18 Gangliogliomas and Other Low Grade Neuronal Neoplasms of the Central Nervous System: Diagnosis, Treatment, and Prognosis

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Contents

Abstract

Glioneuronal tumors of the brain and spinal cord are relatively uncommon but highly interesting neoplasms, whose very existence provides support for current stem cell theories regarding the origins of central nervous system tumors. This chapter describes the clinical presentations, neuroradiological features, and diagnostic pathological characteristics of gangliogliomas, parenchymal neurocytic tumors, and other intra-parenchymal (not intraventricular) neuronal neoplasms of the CNS, together with summaries of current treatment options. Gangliogliomas are tumors composed of mixtures of glial cells, usually astrocytoma cells, with large neoplastic neurons (ganglion cells); the majority are slow-growing, indolent neoplasms which respond best to neurosurgical extirpation. Pleiomorphic Xanthoastrocytomas, subependymal giant cell tumors, and some anaplastic large cell gliomas all may exhibit co-expression of glial and neuronal antigens in the same cells. Parenchymal neurocytic tumors mostly resemble oligodendrogliomas, but like their intraventricular counterparts have immunoreactivity for synaptophysin, neurofilament protein, and other neuronal antigens. These are more controversial entities, with a range of appearances (some have ganglion cells, some lack astrocytic elements whereas in others they are

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present, and many have anaplastic changes such as vascular hyperplasia, necrosis, and high mitotic rates).

Introduction

The majority of intrinsic, neuroepithelial tumors of the brain and spinal cord are classified as gliomas, including astrocytomas, oligodendrogliomas, and ependymomas, and their variants, and are conventionally regarded as arising from glial cells in the relevant lineages. Tumors of neuronal origin or differentiation, or which have mixed glial and neuronal elements, provoke interest because mature neuronal cells are post-mitotic and so it is conceptually difficult to have neoplastic cells with the characteristics of mature neurons. (This necessarily excludes primitive or embryonal tumors with neuroblastic elements, which do not produce such conceptual problems). Nevertheless, it has long been well-recognized that some tumors of the brain and spinal cord consist of, or contain, neoplastic cells with relatively mature neuronal characteristics. These tumors, the best known of which are gangliogliomas and gangliocytomas, but which also include tumors of smaller neuronal cells which generally fit in the broad category of neurocytomatous cells, are usually low grade malignancies which are more common in younger patients and are often associated clinically with epilepsy. Their existence has helped to promote areas of research suggesting that neuroepithelial CNS tumors in fact arise from tumor stem cells or progenitor cells which retain considerable developmental plasticity and can give rise to neoplastic cells with the characteristics of neurons, particular classes of glia, or both. This chapter will review the clinical and pathological diagnostic features of these tumors, particularly but not exclusively gangliogliomas, the current state of treatment for them, and the prognosis of the patients who have them. An accompanying chapter (in volume 6 of this series) has described the special features of neuropathological diagnosis of gangliogliomas, particularly in the spinal cord where there are, perhaps, special difficulties in such diagnosis.

Brain Gangliogliomas

Clinical Presentation

Gangliogliomas are (almost always) slow-growing, low grade tumors which are best known to arise in the temporal lobes, where they frequently present clinically as a cause of complex partial seizures. Those examples which occur in other cerebral lobes, or deeper in cerebral tissues, in the brainstem, or cerebellum and spinal cord, present clinically by virtue of their mass effect and by the focal neurological deficits they produce. In this they are not different from any other CNS neoplasms, except for the usual insidious onset and slow progression of symptoms other than epilepsy.

Gangliogliomas lack distinctive features by computed tomography (CT) although they may, like other low grade neuroepithelial tumors, contain calcium deposits which are easily seen when present on CT. In MRI images they may be solid or cystic, the latter examples often having a solid mural nodule at one border of the cyst (Castillo et al. 1990; Adachi and Yagishita 2008; Im et al. 2002) (Fig. 18.1a–b). They often do not enhance with intravenous gadolinium administration, but some do have some mild enhancement in a diffuse or patchy fashion without any ring appearance (Fig. 18.1b). Conventionally they are said to be sharply circumscribed or bordered against adjacent normal brain tissues by MRI, but some are more infiltrative and are indistinguishable by MRI from diffuse gliomas (astrocytomas, oligodendrogliomas, and mixed gliomas, and other diffuse glioneuronal tumors). In general, the diagnosis may be suggested by clinical features and MRI characteristics, but can only be established by histopathological examination.

Histopathological Diagnosis

The characteristic feature of gangliogliomas is that they contain substantial numbers of large neuron-like cells with large pale nuclei with prominent nucleoli, set in large cell bodies which

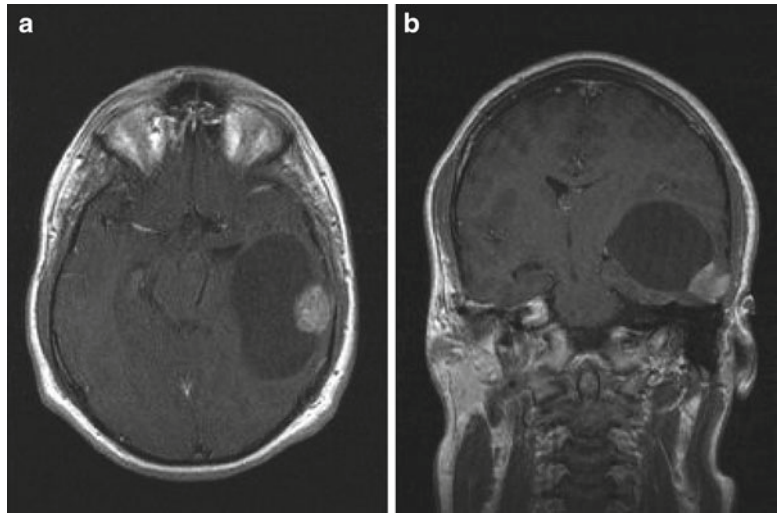

Fig. 18.1 Magnetic Resonance Imaging of gangliogliomas. Large cystic ganglioglioma in the left temporal lobe. (**a**) Axial T1-weighted image after administration of intravenous gadolinium shows the large cystic tumor with an enhancing mural nodule. There is no enhancement around the wall of the cyst separate from the nodule. (**b**) Coronal T1-weighted image of the same tumor

may contain basophilic granules histologically similar to or identical with the Nissl granules of normal neurons (Fig. 18.2a) (Becker et al. 2007; Miller et al. 1993; Miller 2009). If a neoplasm is composed essentially solely of such cells without distinctive neoplastic glial elements, it is termed a gangliocytoma. Gangliocytomas are most uncommon, and the majority of CNS tumors with ganglion cells are gangliogliomas. The glial elements are usually morphologically and immunohistochemically consistent with astrocytes, and resemble the cells of low grade diffuse astrocytomas (Fig. 18.2a), or, in some cases, pilocytic astrocytomas (Fig. 18.2b), complete with Rosenthal fibers or eosinophilic granular bodies; the presence of an apparently neoplastic oligodendroglioma-like population with admixed tumor ganglion cells should suggest that the oligodendroglioma-like cells are more likely neurocytoma cells, which can be demonstrated with appropriate immunostains (Giangasapero et al. 1997; Miller et al. 1993; Brat et al. 2001; Figarella-Branger et al. 2007).

In some cases the ganglion cells are so obvious, and their neuronal character is so unambiguous, that the diagnosis of ganglioglioma can be made solely on the basis of the tumor's appearance in conventional hematoxylin and eosin (H&E) stains (Fig. 18.2a). These classical examples have neurons in a range of sizes, which has been well-described long ago by Russell and Rubinstein (1989) for example, admixed with small bland tumor astrocytes. There is usually little or no discernible mitotic activity, and there is neither necrosis nor vascular hyperplasia such as characterizes high grade gliomas. Many examples have prominent lymphohistiocytic infiltrates around vessels in the tumor, although the absence of such inflammatory reactions do not argue against the diagnosis; and many examples have at least some desmoplasia, that is the deposition of collagen, in the neuropil (Miller et al. 1993; Jaffey et al. 1996).

For the pathologist, gangliogliomas present two potential diagnostic problems. First, a neoplasm may contain large cells that are obviously neurons, but it is unclear whether these are normal neurons entrapped in an infiltrating astrocytoma, or that they are in fact part of the neoplasm. Second, a tumor may contain some large clearly neoplastic cells with large nuclei, prominent nucleoli, but mostly eosinophilic cytoplasm, and these cells might be large tumor astrocytes or

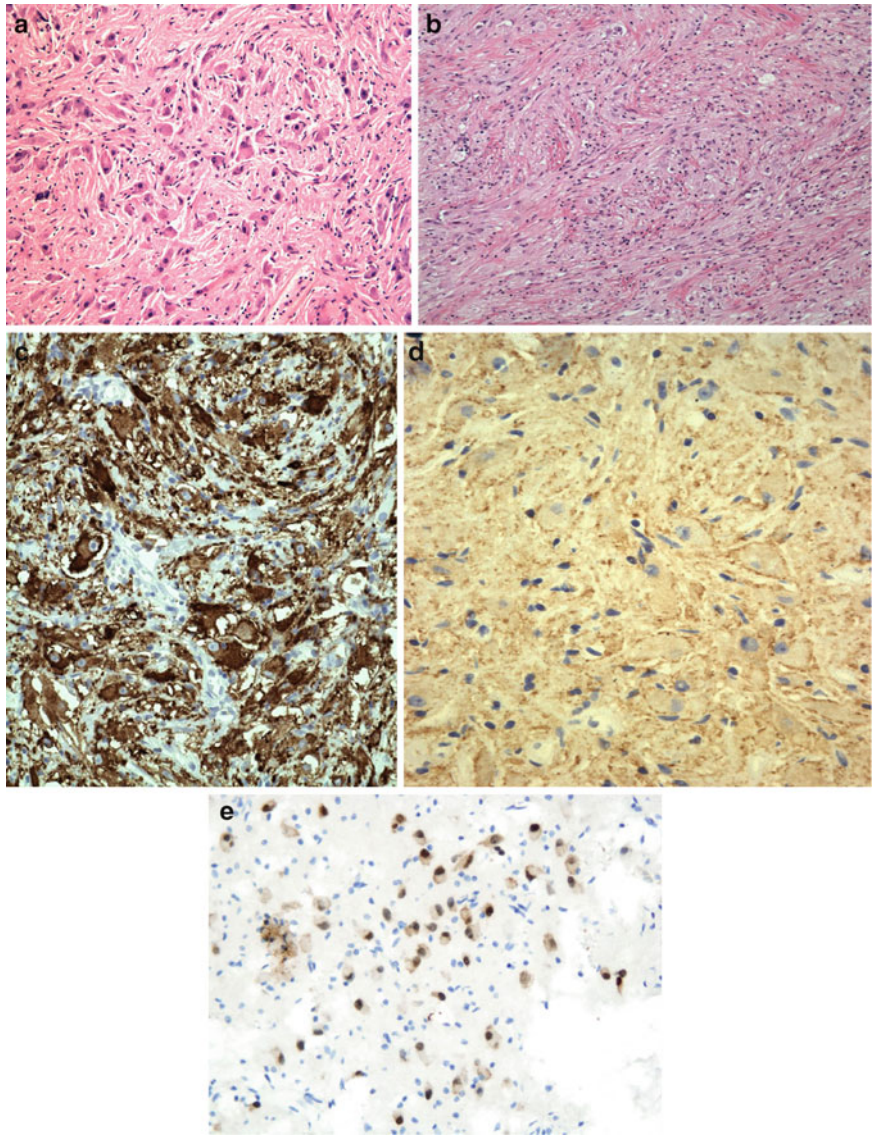

Fig. 18.2 Histopathology and immunohistochemical stains of gangliogliomas. (**a**) This typical ganglioglioma has an abundant population of large ganglion cells with polygonal cell bodies and large pale nuclei with prominent nucleoli; the background has numerous smaller astrocytic cells. H&E, 400× original magnification. (**b**) Another ganglioglioma has a prominent piloid astrocytic background with scattered ganglion cells. H&E, 400× original magnification. (**c**) Synaptophysin immunostain of a ganglioglioma. In this example some of the large neurons have cytoplasmic immunopositivity, suggesting delayed axonal transport, but there is also the characteristic perikaryal granular surface immunopositivity which identifies these as abnormal, *ie* neoplastic neurons. 400× original magnification. (**d**) Another synaptophysin immunostain from a different ganglioglioma has a much less dense and somewhat discontinuous but still identifiable perikaryal surface immunoreactivity around neoplastic neurons. 400× original magnification. (**e**) A Neu-N immunostain of a ganglioglioma variably marks the nuclei (and sometimes less densely the cytoplasm) of some tumor cells, with other obvious ganglion cells not immunopositive or with much less intense nuclear immunoreactivity. Here the variability of immunopositivity, including some wholly immunonegative cells, in cells clearly neuronal by other criteria helps identify these as abnormal neurons as well. 400× original magnification

they might be tumor neurons. For each of these problems, the correct diagnosis can only be determined using immunohistochemistry. The second problem is less difficult, as a variety of neuron-specific markers are now available to characterize tumor cells as neuronal. These include antibodies recognizing neurofilament protein (NFP), particularly the low (NF-L) and intermediate (NF-M) molecular weight types, since the high molecular weight NFP (NF-H) is less commonly recognized in neuronal cell bodies in general and in neoplastic neuronal cell bodies in particular; antibodies to neuronal forms of tubulin, particularly ß-III tubulin, which is relatively neuron-specific in the CNS; antibodies to the neuronal nuclear antigen (Neu-N); and antibodies to synaptic vesicle components, including chromogranin, synapsin-I, and synaptophysin. In the neuropathology practice of the first author, a combination of antibodies to NF-M, Neu-N, and especially synaptophysin have been especially helpful in the diagnosis of gangliogliomas (Miller 2009). If a clearly neoplastic population of large cells marks with one or more of these neuronal markers (Fig. 18.2c–e), then the cells are identified as neoplastic ganglion cells, and the tumor is a ganglioglioma unless it fits certain other special categories (see below). Most commonly, neoplastic ganglion cells will mark in their cytoplasm for NF-M, and will have a distinctive perikaryal surface immunopositivity for synaptophysin (Miller et al. 1990, 1993) (Fig. 18.2c, d); Neu-N immunopositivity is less common (Fig. 18.2e). Other immunostains have been suggested as helpful adjuncts to the diagnosis of ganglioglioma, such as anti-CD34 (Blümcke and Wiestler 2002; Luyken et al. 2004; Miller 2009). When suspect large tumor cells are positive in the right setting, CD34 immunopositivity can be helpful, but the absence of CD34 immunostaining ought not to preclude the diagnosis of ganglioglioma when neuron-specific markers are positive.

Determining whether neuronal cells within a tumor are part of the neoplasm or part of the nervous system infiltrated by a "pure" glioma is a more difficult process. This is not a problem when the tumor is in neocortex or hippocampus as the ordered nature of the neuronal arrangements in those structures makes it easier to recognize normal neurons in such laminar structure; for this purpose a Neu-N immunostain is often most valuable in discerning such structure when it might be obscured in an H&E stained section of tumor. Other brain tissues, such as particularly the amygdala, can be more problematic, however. It is helpful to identify the location of the tumor as in gray matter or white matter with stains for myelin such as Luxol Fast Blue, or for axons (silver stains or NFP immunostains), as a tumor in white matter with a large number of neurons is likely a ganglioglioma. In gray matter, the most useful tool is the pattern of synaptophysin immunopositivity, as the perikaryal surface immunopositivity is not characteristic of normal neurons of cortex, basal ganglia, thalamus, hypothalamus, amygdala, or hippocampus (Miller et al. 1990). There are some difficulties with this in the spinal cord, and perhaps in the lower brainstem, which are better discussed in the companion chapter to this one focused on these issues in the spinal cord.

The indolent character of most gangliogliomas is also reflected in the absence of mitotic figures in most examples, and by a low level of immunopositivity for the Ki67 nuclear cell-cycle associated antigen (usually detected with the antibody MIB1). Typically results of such immunostains are reported as a labeling index (LI), representing the proportion of tumor cell nuclei labeled by the antibody stain (the number of immunopositive from the total number of tumor cell nuclei in a sample of about 1,000 cells). The WHO classifies gangliogliomas as Grade I (although they should probably be Grade II), and the Ki67 LI for most examples is up to 5% but not more. Labeling indices of greater than 10% suggest an anaplastic transformation and mandate diagnosis as a higher grade ganglioglioma (Anaplastic Ganglioglioma, WHO Grade III).

Treatment

Cerebral gangliogliomas are mostly low grade indolent tumors. They respond relatively poorly to radiation and chemotherapy, and these therapies,

particularly radiation, carry risks of inducing transformation to higher grade neoplasia. Treatment in almost all cases, then, is focused on gross total neurosurgical excision of the tumor. Those cases that are apparently circumscribed by MRI lend themselves well to this approach using modern image-guided stereotactic neurosurgical techniques. More infiltrative examples may have to be subtotally resected, and as these tumors are never encapsulated and always have some degree of microscopic infiltration pathologically even gross total excisions will leave behind some cells. In unusual locations, particularly some brainstem sites, gross total excision may not be an option, so if there is substantial residual tumor, radiation may be considered on a case-by-case basis. Several authors have reported on their experience with gangliogliomas in the brainstem, and most feel that a resection of any exophytic portion followed by radiation therapy is the best treatment approach. There have been a few reports on the use of radiation therapy after subtotal resection. Rades et al. (2010) demonstrated that after subtotal resection of a ganglioglioma, whole brain radiation therapy conferred improved local control, but did not improve overall survival. In a smaller study, Liauw et al. (2007) showed that adjuvant radiation therapy for subtotally resected low grade gangliogliomas resulted in a 75% local control rate.

Prognosis

Gangliogliomas may be cured by gross total excision (Lang et al. 1993; Zentner et al. 1994). For those patients in whom seizures were a presenting symptom, excision of the tumor is also the best therapy for the epilepsy. Ogiwara et al. (2010) reported on 30 patients who underwent resection of gangliglioma with a history of medically intractable epilepsy. At 3.5 years, it was shown that 90% of the patients were found to be seizure free and off all seizure medications. Guilioni et al. (2006) analyzed seizure outcomes in 21 patients and showed that 66% were seizure free and 33% showed marked reduction in seizure frequency, with a mean follow up of 5.4 years. A follow-up study, however (Guilioni et al. 2009) suggested yet further improvement in seizure treatment with surgery tailored to resect the tumor and surrounding epileptogenic tissue.

In some patients, presumably due to microscopic residual tumor, a recurrent mass will emerge years after initial treatment; similarly in patients with subtotally resected gangliogliomas recurrent or progressive growth can be seen months to years after excision. Second surgical excision is usually still the best option for patients with progressive/recurrent gangliogliomas, for all the reasons surgery is the best approach for initial therapy of these tumors (Lang et al. 1993).

A small minority of patients with gangliogliomas will have recurrent tumors that have more rapid growth and, when excised, are clearly no longer low grade. The histological appearance may vary, in that the tumor may retain characteristics of a ganglioglioma but will have a detectable mitotic rate, a higher Ki67 labeling index (10% or more, usually), and, often, vascular hyperplasia or necrosis. (One must be careful in interpretation of necrosis if the patient has undergone other treatment, such as radiation). Other examples of high grade tumor following a diagnosis of low grade ganglioglioma lose their neuroglial mixed character, and resemble or constitute high grade "pure" gliomas, including examples resembling or constituting glioblastoma, with necrosis, vascular hyperplasia, increased nuclear pleiomorphism, and high mitotic rates. This may in unusual situations follow excision of a low grade ganglioglioma by as little as a few months. (For this reason, we resist the tendency to characterize ordinary gangliogliomas as "benign"; they behave more like low grade gliomas which have the potential for transformation to higher grade. This is exactly why they are better regarded as WHO Grade II tumors). These high grade histologic appearances have the usual correlation with more aggressive clinical behavior and a poor prognosis. Majores et al. (2008) reviewed their experience with subtotally resected gangliogliomas, and ones with both atypical and/or anaplastic features. They found the 5 year survival rate for "atypical gangliogliomas", which they termed grade II tumors to be 79%,

with survival of only 53% for anaplastic gangliogliomas (grade III).

Contrariwise, El Khashab et al. (2009) found that the achievement of gross total resection, seizures as presenting symptom and hemispheric location all portended good outcome. Similarly, Majores et al. (2008) showed that patients presenting with drug resistant epilepsy had improved outcome. They also showed that the pathological features of a gemistocytic cell component, lack of protein droplets, and positive CD-34 immunolabeling were predictors of an adverse clinical course.

Other CNS Tumors with Ganglion Cell-Like Components

There is a subtype of gangliogliomas which is both clinically and pathologically distinctive, namely the desmoplastic ganglioglioma (often termed "superficial desmoplastic ganglioglioma of infancy", although not all cases occur in infants or even children). These are typically massive cystic and solid tumors with an alarming MRI appearance, which histologically are at least in part densely fibrotic. Ganglion cells are often inconspicuous until immunostains, particularly synaptophysin stains, reveal them hidden in the dense fibrosis and spindle cell astrocytic background. Histologically these are otherwise typical of gangliogliomas and need no extra illustration here. Despite their alarming large MRI presentation patients with these tumors mostly do very well with gross total surgical excision alone (Miller 2009).

Another brain tumor with a histologic mixture of cell types including large neuron-like cells is the pleiomorphic xanthoastrocytoma (PXA) (Kepes et al. 1979; Giannini et al. 2007; Miller 2009). PXAs, like gangliogliomas, often involve the cortex, are often found in the temporal lobes of younger patients, and are often associated with seizures. Most examples, if examined with antibodies to neuronal antigens, have cells which are labeled with these immunostains, so that PXAs are actually glioneuronal tumors (Powell et al. 1996; Im et al. 2004). Also similar to gangliogliomas, PXAs are low grade neoplasms, usually sharply circumscribed but with some infiltrative borders histologically, and some have recurred after gross total excision as higher grade tumors, including some with all the characteristics of glioblastomas. As with gangliogliomas, then, gross total excision may be curative of low grade PXAs, but some will recur or progress and may require second surgery, and some may transform to higher grade tumors with a worse prognosis.

Some high grade gliomas, tumors with the characteristics of glioblastomas but with large pleiomorphic cells as a major component of the cellular populations, include cells which have immunopositivity for neuronal markers, often co-existing in the same cell as immunoreactivity for GFAP, S100 protein, or vimentin, typically markers of glial differentiation. These tumors ought not to be classified as gangliogliomas despite having these large, provably neuronal cells, and they behave as aggressive glioblastoma-like neoplasms (Miller 2009; Varlet et al. 2004; Rodriguez et al. 2005). These tumors, too, support the hypothesis that gliomas arise from multipotential progenitor cells ("tumor stem cells") and that in some cases they retain mixed glial and neuronal characteristics in the same cells.

A tumor with considerable similarity to PXA in regard to co-expression of glial and neuronal phenotypes is the subependymal giant cell astrocytoma, now being suggested to be termed "subependymal giant cell tumor" in view of its mixed glial and neuronal nature. Some but not all of these tumors are associated with Tuberous Sclerosis Complex. All consist of uniformly large cells with large cell bodies which in H&E stains are usually brightly eosinophilic and resemble those of large gemistocytic astrocytes, while the nuclei are also large and have pale chromatin with prominent nucleoli and resemble neuronal nuclei (Miller 2009). These cells regularly co-express GFAP, Vimentin, Synaptophysin, and Neurofilament Protein, and thus are neither astrocytes nor neurons, but hybrids or bipotential cells. Almost all of them occur at the foramen of Monro, and present with obstruction of the foramen and resulting hydrocephalus, often with headache as the presenting symptom.

Their location and uniform MRI appearance is strongly suggestive of the correct diagnosis. Recommended therapy is gross total excision, and recurrences either do not occur in such cases or are very rare; however TSC patients may develop other primary SEGTs after resection of one.

Neurocytomas and Variants

Prior to 1982 there was little use of the term "neurocytoma", and it was not a standard description of any kind of CNS neoplasm. In that year Hassoun et al. (1982) described ultrastructural evidence that oligodendroglioma-like tumors in young adults located in the lateral ventricles attached to the septum pellucidum were in fact tumors of small mature neurons, hence "neurocytoma". Eventually the WHO classification incorporated these lesions as "central neurocytomas". However from the early 1990s the neuropathologist author of this chapter, and several other neuropathologists in other centers, began to describe neuronal differentiation in tumors with oligodendrogliomatous elements (either "pure" oligodendroglioma or mixed gliomas dominated by oligodendroglioma-like cells) in the brain parenchyma, not in the ventricles (Nishio et al. 1990; Miller et al. 1993; Ng et al. 1994; Giangasapero et al. 1997; Brat et al. 2001) (Fig. 18.3a–h). There was no accepted classification for these until recently, and the WHO classification while recognizing their existence still has very little on them (Figarella-Branger et al. 2007). They have been termed "extraventricular neurocytomas", "parenchymal neurocytomas", or, based on their apparent differentiation, "glioneurocytomas", "gangli-oneurocytomas", or "ganglioglioneurocytomas" (Sharma et al. 2006; Miller 2009), the last term reflecting a component with neoplastic ganglion cells in addition to astrocytic, possible oligodendrogliomatous, and neurocytic elements.

These tumors tend to fall into two groups by histological appearance: those that are otherwise ordinary infiltrative gliomas, particularly oligodendrogliomas (Fig. 18.3a, b), and those with special histological features, such as adipose cell differentiation, papillary patterns of growth around blood vessels or the formation of distinctive rosette-like structures (Miller 2009; Kleihues et al. 2007; Nakazato et al. 2007; Hainfellner et al. 2007). They have been described more often in younger patients but are not restricted to any age group, and they have been found in all sites of the neuraxis. Most have the character of low grade (WHO Grade II) tumors, but appropriate investigations of anaplastic oligodendroglioma-like lesions with vascular hyperplasia, high Ki67 LI, or even necrosis have shown that some such tumors are predominately neurocytic. Neuropathological diagnosis depends on appropriate immunostains, as with gangliogliomas, but usually ganglion cell elements are absent or sparse and one must depend on neuronal marker immunopositivity of the smaller neurocytic cells to make the diagnosis (Fig. 18.3d, e, h). Of note here is that, as with "central" (intraventricular) neurocytomas, synaptophysin immunopositivity is rare in the cell bodies of the tumor cells, but is dense, granular, and intense in the neuropil-like tissues between the cells (Fig. 18.3d, h). As this appearance is also seen in normal gray matter, identifying the location of any given tumor sample as within gray matter or white matter is essential to proper interpretation of the synaptophysin immunoreactivity in such tumors (Miller 2009). The diagnosis of neurocytoma instead of oligodendroglioma may be suggested by the presence of rosette-like arrangements around fibrillary neuropil zones resembling Homer-Wright rosettes but larger (Fig. 18.3a, g, h) but still generally requires immunohistochemical confirmation. Of note also is that these parenchymal neurocytic tumors frequently have some cells with either astrocytic appearances or cells otherwise typical of some variants of oligodendroglioma, such that there may be GFAP immunopositivity in some cells (Fig. 18.3c) and there may be "mini-gemistocytes" as described in oligodendroglioma (Fig. 18.3f).

The nosology of and diagnostic criteria for all of these tumors with neurocytic elements is still being developed, hence prognostic statements can at best be tentative. Some suggested entities are so rare that only small numbers have been

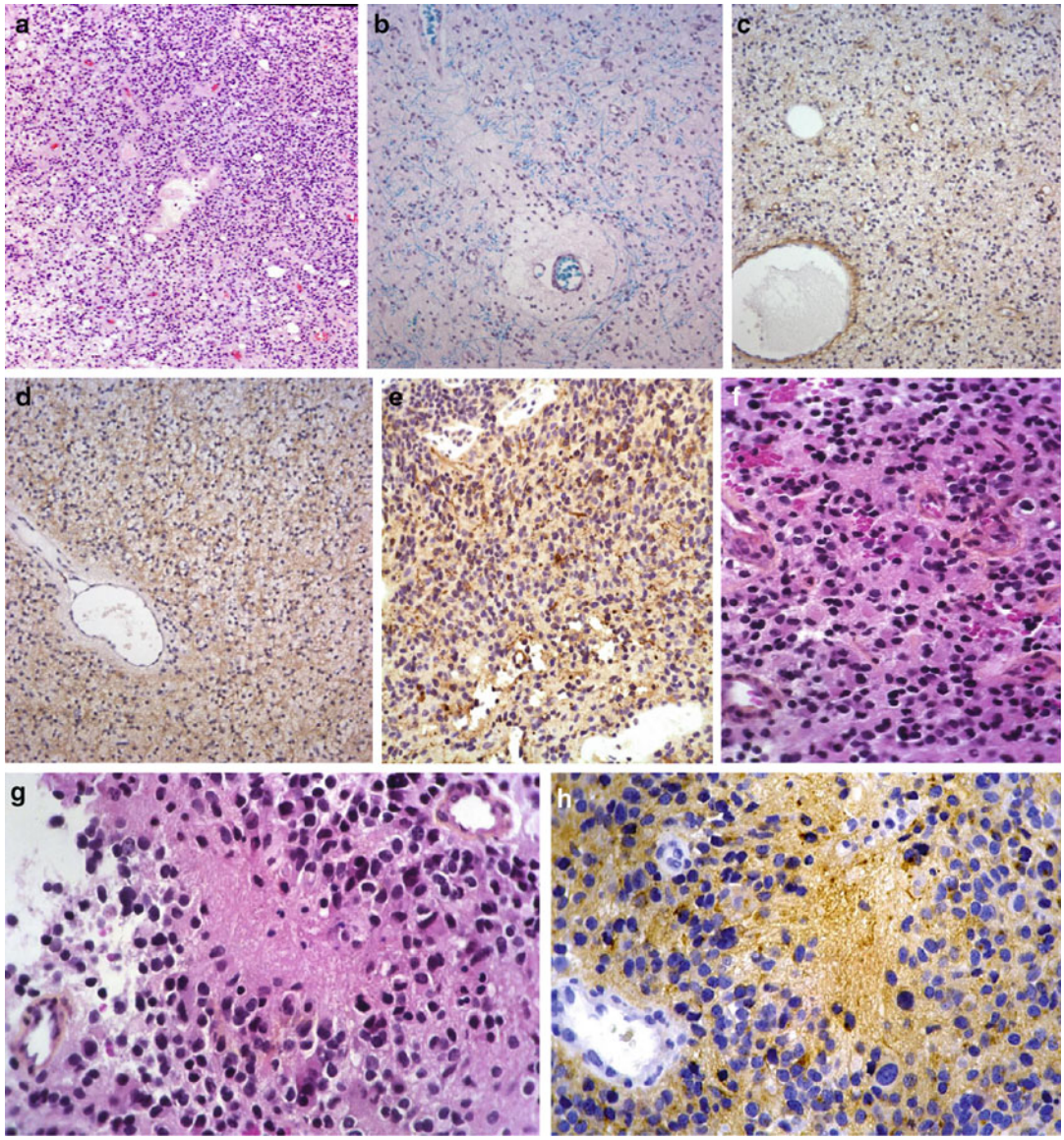

Fig. 18.3 Histopathology and immunohistochemical stains of parenchymal neurocytic tumors. (**a**) Cellular neurocytic tumor composed of small to medium size cells with monotonous bland round nuclei centrally located in the cell bodies, resembling oligodendroglioma. The tumor cells make vague perivascular pseudorosette-like arrangements and some rosette-like arrangements around anucleate neuropil, suggesting the neurocytic rather than oligodendrogliomatous nature of the tumor. H&E, 100× original magnification. (**b**) Infiltrating neurocytic tumor in white matter among myelinated axons, which are *blue* in this myelin stain. Luxol Fast Blue/H&E combination stain, 200× original magnification. (**c**) Sparse astrocytic cells in a parenchymal neurocytoma are highlighted this GFAP immunostain. 200× original magnification. (**d**) The neuropil-like synaptophysin immunopositivity between these tumor cells demonstrates the neurocytic nature of the neoplasm. 200× original magnification. (**e**) Strong cytoplasmic neurofilament protein immunopositivity (antibody RMDO20, to intermediate molecular weight NFP) similarly shows that the oligodendroglioma-like tumor cells are in fact neuronal. 400× original magnification. (**f**) Some neurocytomas have cells with a minigemistocytic appearance just like their oligodendrogliomatous counterparts. Such cells have round nuclei at one side of a small eosinophilic "bag" of cytoplasm. Hematoxylin-Phloxine-Saffranin (HPS), 400× original magnification. (**g**) Neurocytic ("giant Homer Wright") rosette. The tumor cells surround an anuclear fibrillary zone, and send processes into it. This appearance must not be confused with pseudopalisades of tumor cells around necrosis such as is seen in glioblastoma and other high grade gliomas. HPS, 400× original magnification. (**h**) A neurocytic rosette has strong granular immunopositivity for synaptophysin. 400× original magnification

reported, making prognostication statistically impossible. As many examples of oligodendroglioma or mixed glioma are not conventionally investigated for neuronal differentiation, the true incidence of parenchymal neurocytic tumors and any possible prognostic differences between those tumors which have neuronal marker positivity and those oligodendroglioma-like tumors which do not remains unknown. Some authors have suggested that there are distinctions between parenchymal neurocytic tumors ("extraventricular neurocytomas") and oligodendrogliomas with neuronal differentiation, although the diagnostic criteria and means to divide these as two entities are hardly described, much less agreed-upon (Perry et al. 2002). Similarly as noted some gangliogliomas have oligodendroglioma-like elements which by immunohistochemistry are neurocytic (Miller et al. 1993; Chou et al. 2010); now there is a proposal to separate oligodendrogliomas with ganglion cell elements from these ganglioneurocytomas (Perry et al. 2010). This remains an area within neuropathology and neuro-oncology which is unsettled and controversial, and only after additional data are accumulated and at least an international consensus is built will new classification schemes be built. Until such time it seems unreasonable to separate these various "entities", and we prefer to group them as parenchymal neurocytic tumors and specify the identifiable other differentiation (ganglion cells, astrocytes) as necessary.

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