The Expanding Family of Glioneuronal Tumors

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Abstract: Three new entities have been recently added to the group of glioneuronal tumors in the most recent update of the World Health Organization classification of tumors of the central nervous system: papillary glioneuronal tumor, rosetted glioneuronal tumor with neuropil-like islands, and rosette-forming glioneuronal tumor of the fourth ventricle. These tumors are relatively infrequent lesions, and because of that, they can be challenging to diagnose for the practicing pathologist. In this article, we summarize the clinical and pathologic findings of these new lesions.

Key Words: glioneuronal tumors, papillary glioneuronal tumor, rosette-forming glioneuronal tumor of the fourth ventricle, rosetted glioneuronal tumor with neuropil-like islands

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The recently updated World Health Organization (WHO) Classification of Tumors of Central Nervous Systems expands our classification of tumors of mixed glioneuronal type.[1] The classification of tumors in this area has grown in the last few decades, in part, facilitated by the availability of immunostains, which have enabled us to more readily identify neuronal differentiation in tumors which morphologically resemble glial neoplasms.

For most of the 20th century, ganglioglioma has been recognized as a distinct entity. This tumor is marked by the presence of both an atypical ganglion cell component intermixed with a glioma component, the latter usually resembling a low-grade fibrillary astrocytoma, pilocytic astrocytoma, or occasionally a low-grade oligodendroglioma.[2,3] In the recently updated WHO classification, gangliogliomas are designated as grade I tumors with an excellent prognosis.[1] Rare examples of more aggressive behaving gangliogliomas, frequently marked by increased mitotic activity and areas of necrosis, have been recognized, and a designation of anaplastic ganglioglioma (WHO grade III) has been made for those tumors.[4]

In 1987, VandenBerg et al[5] described the desmoplastic infantile ganglioglioma. This tumor is marked by superficial location, early age of presentation, and a morphology marked by a collagenous matrix and a mixture of spindled astrocytic cells and ganglionic cells. Similar to ordinary gangliogliomas, these tumors generally behave in a benign fashion and are designated by the WHO as grade I neoplasms.

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In the following year, the first series of dysembryoplastic neuroepithelial tumors, another distinctive neuronal-glial neoplasm, was published.[6] These grade I tumors are marked by multinodularity, cortical location, and good prognosis. Morphologically, they consist of a proliferation of oligodendroglial-like cells arranged against a microcystic background with a component of neuronal cells demonstrating negligible cytologic atypia. Interestingly, both gangliogliomas and dysembryoplastic neuroepithelial tumors have been associated with adjacent cortical architectural abnormalities (cortical dysplasia, malformations of cortical development), suggesting that these entities may be developmental in their derivation.

In the most recent rendition of the WHO, 3 new glioneuronal tumors have been added to the previously described repertoire: papillary glioneuronal tumor, the rosette-forming glioneuronal tumor (RGNT) of the fourth ventricle, and the rosetted glioneuronal tumor (also known as glioneuronal tumor with neuropil-like islands).

PAPILLARY GLIONEURONAL TUMOR (WHO GRADE I)

In 1997, Kim and Suh[7] reported a case of pseudopapillary neurocytoma, which demonstrated areas of glial differentiation. This tumor likely represented the first reported case of papillary glioneuronal tumor. In the following year, Komori et al[8] reported 9 cases of what they termed papillary glioneuronal tumor; this series established the lesion as a distinct entity.

Because of the paucity of reported cases in the literature,[7–15] information regarding this tumor's incidence in the general population is currently not available. These tumors have been described in patients ranging from pediatric age to 75 years, with a mean age of 27 years. They have an equal sex distribution.[16] The tumor generally arises in the cerebral hemispheres and seems to have a predilection for the periventricular region of the temporal lobe (38% of cases).[12,16] Imaging studies show a well-demarcated, contrast-enhancing solid and cystic tumor which demonstrates little mass effect. Most cases are asymptomatic, but some patients present with focal neural deficits, headaches, and seizures.

Morphologically, the tumor is characterized by a pseudopapillary architectural pattern in which cuboidal, glial fibrillary acidic protein (GFAP)-positive glial cells with generally rounded nuclei and scant cytoplasm line hyalinized blood vessels (Figs. 1A, B). Interspersed between these pseudopapillary structures are collections of neurocytic cells, frequently resembling oligodendroglial-like cells (Figs. 1C, D). Occasionally, mature ganglionic cells may be observed. Ishizawa et al reported, in 2006,[17] a variant of this lesion showing a minigemistocytic component. The lesion may be surrounded by prominent gliosis. The neuronal element of this tumor stains with neural markers including

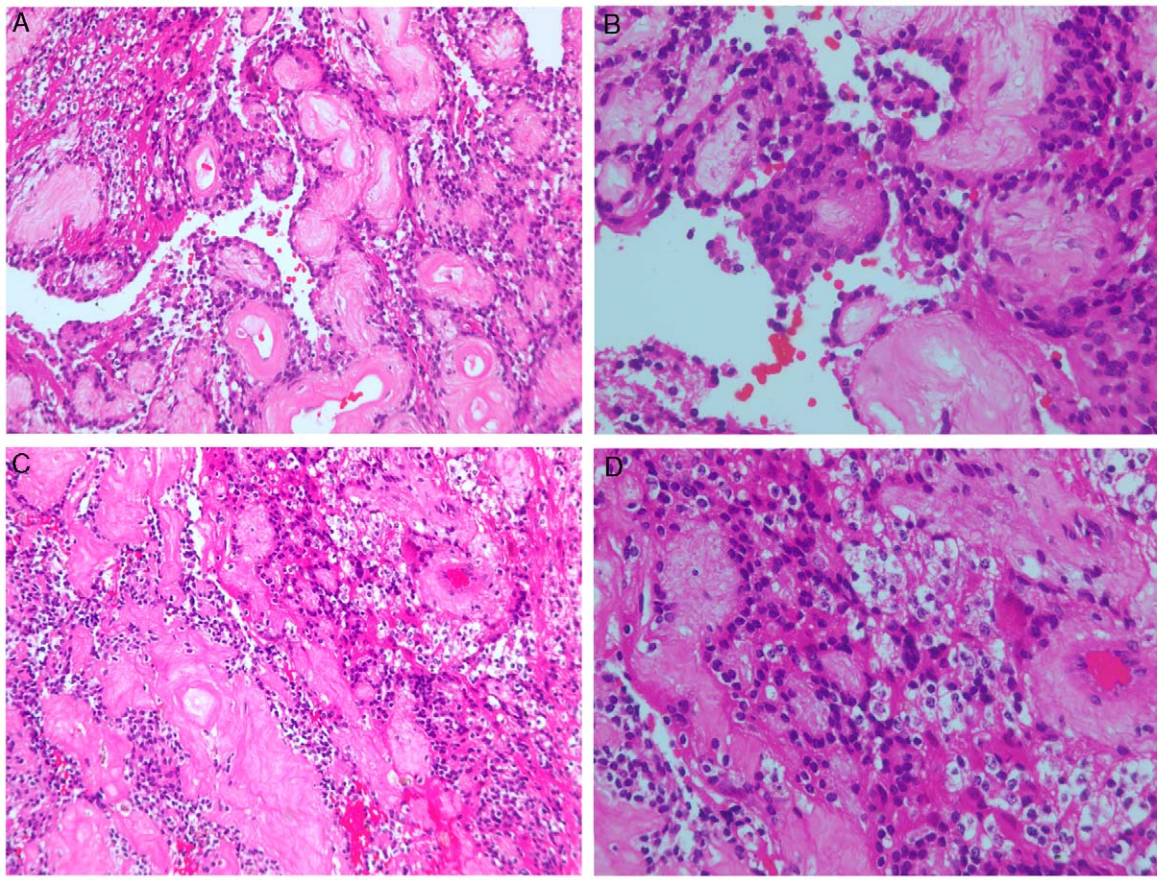

FIGURE 1. Papillary glioneuronal tumor. A, Pseudopapillary architecture lined by glial cells, alternating with areas of hyalinized blood vessels (hematoxylin and eosin, 200 ×). B, The pseudopapillary structures are lined by glial cells with cuboidal shape, scant cytoplasm, and round nuclei (hematoxylin and eosin, 400 ×). C, Interspersed between the pseudopapillary structures are collections of neurocytic cells (hematoxylin and eosin, 200 ×). D, The neurocytic cells resemble in higher magnification oligodendroglial-like cells (hematoxylin and eosin, 400 ×). *a+*

synaptophysin (Fig. 2A), neuron-specific enolase, class III β-tubulin, and NeuN. The glial component is reactive for GFAP (Fig. 2B) and S-100. Prominent mitotic activity, necrosis, and vascular proliferative changes are generally not present. Recent reports on Oligo2, a new immunomarker which preferentially stains oligodendrocytes, have reported positive staining in this tumor.[11,17] Cell proliferation, as evaluated with Ki-67 or MIB-1–labeling indices, is generally low, typically less than 3%, except for the variant with minigemistocytes that has been shown to have increased proliferative activity with a labeling index greater than 10%.[17] Ultrastructural studies show both astrocytic and neurocytic differentiation.[12]

Several lesions morphologically resemble the papillary glioneuronal tumor including pilocytic astrocytoma, gangliglioma, dysembryoplastic neuroepithelial tumor, and extraventricular neurocytoma. On imaging, pilocytic astrocytomas classically have a cyst with enhancing mural nodule configuration, similar to this tumor. Microscopically, pilocytic astrocytomas typically have a biphasic light microscopic appearance, consisting of cells with spindled morphology that are clearly astrocytic and other areas in which the cells may be more rounded. Occasionally, areas with rounded cells resembling oligodendroglia may be observed; such tumors may resemble a glioneuronal tumor. However, there is no evidence of neural differentiation in the rounded cells of pilocytic astrocytoma. Although Rosenthal fibers may be observed at the edge of a papillary glioneuronal tumor, the fibers along with eosinophilic granular bodies are generally not intermixed in the middle of the lesion; this is a feature of pilocytic astrocytoma.

Ganglioglioma differs from papillary glioneuronal tumor in that there is significant cytologic atypia to the neuronal component of the ganglioglioma. Most patients with ganglioglioma typically present with a long history of medically intractable epilepsy, and frequently, there is architectural disorganization in the adjacent cortex (malformation of cortical development or cortical dysplasia).

The dysembryoplastic neuroepithelial tumor is a mixed glioneuronal neoplasm that may arise during embryogenesis. It often presents in young adults as an incidental finding or with seizures. On imaging studies, it usually presents as a multinodular, focally cystic lesion in the temporal or frontal cortex; this is in contrast to the uninodular papillary glioneuronal tumor. It has a good prognosis after excision with only rare recurrence. Histologically, the tumor cells resemble mature oligodendrocytes intermixed with normal appearing neurons that appear to float within mucin pools. Mucinous changes are unusual in the papillary glioneuronal tumor. Like ganglioglioma,

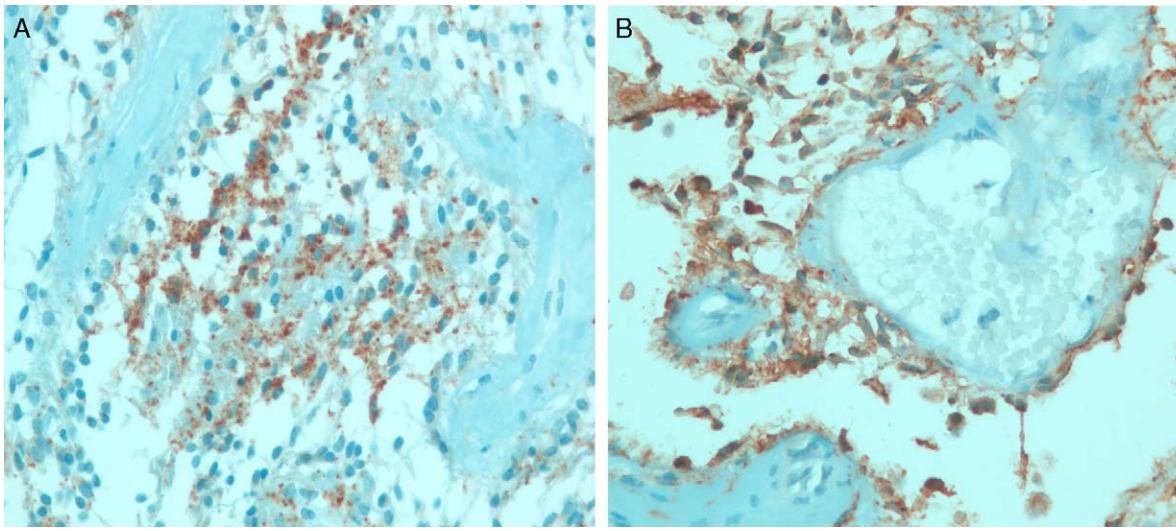

FIGURE 2. Papillary glioneuronal tumor. A, The neurocytic cells stain positively with synaptophysin by immunohistochemistry, 200 ×). B, The glial cells are immunoreactive for glial fibrillary acidic protein, 400 ×). *a+*

adjacent areas of cortical dysplasia can be found in association with the dysembryoplastic neuroepithelial tumor. Extensive GFAP immunoreactivity and papillary architecture are not features of the dysembryoplastic neuroepithelial tumor.

The rare extraventricular neurocytoma is another possible differential diagnostic consideration. These tumors are more frequent in the cerebellum, where they present as well-circumscribed, sometimes cystic lesions. Microscopically, this tumor is marked by sheets, clusters, ribbons, or rosettes of monotonous tumor cells with round and regular vesicular nuclei and distinct nucleoli; tumor cells are embedded in a matrix of fine neuropil. This tumor lacks a pseudopapillary architecture. Ganglion cells can be seen in the majority of cases. The cells are strongly positive for synaptophysin. Focal GFAP immunoreactivity may be observed in up to 46% of the cases, but it is usually not as prominent as with the papillary glioneuronal tumor.

Papillary glioneuronal tumors were reported to have a favorable outcome in the original series of 9 tumors reported by Komori et al.[8] The tumor is considered to have low malignant potential.[16] There was no evidence of recurrence identified after surgery in any of the tumors studied with follow-up periods ranging from 3 to 84 months.[16]

ROSETTE-FORMING GLIONEURONAL TUMOR OF THE FOURTH VENTRICLE (WHO GRADE I)

The RGNT of the fourth ventricle was established as a distinct entity in 2002, based on a series of 11 tumors reported to arise in the posterior fossa region by Komori et al.[18–20] A tumor morphologically resembling this lesion had been previously reported in the cerebellum as a dysembryoplastic neuroepithelial tumor in 1995 by Kuchelmeister et al.[21]

Similar to the papillary glioneuronal tumor, the incidence of this lesion in the general population is not known because of the limited number of cases reported in the literature. Patients have ranged in age from 12 to 59 years, with a mean age of 31 years.[22] The neoplasm is encountered slightly more frequently in females, and it typically presents with symptoms and signs related to hydrocephalus, particularly headaches and ataxia. Tumors are characteristically situated in the midline fourth ventricle. Imaging studies show a relatively circumscribed, solid mass demonstrating high signal intensity on T2-weighted images and low intensity on T1-weighted images.

Morphologically, RGNTs are biphasic tumors with both neurocytic and glial areas. The glial component of the tumor usually predominates and most closely resembles a pilocytic astrocytoma. The glial cells are elongated and may be arranged against a microcystic background (Figs. 3A–D). Rosenthal fibers, eosinophilic granular bodies, and calcifications may be evident. Associated with the gliomatous component are neurocytic areas marked by the formation of rosette and perivascular pseudorosette-like structures (Fig. 4A).[23] Occasionally, ganglion cells may be present. Mitotic activity and necrosis are usually absent. Vascular proliferative changes and sclerosed stroma may be focally evident (Fig. 4B). Ultrastructural studies confirm the presence of both astrocytic and neurocytic cell components. Ki-67 proliferation indices are low.

The RGNT can resemble pilocytic astrocytoma, dysembryoplastic neuroepithelial tumor, or central neurocytoma. The pilocytic astrocytoma is more frequently seen in children below 13 years, whereas RGNT typically arise in older patients. The fourth ventricle would be a very unusual location for the pilocytic astrocytoma, which prefers the cerebellum, region around the third ventricle, and brain stem. Also, pilocytic astrocytoma does not demonstrate a neurocytic component by immunohistochemistry or ultrastructural examination; consequently, the presence of the neurocytic rosettes is not a finding in pilocytic astrocytoma. On imaging, the usual pilocytic astrocytoma tends to be a cystic lesion with a mural nodule that enhances, as opposed to RGNT that presents as a solid mass. Neuronal markers, such as NeuN and synaptophysin can help in the differential diagnosis of RGNT cases with scant neuronal elements.

Most dysembryoplastic neuroepithelial tumors also present in younger patients compared with RGNT. They

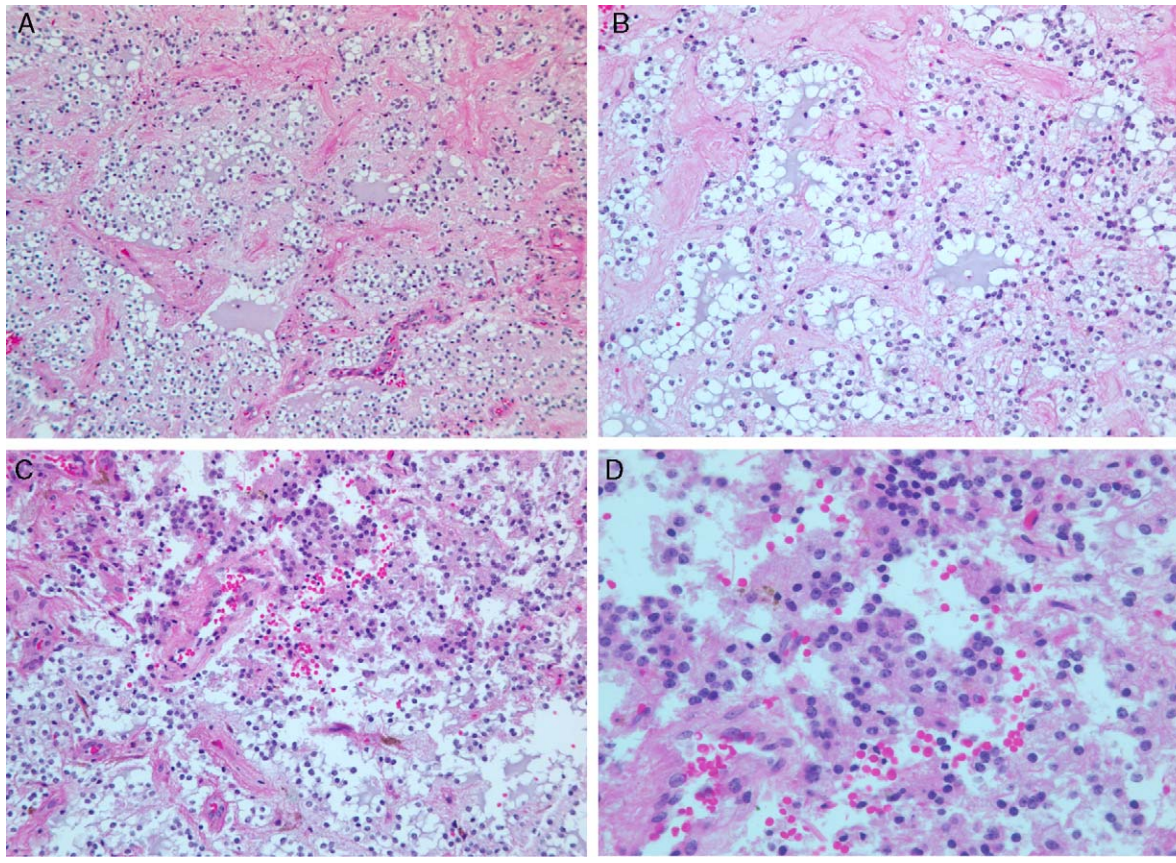

FIGURE 3. Rosette-forming glioneuronal tumor of the fourth ventricle. A, Low magnification view of the oligodendrocytic-like cells arrange in a microcystic pattern with central myxoid material (hematoxylin and eosin, 200 ×). B, The glial cells exhibit cuboidal clear cytoplasm and round nuclei (hematoxylin and eosin, 400 ×). C, This tumor has a biphasic appearance with both neurocytic and glial areas (hematoxylin and eosin, 200 ×). D, The neurocytic cells show scant more eosinophilic cytoplasm and fine chromatin (hematoxylin and eosin, 400 ×). *a+*

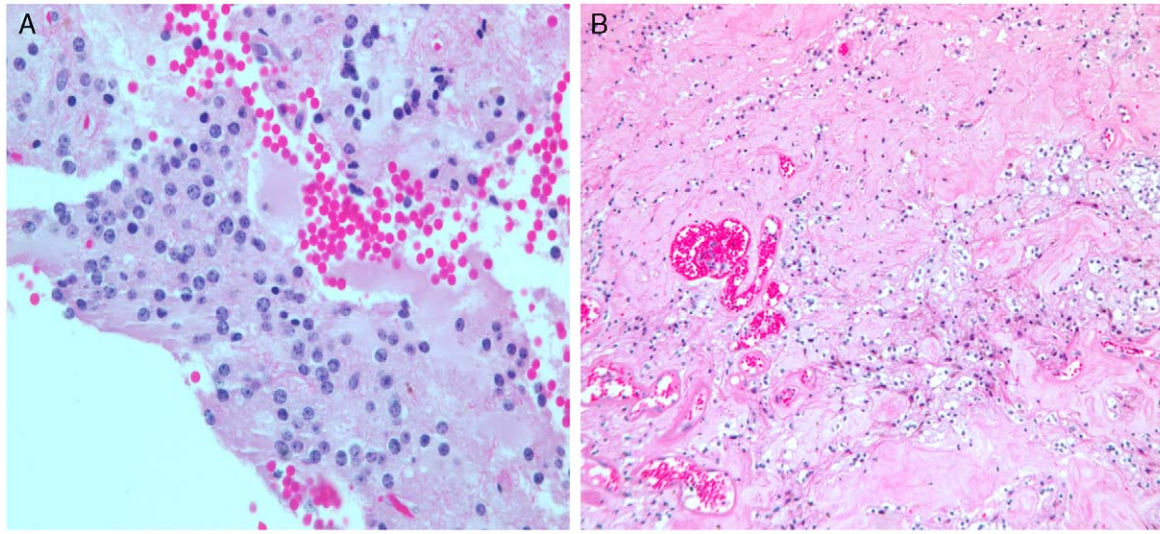

FIGURE 4. Rosette-forming glioneuronal tumor of the fourth ventricle. A, At least focally, the neurocytic component tend to be arranged in poorly formed rosettes (hematoxylin and eosin, 400 ×). B, Areas of sclerosed stroma with occasional granular bodies can be seen (hematoxylin and eosin, 200 ×). *a+*

are supratentorial, parenchymal-based tumors, for the most part situated in the cortex with a typical multinodular architectural pattern. Most RGNT are located in the midline next to the fourth ventricle and are uninodular lesions. In dysembryoplastic neuroepithelial tumors and in RGNT, a glial component is present; in the former, the glial component resembles mature oligodendrocytes and astrocytes, whereas in the latter, it resembles a pilocytic astrocytoma. Also, the "floating neurons in mucin pools" characteristic of dysembryoplastic neuroepithelial tumors are not observed in RGNTs.[24] The adjacent parenchyma in dysembryoplastic neuroepithelial tumors frequently demonstrates some evidence of cortical dysplasia, a feature not described with the RGNT.

Central neurocytoma can also be considered in the differential diagnosis. It often arises from the foramen of Monro or septum pellucidum and extends into the lateral or third ventricle, but is not usually seen in the 4th ventricle. It presents in young adults as a well-demarcated, often calcified lesion. The neuronal component of this tumor is composed of a monotonous proliferation of cells, which can sometimes exhibit salt and pepper chromatin and a "halo" mimicking oligodendrogliomas. Rosettes and perivascular pseudorosettes are a characteristic feature of both lesions. Central neurocytomas sometimes show Homer Wright rosettes with occasional perivascular rosettes.[25] RGNT can have perivascular pseudorosettes as a prominent feature. Central neurocytomas often show an eosinophilic fibrillary background, but "mucin pools," as seen in RGNT, are not identified. By electron microscopy, microtubules, clear vesicles, and neuritic-type processes can be seen in central neurocytomas.

Clinical follow-up in the limited cases of RGNT that have been reported indicates that these tumors have a favorable prognosis, warranting a WHO grade I designation. In the largest series of these tumors reported by Komori et al,[18] follow-up was available in 10 of the 11 reported cases; 9 of 10 patients showed no evidence of recurrence with follow-up intervals ranging from 2 months to 13½ years. The recurrent tumor occurred in a patient who presented with ataxia and 6th and 7th nerve palsies for 3 months. The solid 2 cm mass, located in the fourth ventricle and infiltrating the brain stem, was partially resected. Later, the patient developed progressive neurologic symptoms and underwent radiotherapy. She died after 3 years and 9 months follow-up.

GLIONEURONAL TUMOR WITH NEUROPIL-LIKE ISLANDS (ROSETTED GLIONEURONAL TUMOR) (WHO GRADE II OR III)

In 1999, Teo et al[26] reported 4 cases of a glioneuronal tumor of the adult cerebrum that were marked by neuropil-like or rosetted islands but otherwise resembled diffusely infiltrating astrocytomas. The lesion currently is considered a variant of astrocytoma, WHO grade II or III. Most cases reported in the literature have been located in the cerebrum with the exception of 1 cervicothoracic spinal cord tumor in a 44-year-old woman; the patient clinically presented with hemiparesis and unilateral sensory loss and subsequently developed meningeal dissemination.[27] The typical clinical presentation of this tumor includes seizures, focal neural deficits, or signs of increased intracranial pressure. Imaging studies show increased signal intensity on T2-weighted images usually associated with some edema and variable mass effect, findings similar to astrocytoma.

Morphologically, the tumor is marked by a background, which resembles a fibrillary, gemistocytic, or protoplasmic astrocytoma. Punctuating the tumor are fairly sharply circumscribed, round to oval islands of a neuropil-like matrix rimmed by rounded, oligodendroglial-like cells (Figs. 5A–D),[28] which demonstrate immunoreactivity with neurocytic markers, such as synaptophysin (Fig. 6A), NeuN, and anti-Hu.[12] An astrocytoma-like component, corresponding to WHO grade II or III diffuse or fibrillary subtypes, is also present. The tumor is frequently infiltrative. Scattered mitotic figures may be evident, particularly in grade III tumors. Vascular proliferative changes and necrosis are usually not salient features of this tumor. Occasionally, mature ganglionic cells may also be present. The gliomatous component of the tumor readily stains with GFAP antibody (Fig. 6B) and also demonstrates p53 immunoreactivity. Ki-67 or MIB-1 proliferation indices can be variable and range from very low (1%) up to 18.1%. The proliferating cells are usually restricted to the gliomatous component of the tumor. Even though there are not many cases studied by molecular techniques, gain of chromosome 7q and loss of 9p has been described.[12]

The differential diagnoses include oligodendrogliomas, astrocytomas, and ependymomas. The rosetted glioneuronal tumor at this point is considered a variant of fibrillary astrocytoma, with a similar prognosis grade for grade as the fibrillary astrocytoma. Even though a fibrillary background can be a prominent feature in the rosetted glioneuronal tumor, the distinguishing feature is the presence of neuropil-like islands. Oligodendroglioma cells tend to be more monomorphic than the astrocytoma component of the glioneuronal tumor and the oligodendrogliomas lack the neuropil-like islands. Characteristic 1p and 19q deletions, seen in almost 50% to 80% of the cases of oligodendrogliomas, are not observed in glioneuronal tumors with neuropil-like islands.[29] Exceptional cases of ependymoma showing areas of neuropil-like islands has been reported in the literature.[30,31] However, the intraventricular location, rosettes, and perivascular pseudorosettes that characterize ependymomas are absent in the rosetted glioneuronal tumor.

The clinical outcome of the glioneuronal tumor with neuropil-like islands seems to correspond to the grade of the astrocytoma component. Inclusion of this lesion in the section of anaplastic astrocytoma in the WHO classification implies that these tumors may, in fact, represent a variant of diffuse astrocytoma with aberrant neuronal differentiation rather than a distinct glioneuronal tumor. Even though they can exhibit low-grade morphology and low cell proliferation indices, most cases in the literature have shown progression, so this lesion should be considered as aggressive.[12]

THE FUTURE?

The most recent WHO classification added to the list of recognized distinctive glioneuronal tumor entities. With more experience, we will gain a better understanding of the derivation of these lesions and their biologic behavior.

We can anticipate further expansion of this group of neoplasms in the future. Another fairly poorly understood group of tumors that awaits further delineation are malignant glioneuronal tumors that do not seem to have

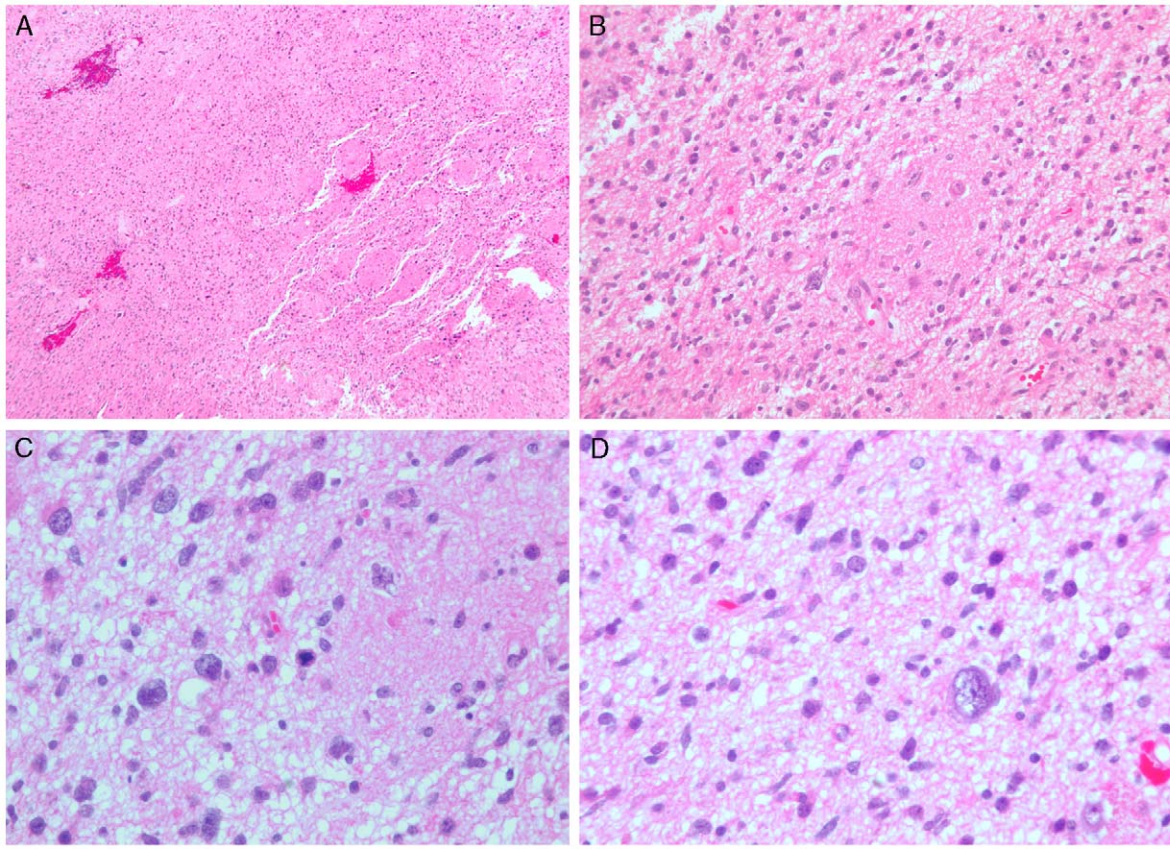

FIGURE 5. Glioneuronal tumor with neuropil-like islands. A, On low magnification, the islands of neuropil-like matrix are easily identified (hematoxylin and eosin, 100 ×). B, Rimming an island, a gliomatous component with occasional ganglion like cells is seen (hematoxylin and eosin, 200 ×). C, The gliomatous component shows pleomorphic cells that can resemble astrocytoma or sometimes oligodendrogliomas, with evident mitotic figures (hematoxylin and eosin, 400 ×). D, Scattered bizarre cells can be seen in a subset of cases (hematoxylin and eosin, 200 ×). a+

arisen from a ganglioglioma. Some of these tumors clearly have a malignant neuronal component to them.[32] Recent recognition of oligodendrogliomas with neurocytic differentiation by Perry et al[33] raises interesting questions about a potential common lineage for neuronal and oligodendroglial tumors. Descriptions of high-grade astrocytomas (glioblastoma) which demonstrate focal areas resembling embryonal tumors have been documented and may further

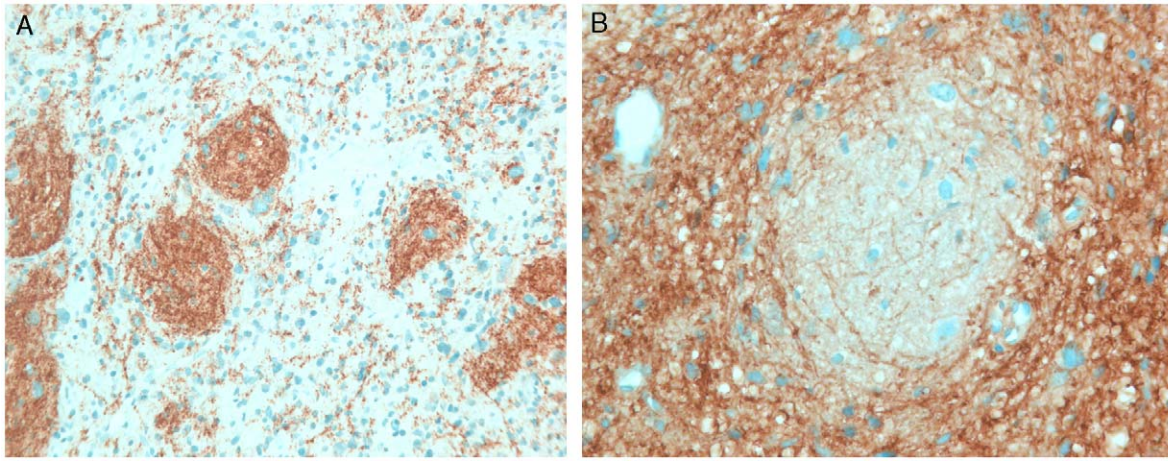

FIGURE 6. Glioneuronal tumor with neuropil-like islands. A, Synaptophysin immunostaining highlights the neuropil-like areas (200 ×). B, Glial fibrillary acidic protein is strongly positive in the gliomatous component of the tumor (400 ×). a+

expand our classification of this family of central nervous system neoplasms.[34,35]

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