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“The Expanding Family of Glioneuronal Tumors”

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Introduction

The recently updated World Health Organization Classification of Tumours 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, 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). 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 described the desmoplastic infantile ganglioglioma (5). 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.

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, three new glioneuronal tumors have been added to the repertoire: papillary glioneuronal tumor, the rosette-forming glioneuronal tumor of the fourth ventricle, and the rosetted glioneuronal tumor (also known as glioneuronal tumor with neuropil-like islands).

**Papillary glioneuronal tumor (WHO grade I) (7-15)**

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

Because of the paucity of reported cases in the literature, information regarding incidence in the general population is currently not available. These tumors have been described in patients ranging from pediatric age to 75 years. The tumor generally arises in the cerebral hemispheres and seems to have a predilection for the temporal lobe. Imaging studies show a well demarcated, contrast enhancing solid and cystic tumor which demonstrates little mass effect. Usual clinical presentations include focal neural deficits, headaches, and seizures.

Morphologically, the tumor is characterized by a pseudopapillary architectural pattern in which cuboidal, GFAP positive glial cells with generally rounded nuclei and scant cytoplasm line hyalinized blood vessels. Interspersed between these pseudopapillary structures are collections of neurocytic cells, frequently resembling oligodendroglial-like cells. Occasionally, mature ganglionic cells may be observed. The lesion may be surrounded by prominent gliosis. The neuronal element of this tumor stains with neural markers including synaptophysin, neuron specific enolase, class III beta-tubulin and NeuN. Prominent mitotic activity, necrosis, and vascular proliferative changes are generally not present. Cell proliferation, as evaluated with Ki-67 or MIB-1 labeling
indices, is generally low, typically less than 3%. Ultrastructural studies show both astrocytic as well as neurocytic differentiation.

Two lesions that morphologically resemble this tumor include pilocytic astrocytoma and ganglioglioma. 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 which 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. Gangliogliomas differ from papillary glioneuronal tumors 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 (cortical dysplasia). Chromosome 1p deletions, observed in a majority of oligodendrogliomas, are not a feature of this tumor.

Papillary glioneuronal tumors were reported to have a favorable outcome in the original series of nine tumors reported by Komori et al (8). There was no evidence of recurrence identified in any of the tumors studied with follow-up periods ranging from 6-45 months.

**Rosette-forming glioneuronal tumor of the fourth ventricle (WHO grade I) (12,15-21)**

Rosette-forming glioneuronal tumor of the fourth ventricle (RGNT) was established as a distinct entity in 2002 based on a series of eleven tumors reported in the posterior fossa region by Komori et al (16). A tumor morphologically resembling this lesion had been previously reported in the
cerebellum as a dysembryoplastic neuroepithelial tumor in 1995 by Kuchelmeister et al (17).

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 in the literature. Reported patients have ranged in age from 12 to 59 years. These tumors typically present with symptoms and signs related to hydrocephalus, particularly headaches, and/or ataxia. Tumors are usually 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 usually 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. 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. Occasionally, ganglion cells may be present. Mitotic activity and necrosis are usually absent. Vascular proliferative changes may be focally evident. Ultrastructural studies confirm the presence of both astrocytic and neurocytic cell components. Ki-67 proliferation indices are low.

The RGNT resembles the dysembryoplastic neuroepithelial tumor and pilocytic astrocytoma, the major differential diagnostic considerations. The pilocytic astrocytoma does not demonstrate a neurocytic component by immunohistochemistry or ultrastructural examination. 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. Most dysembryoplastic neuroepithelial tumors are fairly static, parenchymal based tumors, for the most part situated in the cortex. They typically have a multinodular architectural pattern and generally lack a glial component which resembles pilocytic astrocytoma. The adjacent parenchyma in
dysembryoplastic neuroepithelial tumors frequently demonstrates some evidence of cortical dysplasia, a feature not described with the RGNT.

Clinical follow-up in the limited cases 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 (12), follow-up was available in ten of the 11 reported cases; nine of ten patients showed no evidence of recurrence with follow-up intervals ranging from 2 months to 13½ years. One patient died after three years and nine months follow-up.

Glioneuronal tumor with neuropil-like islands (rosetted glioneuronal tumor) (WHO grade II or III) (12, 15, 22-25)

In 1999, Teo et al reported four cases of a neuronal tumor of the adult cerebrum that was marked by neuropil-like or rosetted islands (22). 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 one spinal cord tumor. The clinical presentation includes seizures, focal neural deficits, or signs of increased intracranial pressure. Imaging studies show an increased signal intense lesion 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 which demonstrate immunoreactivity with neurocytic markers such as synaptophysin or NeuN. Scattered mitotic figures may be evident. Vascular proliferative changes and necrosis are usually not a salient feature of this tumor. Occasionally, mature ganglionic cells may also be present. The gliomatous component of the tumor readily stains with GFAP antibody and also demonstrates p53 immunoreactivity. Ki-67 or MIB-1 proliferation indices can be variable and range from very low to as high as 18.1%. The proliferating cells are usually restricted to the gliomatous component of the tumor.
The clinical outcome of this tumor 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.

In 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 appear to have arisen from a ganglioglioma. Some of these tumors clearly have a malignant neuronal component to them (26). Recent recognition of oligodendrogliomas with neurocytic differentiation by Perry et al raises interesting questions about a potential common lineage for neuronal and oligodendroglial tumors (27).
REFERENCES


