

Development of the WHO Classification of Tumors of the Central Nervous System

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Introduction

The last four decades have seen the formulation of four editions of the World Health Organization (WHO) Classification of Tumors of the Central Nervous System (6, 8, 9, 11, 15), three over the past 17 years alone (6, 8, 9, 11). Each brought with it revisions reflecting changes of concept, some fundamental, as well as minor or subtle alterations. Not all changes met with the unanimous approval of committee participants. Nonetheless, each edition represented an improvement over prior efforts. The history of this process and a chronology of changes from one edition to the other is the substance of this work.

History

Early attempts to establish a systematic approach to brain tumor nomenclature such as the *Unio Internationalis Contra Cancrum* (UICC) (2), *Atlas of the Histology of Brain Tumors* (13), and the *Atlas of Gross Neurosurgical Pathology* (14) were unsuccessful. Even the groundbreaking AFIP Fascicle—*Tumors of the Central Nervous System* by Kernohan and Sayre (5), apparently met with little recognition in Europe. In 1952, a subcommittee of World Health Organization Expert Committee on Health Statistics published its conclusions regarding general principles underlying a statistically useful classification of

human tumors occurring at various organ sites (1). To assure ease and flexibility of coding, three elements of a classification were deemed necessary, including consideration of anatomic site, histologic tumor type, and degree or “grade” of malignancy. It is of note that these efforts were antedated and strongly influenced by the Armed Forces Institute of Pathology (AFIP), Washington, D. C. Fully 27 years prior to the appearance of the first WHO “Blue Book,” *Histological Typing of Tumors of the Central Nervous System* (5), this body had undertaken the publication of the first series of AFIP Fascicles under the auspices of the National Research Council-National Academy of Science, Subcommittee of Oncology. These atlases, accompanied by criteria and informative text, were the inspiration of, among others, Drs. Lauren V. Ackerman and Arthur Purdy Stout. Furthermore, Dr. Ackerman was involved with an *Illustrated Tumor Nomenclature* in English, French, German, Latin, Russian, and Spanish published by the International Union Against Cancer (UICC) (2).

In 1956, the World Health Organization executive board passed a resolution requesting the Director-General to consider establishing centers worldwide charged with the development of histologic definitions and facilitating the adoption of a uniform nomenclature for tumors of various organ types. In 1957, the Tenth World Health Assembly endorsed the plan. That same year, a Study Group on Histological Classification of Cancer Types met in Oslo, Norway, to advise the World Health Organization. The plan was to assemble experts, up to ten pathologists for each center, to develop a publication replete with numerous photomicrographs of the selected tumors. In addition, the centers were charged

with the production of up to 100 microscopic slide sets illustrating these entities. Since 1958, 23 centers manned by approximately 300 pathologists from 50 countries had been established.

With respect to tumors of the central nervous system, the position of head of the WHO Collaborating Centre for the Histologic Classification of Tumors of the Central Nervous System was given to Dr. Klaus J. Zülch of the Max-Planck Institute for Brain Research in Cologne, Federal Republic of Germany (16). Among the initial ten participants and the subsequently organized group of reviewers were Dr. Kenneth M. Earle of the Armed Forces Institute of Pathology, Washington, D.C., Dr. Lucien J. Rubinstein, Department of Pathology (Neuropathology), Stanford University, Stanford, CA, and Dr. John J. Kepes, University of Kansas, Kansas City, KS. Dr. Leslie H. Sobin of the WHO, Geneva, Switzerland was the series editor. From 1974 through 1976, some 230 cases were reviewed. The sessions can best be described as “stormy,” and the results were said to have left key participants “reasonably unhappy.” One glaring example of the contentious issues that surfaced centered upon the poorly understood “monstrocellular sarcoma,” a lesion championed by Dr. K. J. Zülch of Germany, which was, rightly, considered a giant cell glioblastoma by Dr. Lucien J. Rubinstein of the United States. The unhappy compromise double inclusion of the lesions in both section V Tumors of Blood Vessel Origin and under in glioblastoma in section I, subsection F—Poorly Differentiated and Embryonal Tumors. Despite its painful gestation, a classification replete with precise definitions and nomenclature was developed. The product was the first

international “Blue Book,” the 21st in the series of WHO publications. It was not intended as a textbook, but as a concise, illustrated, nosologic standard. An overview of the work in addition to some commentary regarding variations in concept among working group members is summarized in a 1980 article by K. J. Zulch, head of the WHO Collaborating Centre and author of the book (16). Overview commentaries occasionally followed the publication of subsequent “Blue Books” as well (7, 10).

Formulation of the classification had its inherent problems. At times, definitions proved elusive. For instance, both clinical and histologic malignancy had to be taken into consideration. Clinical malignancy was ascribed to any uncontrollably growing intracranial mass capable of lethality. This loose definition, of course, included tumors histologically benign. Alternatively, lethal tumors could produce localized pressure upon vital centers, cerebrospinal fluid obstruction with secondary hydrocephalus and brain herniation, and infiltrative tumor growth with or without metastasis. These mechanisms of death did not necessarily equate with malignancy in the histopathologic sense. As a result, both biologic and histologic grading schemes were developed. A similar biologic scheme of Dr. Zulch’s grouped tumors of similar prognosis regardless of histology or cytologic considerations (12) (see table below).

Proposed Five-Grade Scale of Malignancy of Intracranial Tumors According to Intrinsic Growth Properties

0. Neurinomas, meningiomas, craniopharyngiomas, hypophyseal adenomas, epidermoids, dermoids, teratomas, and lipomas
- I. Spongioblastomas, ependymomas of the ventricle, angioblastomas, plexus papillomas, and temporobasal gangliocytomas
- II. Oligodendrogliomas, astrocytomas, other gangliocytomas, and ependymomas of the cerebral hemispheres
- III. Pinealomas, malignant oligodendrogliomas, malignant astrocytomas, malignant gangliocytomas and malignant meningiomas
- IV. Medulloblastomas (including retinoblastomas), glioblastomas, and primary sarcomas

This dual biologic malignancy/histologic malignancy approach continued to influence grading in subsequent editions of the WHO Classification of Tumors of the Central Nervous System. A three- or four-tier (WHO I-IV) scheme of histologic malignancy was also developed, particularly for application to the spectrum of astrocytic, oligodendroglial, ependymal, and meningothelial tumors in which morphologic criteria of malignancy became increasingly clear. Prognosis and survival data were thus played off against histology and its time-honored parameters (cellularity, atypia, mitoses, atypical mitoses, stromal/vascular proliferation and necrosis). Tumor staging (TNM) was the function of the UICC, though it was of limited value in CNS pathology. Tumor coding, initially developed by the Manual of Tumor Nomenclature and Coding, American Cancer Society (3), subsequently became the International Classification of Diseases for Oncology (ICD-O) published by the World Health Organization (4).

Alterations Over Time

Listed below according to tumor group is a summary of changes in the 1979, 1993, 2000, and 2007 editions.

Astrocytic Tumors

1979—

- Category includes astrocytoma and anaplastic astrocytoma (but not glioblastoma), astroblastoma, pilocytic astrocytoma, and subependymal giant cell astrocytoma.
- Note—glioblastoma is defined as “An anaplastic, highly cellular tumor consisting of fusiform cells, small, poorly differentiated round cells, or pleomorphic cells alone or in varying combinations. Necrosis, pseudopalisading, fistulous vessels, and vascular endothelial proliferation, hemorrhage, and invasive growth and usually prominent features ...”
“Some typical glioblastomas show no evidence of a more differentiated tumor, whereas others are predominantly glioblastomas with focal areas of recognizable astrocytoma, less commonly oligodendroglioma, or exceptionally, ependymoma. Any of these gliomas may, in fact, terminate as a glioblastoma.”
- Giant cell glioblastoma was considered both a glioblastoma variant and a Tumor of Blood Vessel Origin (“monstrocellular sarcoma”).

1993—

- Pleomorphic xanthoastrocytoma added to astrocytic tumors.
- Glioblastoma added to the spectrum of astrocytic tumors.

- Astroblastoma moved to Tumors of Uncertain Histogenesis.
- St. Anne Mayo Grading Scheme adopted as WHO method of astrocytoma grading.

2000—

- No substantial changes.

2007—

- Pilomyxoid astrocytoma added as a subset of pilocytic astrocytoma.

Oligoastrocytomas and Mixed Gliomas

1979—

- Variants include oligodendroglioma and mixed oligo-astrocytoma, as well as anaplastic oligodendroglioma.
- No anaplastic form of oligoastrocytoma recognized.

1993—

- Anaplastic oligoastrocytoma recognized.

2000—

- No substantial change.

2007—

- Very high-grade oligo-astrocytic tumors with necrosis are considered “glioblastoma with oligodendroglial component.”

Ependymomas

1979—

- Variants include myxopapillary and papillary ependymoma as well as subependymoma.

1993—

- Clear cell variant added.

2000—

- Tanycytic variant added.

2007—

- No substantial change.

Pineal Tumors

1979—

- Variants include pineocytoma and pineoblastoma.

1993—

- Mixed/transitional pineal tumors added.

2000—

- Mixed/transitional category deleted.
- Pineal parenchymal tumor of intermediate differentiation added.

2007—

- Consideration given to splitting pineal parenchymal tumor of intermediate differentiation into low (grade II) and high (grade III) forms.
- Papillary tumor of the pineal region added.

Choroid Plexus Tumor

1979—

- Variants include choroid plexus papilloma and anaplastic choroid plexus papilloma.

1993—

- No substantial change.

2000—

- No substantial change.

2007—

- Atypical choroid plexus papilloma added.

Neuroepithelial Tumors of Uncertain Origin (Glial Tumors of Uncertain

Origin)

1993—

- Polar spongioblastoma and gliomatosis cerebri moved to this category from Poorly Differentiated and Embryonal Tumors category.
- Astroblastoma moved to this category from Astrocytic Tumors.

2000—

- Chordoid glioma added.
- Polar spongioblastoma deleted.

2007—

- Angiocentric glioma added.

Neuronal (Mixed Neuronal-Glial) Tumors

1979—

- Variants include gangliocytoma, and ganglioglioma, anaplastic gangliocytoma and ganglioglioma, neuroblastoma and ganglioneuroblastoma.

1993—

- Dysplastic gangliocytoma of cerebellum (Lhermitte-Duclos disease) added.
- Desmoplastic infantile ganglioglioma added.
- Dysembryoplastic neuroepithelial tumor (DNT) added.
- Central neurocytoma added.
- Paraganglioma of filum terminale added.
- Olfactory neuroblastoma added.
- Neuroblastoma and ganglioneuroblastoma deleted.

2000—

- Cerebellar liponeurocytoma added.
- Olfactory neuroblastoma and neuroblastoma of adrenal/sympathetic nervous system moved to new category of Neuroblastic Tumors.

2007—

- Extraventricular neurocytoma added.
- Papillary glioneuronal tumor added.
- Rosette-forming glioneuronal tumor added.

Poorly Differentiated and Embryonal Tumors (Embryonal Tumors)

1979—

- Category includes glioblastoma, gliosarcoma, giant cell glioblastoma (“monstrocellular sarcoma” considered synonymous with the latter) and gliomatosis. Category also includes medulloblastoma with desmoplastic and medullomyoblastic variant, medulloepithelioma, and primitive polar spongioblastoma.

1993—

- CNS neuroblastoma and ganglioneuroblastoma added.
- Note—Olfactory neuroblastoma and neuroblastic tumors of the adrenal gland and sympathetic nervous system entered into the classification under a new category of Peripheral Neuroblastic Tumors.
- Ependymoblastoma added.
- Primitive neuroectodermal tumor (PNET) added as a category for medulloblastoma-like tumors outside the cerebellum.
- Melanotic medulloblastoma added as a medulloblastoma variant.

2000—

- Desmoplastic and large cell medulloblastoma variants added.
- Atypical teratoid rhabdoid tumor added.

2007—

- Extensively nodular and anaplastic variants added to medulloblastoma.
- PNET now includes not only small cell-containing tumors but also medulloepithelioma.

Meningiomas

1979—

- Category includes meningotheliomatous, fibrous, transitional, psammomatous, angiomatous, hemangioblastic, hemangiopericytic, papillary and anaplastic meningioma.

1993—

- Microcystic, secretory, clear-cell, chordoid, lymphoplasmacytic, and metaplastic meningioma added.
- Atypical meningioma introduced as a category but not clearly defined.
- Hemangioblastic category deleted.
- Hemangiopericytoma moved to Mesenchymal, Non-Meningothelial Tumors category.

2000—

- Rhabdoid meningioma added.
- Atypical and anaplastic meningioma categories clearly defined by histologic criteria.

2007—

- No substantial change.

Tumors of Nerve Sheath Cells (Tumors of Cranial and Spinal Nerves)

1979—

- Category included schwannoma, anaplastic schwannoma, neurofibroma, and anaplastic neurofibroma.

1993—

- Cellular schwannoma and malignant peripheral nerve sheath tumor with divergent differentiation added.
- Melanotic malignant peripheral nerve sheath tumor added.
- Cellular plexiform and melanotic schwannoma added.

2000—

- Intraneural and soft tissue perineurioma added.
- Malignant melanotic schwannoma and its psammomatous variant added.

2007—

- No substantial change.

Primary Melanocytic Tumors

1979—

- Category included melanoma and meningeal melanomatosis.

1993—

- Diffuse melanosis and melanocytoma added.
added.

2000—

- No substantial change.

2007—

- No substantial change.

Tumors of the Anterior Pituitary (Tumors of the Sellar Region)

1979—

- Category included pituitary adenoma and pituitary adenocarcinoma.

1993—

- Adamantinomatous and papillary craniopharyngioma added.

2000—

- Granular cell tumor added.

2007—

- Pituicytoma and spindle cell oncocytoma added.

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**USCAP-American Association of Neuropathologists
Companion Society Meeting - 2008**

Richard Prayson, MD. “The Expanding Family of Glioneuronal Tumors”

The category of mixed glioneuronal tumors of the central nervous system has expanded due to the availability of immunostains that have enabled us to more readily identify neuronal differentiation in tumors which morphologically resemble glial neoplasms.

In the most recent rendition of the WHO, three new glioneuronal tumors have been added: 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).

The papillary glioneuronal tumor, which typically arises in the cerebral hemispheres, and the rosette-forming glioneuronal tumor of the fourth ventricle are both low grade and circumscribed, corresponding to WHO grade I; the rosetted glioneuronal tumor is an infiltrative neoplasm that corresponds to WHO grade II or III.

Arie Perry, MD. “Gray Zones in Brain Tumor Classification: Evolving Concepts”

The definition of an oligodendroglial component within a diffuse glioma is critical not only for cellular classification, but also for grading, yet the minimal requirements for the

diagnosis of an oligodendroglial component in mixed oligoastrocytomas remain highly contentious.

Variants of glioblastoma (GBM) that have new objective definitions and genetic features defined include the small cell GBM, GBM with oligodendroglioma component and GBM with PNET-like foci.

Brain invasive meningiomas are now defined as WHO grade II, even when appearing otherwise benign.

Greg Fuller, MD, PhD. “The Increasing Diversity of Pineal and Sellar Region Tumors”

The most common tumor of the sellar/suprasellar region that the surgical pathologist will encounter is pituitary adenoma, but the potentially challenging question often arises: “It’s not a pituitary adenoma, so what is it?”

The sellar/suprasellar region tumors of the 2007 WHO classification include four grade I neoplasms: pituicytoma, spindle cell oncocytoma of the adenohypophysis, granular cell tumor of the neurohypophysis and craniopharyngioma.

The papillary tumor of the pineal region (PTPR) is a newly codified neoplasm that arises in adults and is characterized by papillary architecture, epithelial cytology and a moderately aggressive clinical course corresponding to WHO grade II or III.

Tarik Tihan, MD, PhD. “New Entities in Gliomas: Angiocentric Glioma and Pilomyxoid Astrocytoma”

Angiocentric gliomas are slowly growing, cerebral hemispheric tumors occurring in children that typically present with intractable seizures. Their defining histological feature is the presence of monomorphous, bipolar tumor cells associated with vessels of involved cortex and white matter. They are considered WHO Grade I lesions.

Pilomyxoid astrocytomas are tumors of early childhood that occur in the hypothalamic/chiasmatic region and have a markedly monomorphous histologic appearance with bipolar cells cast in a rich myxoid background with a predominantly angiocentric arrangement. They are an aggressive variant of pilocytic astrocytoma and have been designated WHO grade II.

American Association of Neuropathologists Companion Society Meeting - 2008

“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).

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Gray Zones in Brain Tumor Classification: Evolving Concepts

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Whereas the WHO 2007 scheme¹ is extremely useful, up to date, and user friendly, many “gray zones” remain and are likely to persist for some time to come, pending the development of more specific and reliable biomarkers. Given time constraints, I will focus on three of the most common areas of difficulty and confusion, including the topics that have been of primary focus in my own research over the last decade. Not surprisingly, these same issues are often the ‘bread and butter’ of my consult service and problematic cases that colleagues have graciously shared with me over the years have influenced many of my current approaches. In that respect, a disclaimer is probably needed in that “the opinions portrayed in the following presentation in no way reflect the views of the USCAP companion meeting organizers, who clearly cannot be held liable for the sometimes creative, though hopefully expert opinions of the presenter.” With that in mind, the topics for discussion are as follows:

1. Oligodendroglial features; the “grayest of the gray”.

Minimal requirements for the diagnosis of an oligodendroglial component in mixed oligoastrocytomas (MOAs) remain amongst the most contentious and “grayest” of all issues in Neuropathology². Given that this has significant clinical implications, it is a source of great frustration for pathologists and clinicians alike. Even in terms of grading for example, the finding of just 2 or 3 mitoses in the entire specimen of a pure astrocytoma is considered enough for an anaplastic (WHO grade III) designation. In

contrast, MOAs are graded similarly to pure oligodendrogliomas and require frequent mitoses or as vaguely defined by the WHO, “increased cellularity, nuclear atypia, pleomorphism and increased mitotic activity”³. Since Giannini and colleagues have shown that microvascular proliferation and/or the presence of ≥ 6 mitoses per 10 HPF (even focally) are associated with statistically significant decreases in patient survival⁴, these are the criteria that we have adopted at Washington University for anaplasia in both pure oligodendrogliomas and oligoastrocytomas. Nevertheless, this means that a diffuse glioma with scattered mitoses (but $< 6/10$ HPF) would be considered WHO grade II if designated a MOA versus WHO grade III if diagnosed as a pure astrocytoma. If you now add microvascular proliferation, the differential is between anaplastic MOA, WHO grade III and GBM, WHO grade IV. Therefore, the definition of an oligodendroglial component becomes critical not only for cellular classification, but also for grading (and therefore, therapeutic decisions).

In my opinion, nuclear cytology is still the most important part of the definition. Low-grade oligodendroglioma cells (in pure form or in MOA) have round, uniform nuclei with crisp nuclear membranes, delicate (often “salt and pepper”) chromatin, and inconspicuous to small nucleoli. Unfortunately, this cytology is often distorted in frozen sections and poorly preserved specimens. Clear perinuclear haloes are useful, but not necessary. Anaplastic transformation is often recognized by more solid, vaguely nodular, cellular proliferations with enlarged epithelioid to plasmacytoid cells containing moderate eosinophilic cytoplasm. The nuclei become a bit more pleomorphic, but often retain an overall sense of regularity and roundness, typically with more vesicular chromatin and increased nucleolar prominence. GFAP is either negative or highlights

minigemistocytes and gliofibrillary oligodendrocytes. The cells are usually p53 negative, but this is not entirely reliable. Synaptophysin positivity is surprisingly common and a paranuclear dot-like pattern is often associated with chromosome 1p/19q codeletions by FISH or LOH. The latter “genetically favorable” pattern is strong evidence in favor of oligodendroglioma, but is only encountered in 15-20% of MOAs⁵. In other words, H&E remains the gold standard! Despite the subjective nature, MOAs display survival curves intermediate between pure astrocytomas and pure oligodendrogliomas, even after adjusting for grade and 1p/19q status⁶.

2. ‘New’ GBM variants and patterns: Small cell vs. GBM-O vs. GBM-PNET.

Although none of these histologic patterns are absolutely new, objective definitions and genetic features have only recently been published⁶⁻¹⁰. Given that they have not been in the literature that long and they overlap in terms of high cellularity, minimal cytoplasm, and marked proliferation, they have generated considerable confusion. Common distinguishing features are listed below. All of them also often show features of conventional glioblastoma at least focally. The small cell glioblastoma is most often mistaken for a high-grade oligodendroglial neoplasm, given its bland nuclear cytology and overlapping features, such as microcalcifications, “chicken wire” capillaries, perinuclear haloes, and perineuronal satellitosis; unlike oligodendrogliomas however, they lack mucin-filled microcystic spaces and frequently show EGFR amplification and 10q deletion, rather than 1p/19q codeletion^{8,9}. Glioblastomas with oligodendroglial components (GBM-O) remain controversial, but are now accepted in the WHO 2007 scheme¹ and are synonymous with “grade IV mixed oligoastrocytomas”, a

term that was preferred by a minority of the WHO participants. Based on a series of 1093 high-grade gliomas diagnosed at Washington University, we found that the MOAs containing necrosis did considerably worse than anaplastic MOA without necrosis, but better than conventional GBMs (i.e. purely astrocytic); the mean survival for GBM-O patients was estimated at just under 2 years, as compared with 10 months for GBM and >7 years for anaplastic MOA⁶. Lastly, there have been rare case reports of GBM or gliosarcoma developing neuroblastic or PNET-like foci, often as discrete hypercellular nodules with medulloblastoma-like cytology, Homer Wright rosettes, extensive synaptophysin immunoreactivity, and/or MYC gene amplifications^{7, 10}. Many of them additionally show increased cell size and pleomorphism, cell wrapping, and other features resembling anaplastic/large cell medulloblastomas. We have recently summarized our experience with 52 GBM-PNETs (submitted) and the main clinical implications are 1) a significantly increased risk of CSF dissemination and 2) the possibility of response to platinum based chemotherapy regimens¹¹.

	Small Cell GBM	GBM-O	GBM-PNET
Nuclear cytology	Oval bland nuclei resembling LGG, but many mitoses	Round bland nuclei or large epithelioid cells with nucleoli	Dark oval to carrot shaped nuclei or large cell/anaplastic
Architectural clues	Invasive, “chicken wire” capillaries	Invasive, mucin-rich microcystic spaces	Discrete cellular nodules, Homer Wright rosettes, desmoplasia
IHC	GFAP+ processes, EGFR-vIII+, SYN-	GFAP+ gliofibrillary oligodendrocytes and minigemistocytes, SYN- or dot-like+	PNET = SYN+, minor GFAP+, often diffusely p53+
FISH	EGFR-AMP (70%), -10q (95%)	Nonspecific in most, 1p/19q codeletion (15-20%)	-10q (50%); in PNET: N-myc or c-myc AMP (40%)

3. Meningioma Classification and Grading

Although there were only a few changes in the meningioma chapter in the 2007 WHO scheme¹² compared with the 2000 version (which was extensively revised from the 1993 scheme), there are a few “gray zones” worth discussing. The most significant change is that brain invasive meningiomas are now defined as WHO grade II, even when appearing otherwise benign. This has been a long debated issue, since for many years (going all the way back to Cushing and Eisenhardt), brain invasion was considered the most reliable sign of malignancy. In contrast, many of the European pathologists had disregarded this feature altogether arguing that some of these tumors appear benign, they don’t always do poorly, and they often don’t show the typical genetic features of higher grade meningiomas. In two large Mayo Clinic series, brain invasion in the absence of frank anaplasia was statistically shown to be associated with recurrence and death rates virtually identical to those of atypical meningiomas (WHO grade II)^{13, 14}. Brain invasion is defined as the presence of tongue-like protrusions of tumor that breach the pial surface of the adjacent brain. Perivascular spread along Virchow-Robin spaces is insufficient, though fortunately a rare finding. In borderline examples of brain invasion, GFAP is extremely helpful to highlight entrapped glial elements within the substance of the tumor.

Only a few rare new patterns of meningioma have been reported since the 2000 edition (e.g. oncocytic), but it was not felt that there was sufficient experience with these to warrant the inclusion of new variants in the 2007 WHO scheme. The rare lymphoplasmacyte-rich variant remains enigmatic, since some of the cases described behave more like inflammatory processes than true tumors (e.g. regressing in one area and recurring in another). One possibility highlighted in the new WHO is that some of

these may in fact be inflammatory conditions that have induced meningeal hyperplasia, rather than the other way around, wherein a meningioma has elicited an intense inflammatory response. In terms of other variants, the most difficult question is: how much of high-grade variant histologies (chordoid, clear cell, rhabdoid, papillary) are needed before automatically using the recommended WHO grade? For example, if a benign-appearing conventional meningioma shows focal rhabdoid features, is that sufficient for a grade III designation? All of the participants in the WHO Meningeal Tumours subgroup felt that the answer to that for now is 'No'. Until such cases are studied in greater detail, the presence of these variant morphologies only focally is considered insufficient. In my own practice, I have only utilized the recommended WHO grades when the majority of the tumor (>50%) shows chordoid, clear cell, rhabdoid, or papillary features.

Other Gray Zones (to be discussed some other day)

1. Criteria for anaplasia in favorable variant tumors, such as pleomorphic xanthoastrocytoma, ganglioglioma, and pilocytic astrocytoma
2. Grading of ependymomas
3. Neuronal features, new glioneuronal tumors, and synaptophysin positivity in an otherwise classic glioma

4. Low grade tumors with high Ki-67 labeling indices

5. Why is pineocytoma a WHO grade I tumor, while histologically analogous tumors, such as central neurocytoma and extraventricular neurocytoma are considered WHO grade II?

6. Is there really sufficient data to stratify pineal parenchymal tumors (PPTs) into 4 WHO grades? If so, how does one separate intermediate differentiation PPT grade II from grade III?

7. If central neurocytoma is WHO grade II, what do you do with “atypical neurocytomas”?

8. How nodular does extensively nodular medulloblastoma need to be before it is diagnosed that way? How anaplastic does anaplastic medulloblastoma need to be?

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**THE INCREASING DIVERSITY OF PINEAL AND SELLAR REGION
TUMORS**

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INTRODUCTION

The volume of the central nervous system that is occupied by the sellar and pineal regions is quite small but the range of tumor types that arise in those two locations is remarkably large. This can be explained in part by the broad diversity of cellular constituents native to the pineal and sellar areas. The 2007 revision of the WHO Classification of Tumours of the Central Nervous System has increased the number of formally codified tumor entities at both sites (“new” tumors). Use of the term “new” when applied to tumor subtypes must be qualified (Table 1). “New” tumors can in general be parsed into at least three different categories: 1) newly extant, 2) newly recognized, and 3) newly codified. Most tumors that are loosely described as “new” are not actually newly extant, that is, they have in fact been around for some time but arise with such relative rarity that they were not recognized as unique entities *sui generis*, but instead were variously misclassified according to the “best fit” of their features with those of better characterized entities until a collective series could be assembled that was large enough to conclusively document characteristic, reproducible histopathologic features of demonstrated clinical significance; good examples of this type of “new” tumor include angiocentric glioma and papillary tumor of the pineal region. Other “new” CNS tumors have been recognized by neuropathologists for quite awhile, but only recently has sufficient general consensus been achieved so as to warrant formal acceptance and codification in the WHO Classification.

Table 1. Categories of “New” Tumors

Newly Extant

Newly Recognized

Newly Codified

Newly Codified Sellar/Suprasellar Region Tumors (“It’s Not A Pituitary Adenoma, So What Is It?”)

The WHO 2007 Classification includes descriptions of four sellar region tumors (Table 2): craniopharyngioma (WHO Grade I), granular cell tumor of the neurohypophysis (WHO Grade I), pituicytoma (WHO Grade I), and spindle cell oncocytoma of the adenohypophysis (WHO Grade I). Note that all of these tumors are low-grade (WHO grade I). The WHO 2007 Classification of CNS tumors does not include pituitary adenomas.

Table 2. WHO 2007 Tumors of the Sellar Region (Chapter 14)

Craniopharyngioma (WHO grade I)

Granular cell tumor of the neurohypophysis (WHO grade I)

Pituicytoma (WHO grade I)

Spindle cell oncocytoma of the adenohypophysis (WHO grade I)

Pituicytoma (WHO GRADE I)

The WHO 2007 definition of pituicytoma is as follows:

“A rare, circumscribed and generally solid, low-grade, spindle cell, glial neoplasm of adults that originates in the neurohypophysis or infundibulum.”

Older synonyms for pituicytoma based on the specific anatomic site of origin include “posterior pituitary astrocytoma” and “infundibuloma”. All cases so far have arisen in adults and, as would be expected for a slowly enlarging mass in this anatomic vicinity, the typical symptoms are identical to those of a non-functional pituitary adenoma, namely, panhypopituitarism and stalk effect (mildly elevated prolactin). Pituitary adenoma is typically favored in the preoperative imaging and clinical differential diagnosis. The three principal entities in the histologic differential diagnosis are pilocytic astrocytoma, granular cell tumor, and spindle cell oncocytoma. Pituicytomas are postulated to arise from pituicytes,

which are specialized glial cells of the neurohypophysis. Being a glial tumor, pituicytomas are typically strongly and diffusely positive for S-100 protein, and usually show at least patchy positivity for GFAP. Pituicytomas do not exhibit the biphasic architecture, Rosenthal fibers, or eosinophilic granular bodies of pilocytic astrocytoma; they do not show the cytoplasmic granularity characteristic of granular cell tumor; and they do not exhibit the oncocytic change that is the hallmark of granular cell oncocytoma. The treatment for pituicytoma is surgical resection. Incompletely excised tumors may slowly regrow, but there have been no reports of anaplastic progression or distant metastasis. Pituicytoma, although rare, should be included in the differential diagnosis of every patient that presents with a circumscribed mass of the sellar, suprasellar, or combined sellar/suprasellar regions. *One caveat for the surgical pathologist:* when encountering spindled glial tissue in a transphenoidal resection for suspected pituitary adenoma, always consider normal neurohypophyseal tissue! See *Histology for Pathologists* for a review of posterior pituitary histology!

Granular Cell Tumor of the Neurohypophysis (WHO Grade I)

The WHO 2007 definition of granular cell tumor (GCT) is as follows:

“An intrasellar and/or suprasellar mass arising from the neurohypophysis or infundibulum, composed of nests of large cells with granular, eosinophilic, cytoplasm due to abundant intracytoplasmic lysosomes.”

GCTs are circumscribed tumors that arise principally in adults with only very rare childhood examples. Microscopic examples (termed granular cell “tumorlets” or “tumorettes”) are encountered relatively frequently as an asymptomatic incidental finding at autopsy. GCT, like pituicytoma (under which name some cases were described in the older literature), is postulated to arise from the specialized glial cells of the neurohypophysis, the pituicytes. The most distinctive histologic feature is conspicuous cytoplasmic granularity, which corresponds to abundant lysosomes ultrastructurally. Cell morphology ranges from the characteristic

plump epithelioid cells to spindled forms. Most granular cell tumors are positive for S-100 protein (like pituicytomas), but usually negative for GFAP (unlike pituicytomas, which are usually at least focally positive). However, GFAP-positivity has been observed in a subset of granular cell tumors, and, in addition, as described above, they may also exhibit a spindle cell component; thus, an overlap of GCT with pituicytoma has been noted by many neuropathologists. It is of some comfort in this regard to know that the treatment for both tumors is surgical resection alone, without adjuvant therapy, and that both are low-grade (WHO Grade I) tumors with no recognized proclivity for malignant transformation or metastasis.

Spindle Cell Oncocytoma of the Adenohypophysis (WHO GRADE I)

The WHO 2007 definition of spindle cell oncocytoma is as follows:

“A spindled to epithelioid, oncocytic, non-endocrine neoplasm of the adenohypophysis that manifests in adults and follows a benign course.”

SCO was advocated as a legitimate tumor entity *sui generis* by Roncaroli, Scheithauer and colleagues in 2002. This tumor has been postulated to arise from the folliculostellate cells of the adenohypophysis. Suprasellar extension is common. Symptoms are the same as other sellar/suprasellar non-endocrine tumors and non-functional pituitary adenomas: panhypopituitarism and stalk effect. The eosinophilic cytoplasm of SCOs is laden with mitochondria, as reflected by the oncocytic morphology and as demonstrated ultrastructurally. SCOs are immunopositive for S-100 protein and negative for GFAP. The treatment is surgical resection.

Summary of Sellar/Suprasellar Region Tumors for the Surgical Pathologist

Without question, the most common tumor of the sellar/suprasellar region by far that the surgical pathologist will encounter is pituitary adenoma. An additional entity of this anatomic vicinity with which the surgical pathologist is familiar is craniopharyngioma, with its two variants, adamantinomatous and papillary. A third lesion, also familiar to the general pathologist, is Rathke cleft cyst, which occasionally is spiced up a bit by the additional presence of salivary gland rests adjacent to the cyst lining. Beyond these three relatively common lesions in the sellar/suprasellar mass differential diagnosis is a lengthy list of uncommon-to-extremely rare sellar/suprasellar neoplastic and non-neoplastic entities, including germinoma, Langerhans cell histiocytosis, lymphocytic hypophysitis, intrasellar meningioma, schwannoma, lymphoma and chordoma, solitary metastasis to the pituitary gland, and the three entities that are the focus of the present review: pituicytoma, granular cell tumor, and spindle cell oncocytoma. Although all three are uncommon, a simple awareness of their existence should suffice to prompt the surgical pathologist to consider them when addressing the potentially challenging question: “It’s not a pituitary adenoma, so what is it?”

Newly Codified Pineal Region Tumor

Papillary Tumor of the Pineal Region (PTPR; WHO GRADE II-III)

Four tumors are included in the revised WHO 2007 Classification as tumors of the pineal region (Table 3): pineocytoma, pineal parenchymal tumor of intermediate differentiation, pineoblastoma, and, “new” for 2007, papillary tumor of the pineal region.

Table 3. WHO 2007 Tumors of the Pineal Region (Chapter 7)

Pineocytoma (WHO grd I)

Pineal parenchymal tumor of intermediate differentiation (WHO grd II or III)

Pineoblastoma (WHO grd IV)

Papillary tumor of the pineal region (WHO grd II - III, tentative)

Papillary tumor of the pineal region (PTPR) is one of those rare mimickers that has doubtless been observed periodically by pathologists for decades and ultimately misclassified as either an unusual choroid plexus tumor, pineal parenchymal tumor (“papillary pineocytoma”), papillary ependymoma, papillary meningioma, or metastatic papillary carcinoma from an unknown primary. In 2003 Jouvett and colleagues reported 6 cases under the title “Papillary Tumor of the Pineal Region.” The tumor’s clinicopathologic characteristics as described and illustrated in that series resonated with many neuropathologists across the globe who had each encountered a few examples of puzzling cases with very similar features, and Jouvett’s initial description was quickly followed by multiple independent confirmatory reports. A PubMed search performed in December, 2007, yielded 22 papers on papillary tumor of the pineal region, with 9 new publications appearing in 2007 alone.

The WHO 2007 definition of PTPR is as follows:

“A rare neuroepithelial tumour of the pineal region in adults, characterized by papillary architecture and epithelial cytology, immunopositivity for cytokeratin and ultrastructural features suggesting ependymal differentiation.”

Characterization of the clinicopathologic features, molecular biology and clinical behavior of PTPR is ongoing. These tumors typically present as relatively large, circumscribed mass lesions of the pineal region. One preliminary report based on a small series suggests that, in contrast to other pineal region tumors, PTPRs may exhibit hyperintensity on pre-contrast T1-weighted MRI sequences. Histologically, PTPRs are circumscribed, solid, densely cellular, and typically show areas of papillary as well as compact, sheet-like, architecture, with the latter often exhibiting clear cell morphology. The papillary areas are distinctly

epithelial in character and exhibit strong immunoreactivity for several anti-keratin antibodies, including AE1/AE3, CAM5.2 and CK18. PTPRs are also typically positive for S-100 protein and transthyretin, but only focally positive for GFAP. Features suggestive of ependymal differentiation include membranous or dot-like positivity for EMA and ultrastructural characteristics. Based on this constellation of features, the characteristic anatomic localization in the posterior 3rd ventricular region, and gene expression data, an origin has been suggested from the modified ependyma of the subcommissural organ, which is one of the circumventricular organs, many of which have a relationship to specific CNS tumors (Table 4). Although the subcommissural organ is vestigial in the adult human, remnants persist.

Table 4. Circumventricular Organs and Related Tumors

Pineal gland	Pineal parenchymal tumors
Neurohypophysis	Pituicytoma
OVL^T*	Chordoid glioma of the 3rd ventricle
Subcommissural organ	Papillary tumor of the pineal region

*OVL^T: organum vasculosum of the lamina terminalis

Symptoms are typically related to obstructive hydrocephalus secondary to compression of the cerebral aqueduct. Data to date indicate that progression occurs in almost 75% of patients, and incomplete surgical resection and mitotic activity of 5 mitoses or more per 10 high-power fields are negative prognostic factors.

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LECTURE NOTES

New Entities in Gliomas: Angiocentric Glioma and Pilomyxoid Astrocytoma

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INTRODUCTION

The revised “WHO classification of the Tumors of the Central Nervous System” is an exciting step towards a better understanding of neoplasms and tumorigenesis in the central nervous system (1). There are a number of changes, but the more important change is the incorporation of genotype-phenotype relationship with a measured attitude. The effort is neither overzealous in incorporating every little, sometimes unverified, molecular finding, nor an isolated attempt to interpret morphological features devoid of a molecular perspective. In this aspect, the WHO 2007 edition continues the paradigm shift initiated with the WHO 2000 scheme (2).

A welcome approach by the drafters of the WHO 2007 is an attempt to define “entity”, “variant”, and “pattern”, which will certainly allow a better clinical interpretation of the new names sure to emerge in our final pathology reports. An “entity” is defined as a unique clinicopathological form of disease and is given its own chapter in the WHO book. “Variant” of an entity represents a significant subtype with different biologic properties or clinical behavior and is considered in a separate section within a chapter. Tissue or histological “pattern” of an entity represents a particular differentiation pattern that may not correspond with distinct clinical behavior or altered prognosis.

A number of new entities, variants and patterns of glioma has been described in the WHO 2007. Angiocentric Glioma is a new entity that is placed under “Other Neuroepithelial Tumors” category along with astroblastoma and chordoid glioma. Gliomatosis Cerebri, which also used to be in this category, is now considered within the “Astrocytic Tumors” category as a distinct entity. Pilomyxoid Astrocytoma has been described as a new variant of pilocytic astrocytoma (3). In addition, two variants, gliosarcoma and giant cell glioblastoma are integrated into the glioblastoma chapter. The “small cell glioblastoma outlined by Perry et al. is also included in the glioblastoma chapter as a tissue pattern (4), as is the “glioblastoma with oligodendroglioma component (5)”. The latter is likely to fuel the debate on astrocytoma-oligodendroglioma dichotomy.

In this lecture, we will talk about the new entity “Angiocentric Glioma”, and the new variant “Pliomyxoid Astrocytoma”.

Angiocentric Glioma (AG)

AG was introduced to the literature in 2005 by two independent and almost simultaneous reports (6, 7). These peer-reviewed articles, and an additional report in abstract form (8), described a total of 26 patients that constitute the experience that shape the WHO characterization of this new entity. Obviously, there is only so much insight 26 cases can provide regarding the nature of a neoplasm, and there is much to be learned. AG is among the “other neuroepithelial tumors”, which implies the uncertainty of its cell of origin. Some degree of ependymal differentiation has been reported in all three neoplasms.

AGs are slowly growing, cerebral hemispheric tumors occurring in children and young adults that typically present with intractable seizures. They are considered WHO Grade I lesions. The most common location is the frontal lobe, followed by temporal and parietal lobes. Although typically centered in cortex, they may extend into the underlying white matter. On MRI, they are T2- or FLAIR hyperintense and do not show enhancement. The original descriptions of these tumors suggest indolent behavior, a stable clinical course, and probable cure by surgical resection alone. The majority of patients undergoing subtotal resections have shown stable, residual tumor on follow-up.

The defining histological feature of AG is the presence of a monomorphous, bipolar tumor cells associated with vessels of involved cortex and white matter. The elongate, slender cells are often oriented parallel to vessels, sometimes expanding perivascular spaces with streaming arrays of either single or multilayered cells. In some examples, tumor cells are oriented in a pattern reminiscent of ependymal rosettes. A similar tendency to accumulate perpendicularly beneath the pia mater is seen in a small subset of tumors, imparting a palisading appearance. Small numbers of cells are arranged in nests or nodules within brain parenchyma between affected blood vessels. Mitoses are only rarely encountered. The MIB-1 proliferation index ranges from 1% to 5%,

with the majority at the lower end of this spectrum. Immunoreactivity is consistently strong for GFAP, S-100, and vimentin. Tumor cells have also been said to show surface and perinuclear/intercellular, “dot-like” staining for EMA—a pattern typical of ependymoma. Ependymal differentiation has also been shown by ultrastructure, which demonstrates microlumen formation, microvilli, cilia, and complex, zipper-like intermediate junctions. Neurons trapped within the glial cells are often conspicuous and represent normal neurons. Not surprisingly, these neurons show immunoreactivity for neurofilament protein, synaptophysin, Neu-N and chromogranin (7). The molecular genetic properties of these tumors have yet to be fully studied. .

Pilomyxoid Astrocytoma (PMA)

PMA was introduced as a clinicopathological entity less than ten years ago (3). Subsequent reports contributed to better understand these tumors, and underscored a more aggressive behavior compared to typical pilocytic astrocytoma (PA)(3, 9, 10). There is good evidence for their close relationship to PA (11) PMA conforms to a WHO Grade II neoplasm, as a variant of PA.

Typical PMA is tumor of early childhood, and most have been recorded in the very young, and within the hypothalamic/chiasmatic region. Thus, the signs and symptoms of pilomyxoid astrocytomas are a reflection of their mass effect within this region. Most tumors are associated with poor weight gain or “failure to thrive” associated with developmental delay, vomiting and feeding difficulties. Radiological examination is helpful in outlining a neoplastic process within the hypothalamic region and often highlights a well-circumscribed mass with relatively distinct borders. The most distinguishing radiological feature is the predominantly solid nature with a homogenous contrast enhancement (12).

PMA is a markedly monomorphous tumor with bipolar cells cast in a rich myxoid background with a predominantly angiocentric arrangement. The tumor is predominantly solid, but can have infiltrative character in the periphery. The major caveat to these features is that any one of them can be observed in an otherwise typical PA and even in high grade infiltrating astrocytomas, and caution

should be exercised in the diagnosis of this neoplasm. The critical features of most bona fide PMAs are their increase cellularity and the striking monomorphous appearance unlike the biphasic or complex appearance of typical PA. The neoplasm typically exhibits a compact, non-infiltrative architecture, except for peripheral infiltrative foci, not unlike some typical PAs. Tumors do not contain Rosenthal fibers, and only an exceptional example harbors rare eosinophilic granular bodies. Mitotic figures can be seen, but are not readily identifiable. In rare examples, focal nuclear pleomorphism may be observed, but this is not a prominent feature of the tumor. Immunohistochemical staining demonstrates a strong and diffuse GFAP as well as Vimentin positivity. Staining for neuronal markers is negative. The staining with the MIB-1 (ki-67) antibody typically shows a labeling index around 5%, but a detailed analysis of proliferative index of PMA has not been performed. Rare tumors have demonstrated p53 protein positivity, but it was not clear whether this represented mutation of the TP53 gene. There are no large studies analyzing the cytogenetic and molecular genetics of PMAs.

The cell of origin for PMA is currently unclear as is the cell of origin for PA. Typically PA is considered to be related to the astrocyte, especially with the ability to form Rosenthal fibers, a feature also inherent in reactive astrocytes. A recent study concluded that PAs were genetically unique gliomas with gene expression profiles that resemble those of fetal astrocytes and, to a lesser extent, oligodendroglial precursors (13). This assertion is partly supported by an earlier in-vitro study characterizing precursor cells in gliomas including PA (14).

Similar to many other clinicopathological entities, the diagnosis of PMA also seems to have suffered from diagnostic reproducibility. Recent case reports outside the confines of the typical definition challenge our view of this entity, and further challenges the neuro-oncologist in treatment decisions(15, 16). This dilemma is further complicated by reports of hybrid tumors with features of both PA and PMA. It is not clear whether such tumors with focal myxoid and/or angiocentric features should be considered PMA, or simply PA. We believe that since most individual phenotypic characteristics of PMAs can be observed in

typical PAs, the diagnosis of PMA should be restricted to tumors that exhibit homogenously, all of the relevant features described above in the definition. In some cases, the original histological findings of PMA are replaced by that of PA after surgical resections and adjuvant therapy.

Undoubtedly, cases of PA with atypical histopathological features exist, and are not at all necessarily PMA (17, 18). Specifically, classical PAs can have bizarre nuclei, oligodendroglioma-like areas, infiltrative foci, and it may also be difficult to identify Rosenthal fibers. The significance of these histological features still remain to be determined.

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