often looks like a separate clone with nodules of markedly increased cellularity, high nuclear-cytoplasmic ratios, markedly hyperchromatic cells, remarkably high mitotic and Ki-67 indices (close to 100% in some, Figure 10, D), and convincing evidence of neuronal or neuroblastic differentiation, such as Homer-Wright rosettes (Figure 10, B) and expression of neuronal antigens (eg, synaptophysin [Figure 10, C], Neu-N, neurofilament protein, neuron-specific enolase). To date, too few cases have been reported to determine the behavior or optimal therapy, although most of the patients we have encountered have died in less than a year, analogous to GBM in general.

CONCLUSION

Glioblastoma multiformes are morphologically diverse neoplasms with poor prognosis. Precise subclassification is becoming increasingly important, as several of the newly defined variants described since the publication of the WHO classification in 2000 have significant morphologic overlap with tumors that have more favorable prognosis and treatment response rates. Some of the variants described in this article have recently been added to the upcoming WHO 2007 scheme as distinctive “patterns” of GBM. More widespread application of the principles described in this review may permit more accurate prognostication and appropriate treatment planning in the future.
Figure 10. Glioblastoma multiforme with neuronal peripheral neuroectodermal tumor–like features. These tumors contain both astrocytic (A) and primitive neuronal (B) components. The latter element is characterized by Homer-Wright rosettes (B) and synaptophysin immunoreactivity (C). Marked proliferative activity is evident (D) (hematoxylin-eosin, original magnifications ×200 [A] and ×400 [B]; immunoperoxidase, original magnifications ×100 [C] and ×200 [D]).

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