2 NEUROPATHOLOGY AND MOLECULAR BIOLOGY OF INTRACRANIAL TUMORS

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CHAPTER OVERVIEW

More than 120 types of primary brain tumor have been recognized and codified by the World Health Organization. As part of the patient's clinical team, the neuropathologist identifies the tumor type and grade. Contemporary

oncologic neuropathology uses a broad array of morphologic, immunohistochemical, and molecular biologic techniques to accomplish this task. Knowledge of normal morphology, disease morphology, and the patient's clinical information (including age, relevant clinical history, location of the lesion, neuroimaging features of the lesion, and type and duration of the presenting symptoms) are prerequisites for competent histopathologic diagnosis of brain and spine tumors. The neuropathologist must stay abreast of developments in this dynamic field because new tumor types, diagnostic antibodies, and molecular tests are being introduced into the practice of surgical neuropathology with increasing frequency.

INTRODUCTION

At M. D. Anderson Cancer Center, the neuropathologist works closely with other members of the clinical team to deliver the best possible care for patients with brain tumors. The neuropathologist uses morphologic, immunohistochemical, and molecular biologic techniques to identify tumor types and grades. The increasing use of molecular genetic evaluation of tumors is rapidly changing the practice of clinical oncologic neuropathology.

CORNERSTONES OF CLINICAL ONCOLOGIC NEUROPATHOLOGY

The competent diagnosis of central nervous system (CNS) lesions relies on knowledge of normal morphology, knowledge of disease morphology, and knowledge of the patient's clinical information. Familiarity with these 3 cornerstones is critical not only for facilitating an accurate diagnosis but also for avoiding the common pitfalls and the subsequent adverse sequelae of misdiagnosis.

Knowledge of Normal Morphology

Accurate identification of the abnormal is predicated on a thorough knowledge of the normal. Normal microscopic morphology of the CNS includes not only the hematoxylin and eosin (H&E)-stained, immunocytochemical, and ultrastructural features of various cell types (Table 2–1) but also the specialized regional histology seen throughout the CNS. The most salient regions include the pituitary gland, pineal gland, choroid plexus, olfactory bulbs and tracts, optic nerves and their meningeal coverings, lumbar cistern and its contents, circumventricular organs, and cerebellopontine angle. Several reference works are available to those who seek to become more fully conversant in normal neurohistology (see Suggested Readings).

Table 2–1.   Unique Cell Types of the CNS

Neuron	Choroid plexus cell
Microglial cell	Arachnoid cell
Astrocyte	Melanocyte
Ependymal cell	Pineocyte
Oligodendrocyte	Pituicyte

Knowledge of Disease Morphology

More than 120 types of primary tumor of the brain and meninges have been recognized by the World Health Organization. The neuropathologist must be familiar with the different entities and the broad range of morphologic variations that each tumor may assume. Many of these variants have not been formally classified by the World Health Organization, but the neuropathologist must be able to recognize them. An important example of such morphologic variation is seen in glioblastoma, for which there are at least 10 morphologic variants: giant cell, small cell, spindle cell, bland cell, myxoid, epithelioid, inflammatory, lipid rich, rhabdoid, and gliosarcoma.

Knowledge of the Patient's Clinical Information

It is critical that the neuropathologist be familiar with the patient's clinical information before rendering a diagnosis. Essential clinical information includes the anatomic location of the lesion, the neuroimaging characteristics of the lesion, and the type and duration of clinical signs and symptoms that lead to clinical presentation. The patient's age and relevant clinical history (e.g., history of CNS or systemic malignancy) must also be known. Each of these factors affects the neuropathologist's formulation of the differential diagnosis before surgery as well as the final diagnosis that follows the thorough evaluation of the histopathologic, immunophenotypic, and clinical features of the lesion.

Anatomic Location of the Lesion

Knowledge of the anatomic location of the lesion is very important. For example, a solitary mass located in the lumbar cistern is most likely a schwannoma, meningioma, myxopapillary ependymoma, or paraganglioma of the filum terminale. Similarly, specific tumors are the most likely possibilities for a mass located in the lateral ventricle, the cerebellopontine angle, and many other specific neuroanatomic regions. The anatomic relationship of the lesion to intracranial structural compartments can also provide useful diagnostic information. For example, the differential diagnosis for an extra-axial, dural-based mass may include specific mesenchymal and hematopoietic tumors as well as several nonneoplastic entities.

Neuroimaging Features

The neuropathologist is not expected to match the expertise of radiologists in interpretating neuroimaging studies. However, the neuropathologist must be aware of the major features of the patient's preoperative magnetic resonance (MR) images, computed tomographic images, and special imaging studies, which can be obtained from the radiologist's reports and, whenever possible, from direct examination of the imaging studies.

Type and Duration of Clinical Signs and Symptoms

For the neuropathologist's purposes, the type and duration of clinical signs and symptoms can often be simplified as acute (e.g., headache, nausea, vomiting, incoordination, visual disturbance, or paresis) or chronic (e.g., seizure). A long-standing history of chronic symptoms tends to indicate a more indolent lesion than acute-onset presentation does.

HANDLING OF BIOPSY TISSUE DURING INTRAOPERATIVE CONSULTATION

The intraoperative review of biopsy samples sent for frozen section is one of the most important tasks performed by the surgical pathologist. Proper tissue handling is particularly crucial at this stage of the patient's care. For almost all tumors, regardless of the sample size (e.g., obtained by stereotactic biopsy, partial resection, or lobectomy), 3 types of specimens are prepared: cytologic specimens, frozen tissue sections, and permanent formalin-fixed, paraffin-embedded tissue sections. In some instances, it is also prudent to place a small representative piece of tissue in glutaraldehyde for possible ultrastructural examination.

Preparation of Cytologic Specimens

Cytologic specimens prepared during intraoperative consultation can be very helpful. The cytologic preparation, which uses fixation in 95% ethanol, yields exquisite cytoplasmic and nuclear detail that is free of the distortion produced by freezing.

One of 4 cytologic preparation techniques can be used, depending on the type and consistency of the tumor (Table 2–2). For a suspected pituitary adenoma, the procedure of choice is always the touch (also called imprint) preparation. This procedure takes advantage of the differentially greater shedding by adenomas than by the normal adenohypophysis, the cells of which are tightly packaged by fibrovascular septa that adenomas lack. By taking advantage of the differential adhesion of various cell types of the tumor ex vivo, the squash (also called smear or crush) preparation can be very informative for the vast majority of intra-axial brain tumors,

Table 2–2.   Rapid Intraoperative Cytologic Techniques

Technique	Tumor Tissue Characteristics	Representative Tumors
Touch (imprint) preparation	Soft and discohesive	Pituitary adenoma, lymphoma, melanoma
Squash (smear, crush) preparation	Soft or friable	Glioma, metastatic carcinoma
Scrape preparation	Dense, hard, rubbery, or desmoplastic	Desmoplastic primary tumor, dural metastasis, some meningiomas
Drag preparation	Necrotic or cauterized	Extensively necrotic metastasis

including gliomas and metastases. Scrape preparations are used for densely desmoplastic or fibrous tumors, such as many dural metastases and paraspinal tumors, which do not squash or smear very well and tend to show mostly red blood cells on touch preparations. In the scrape procedure, a scalpel is used to repeatedly scrape the cut surface of the tissue, and the material thus collected on the scalpel blade is then smeared onto a glass slide. The drag preparation is useful for extensively necrotic tumors for which a single frozen section or squash preparation is likely to show only nonspecific necrosis. In this procedure, as large an area as possible of the resected tissue is sampled for the potential presence of small remaining clusters of viable tumor cells. Multiple necrotic tissue fragments, one after another, are rapidly dragged with forceps across the same glass slide. This technique maximizes the chance of detecting isolated viable tumor cell clusters in an otherwise overwhelmingly necrotic tissue sample while avoiding the time, labor, and expense of freezing an entire Petri dish of tissue fragments.

For the fixation and staining of cytologic preparations, the preferred approach is rapid fixation with no air-drying artifact in 95% ethanol, H&E staining, and coverslipping with permanent mounting medium. As an alternative or in addition, a 1-step DiffQuick stain with water coverslipping can be used for a quick "first look."

Preparation of Frozen Tissue Sections

Depending on the procedures in place at the neuropathologist's hospital and frozen section laboratory, some representative tumor tissue may be snap frozen in liquid nitrogen for archiving in the tissue bank. If diagnostic tissue is present in the frozen section block, this sample can be stored frozen in the tissue bank rather than processed into paraffin.

In contrast to cytologic preparations, which provide cytoplasmic and nuclear detail, frozen sections provide a snapshot of the architectural features of the tissue. Thus, the cytologic and frozen tissue section preparations reveal unique morphologic information and complement each other.

Preparation of Formalin-Fixed, Paraffin-Embedded Tissue Sections

This technique is standard in all U.S. pathology laboratories and typically involves immersion in 10% formalin for fixation and then automated enclosure in a paraffin block for long-term storage. Not all immunostains work on tissue processed in this way, and antibodies to new antigenic targets should always be validated by comparing their reactivity against frozen sections of similar tissue.

Preparation of Tissue for Ultrastructural Examination

It is sometimes prudent to place a representative piece of tissue in glutaraldehyde for possible ultrastructural examination (i.e., electron microscopy). If glutaraldehyde fixative is not available, the next best approach is to retain some tissue in formalin without processing it into paraffin; procedures are available for "postfixing" wet tissue in formalin for electron microscopy. Ultrastructural examination of tissue retrieved from paraffin blocks may also be warranted in some circumstances, but this procedure yields the poorest results.

   One of the most common procedures for which tissue is placed "on hold" in glutaraldehyde is spinal cord biopsy. The 2 most common tumors of the spinal cord are diffuse astrocytoma and ependymoma. In very small biopsy samples (which spinal cord biopsy samples tend to be), it may be difficult to distinguish these 2 tumor types on H&E-stained tissue sections if the characteristic perivascular pseudorosettes of ependymoma are not seen in the limited amount of tissue available for examination. Immunohistochemical analysis conducted with currently available differentiation marker antibodies cannot resolve the issue because both tumor types are gliomas, which typically show immunoreactivity for the glial markers S-100 protein and glial fibrillary acidic protein. In contrast, the hallmark ultrastructural features of extensive intercellular junctional complexes and lumens filled with microvilli and cilia are characteristic of ependymoma but not astrocytoma.

IMMUNOCYTOCHEMICAL STUDIES IN
ONCOLOGIC NEUROPATHOLOGY

New Immunohistochemical Markers

New immunohistochemical markers of potential clinical utility are constantly being introduced. These markers can be loosely categorized as "homegrown" monoclonal and polyclonal antibodies generated by research laboratories, as commercially available antibodies that are not easy to use or have not been adequately independently validated, or as commercially available antibodies that perform well and have been independently verified by multiple experienced laboratories as markers that contribute useful
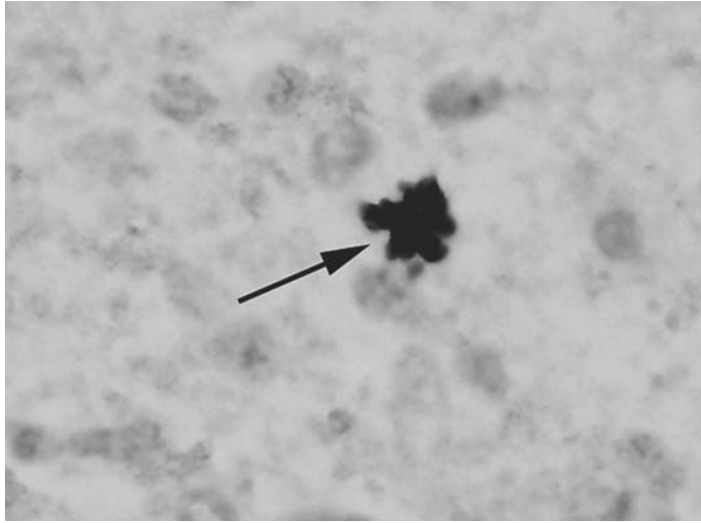
Figure 2–1. Commercially available antibody directed against pHH3 facilitates rapid identification and quantitation of mitotic figures (arrow) (pHH3 immunostain with hematoxylin counterstain, original magnification × 400).

diagnostic or prognostic information. Examples of the latter category of recently introduced markers relevant to oncologic neuropathology are the anti-INI1/hSNF5/SMARCB1/BAF47 antibody for atypical teratoid/rhabdoid tumors and the anti-OCT4 antibody for germinoma.

Proliferation Markers

Currently, the most widely used proliferation marker is the Ki-67 antigen, for which there is a commercially available antibody (MIB-1) that works well in formalin-fixed, paraffin-embedded tissue. An increasingly popular class of proliferation markers, as typified by anti-phosphohistone H3 (pHH3) antibody, essentially functions as mitotic figure immunostains (Figure 2–1). Immunostaining for pHH3 has several advantages over traditional mitotic figure quantitation using H&E-stained tissue sections, including the unambiguous identification of mitoses based on the combination of chromogenic reaction product and morphologic features of mitotic figures and the greatly expedited microscopic review secondary to the ease of mitotic figure identification.

NEW TUMOR ENTITIES

Brain tumor classification is not a static field. In addition to the increasing contributions of molecular and genomic testing to the refinement of

Table 2–3.   Brain Tumor Types Newly Described In the Past 30 Years

Tumor Type	Year Described
Pleomorphic xanthoastrocytoma	1979
Central neurocytoma	1982
Dysembryoplastic neuroepithelial tumor	1988
Chordoid glioma	1988
Papillary glioneuronal tumor	1988–1989
Rosetted glioneuronal tumor	1988–1989
Pilomyxoid astrocytoma	1999
Rosette-forming glioneuronal tumor of the fourth ventricle	2002
Papillary tumor of the pineal region	2003
Monomorphous angiocentric bipolar glioma	2005

tumor stratification within long-standing brain tumor categories, new tumor entities are periodically identified. Ten types of brain tumor newly described in the past 30 years are listed in Table 2–3.

MOLECULAR BIOLOGIC STUDIES IN ONCOLOGIC NEUROPATHOLOGY

The 3 most common molecular or cytogenetic markers being studied as potential prognostic or diagnostic markers are chromosome arms 1p and 19q deletion status, O^6-methylguanine-DNA methyltransferase (*MGMT*) promoter methylation status, and epidermal growth factor receptor (*EGFR*) gene amplification or overexpression. Other potential markers are chromosome arms 9p and 10q deletion status and *EGFRvIII*, *PTEN*, *TP53*, and *P16^{INK4a}* amplification, overexpression, or mutation.

Molecular Testing of Oligodendroglial Tumors for Deletion Status of Chromosome Arms 1p and 19q

Over the past 7 years, studies have shown that the combined deletion of chromosome arms 1p and 19q predicts an increased response to chemotherapy and radiotherapy for both low-grade and high-grade oligodendrogliomas, thereby resulting in increased recurrence-free survival rates. Initial reports that this combined loss is predictive of response to chemotherapy in particular have been revised with additional experience. The current thinking is that this molecular signature is predictive of a more treatment-responsive tumor in general.

Several methods are available for testing the deletion status of a chromosome, including conventional loss of heterozygosity, fluorescence in situ hybridization, and quantitative microsatellite analysis. Additional

details are provided in the resources listed in Suggested Readings. Because fluorescence in situ hybridization has several advantages, it is the preferred method of deletion testing at many institutions.

Molecular Testing of Glioblastomas for *MGMT* Promoter Methylation Status

Recent studies have demonstrated a correlation between gene silencing of *MGMT* through methylation of its promoter and response to temozolomide chemotherapy in patients with glioblastomas. As of this writing, this finding has not been independently confirmed, and *MGMT* promoter methylation testing as a means to determine therapy for the individual patient awaits validation.

Molecular Testing of Glioblastomas for *EGFR* Alterations

The recent finding that *EGFR* alterations are predictive of response to anti-EGFR therapies in patients with lung cancer has spurred interest in whether *EGFR* amplification in glioblastomas is predictive of response to those therapies. To date, there is no evidence that *EGFR* aberrations in gliomas are associated with response to targeted therapies; additional information is required for a definitive answer. Nevertheless, the fact that *EGFR* amplification is essentially restricted to glioblastoma has a diagnostic application. Occasional cases are encountered in which high-grade features (e.g., marked hypercellularity and prominent mitotic activity) are present but the requisite diagnostic criteria (i.e., microvascular proliferation and tumor necrosis) for glioblastoma are lacking in the tissue available for examination. In such cases, strong EGFR positivity suggests that the tumor will exhibit the clinical behavior typical of glioblastoma.

Sources of Error in the Interpretation of Brain Tumor Histopathology

Almost all diagnostic mistakes made in surgical neuropathology fall under at least 1 of the 10 major categories of error (Table 2–4). There are many different examples of each type of error, and active awareness of the various sources of diagnostic error goes a long way toward preventing their occurrence.

A common source of serious diagnostic error that warrants specific mention is overgrading (i.e., misdiagnosing a circumscribed low-grade tumor as a high-grade tumor), which can lead to inappropriate therapy. Table 2–5 lists the most common circumscribed low-grade tumors of the CNS, which typically show little infiltration of the surrounding brain parenchyma and are often initially treated with surgical resection alone. The neuropathologist should be familiar with the clinicopathologic

**Table 2–4.   Categories of Diagnostic Error in Interpreting Brain Tumor
                        Histopathology**

Mistaking normal structures for pathologic processes
Mistaking nonneoplastic diseases for tumors
Mistaking one tumor type for another
Not recognizing common tumors arising in uncommon locations
Not being familiar with rare tumor types
Not being familiar with recently described tumor types
Being misled by sample preparation artifacts
Not recognizing inadequate or nonrepresentative biopsy samples
Not performing appropriate diagnostic procedures
Not formulating an appropriate differential diagnosis

Table 2–5.   The Most Common Circumscribed Low-Grade Tumors of the CNS

Pilocytic astrocytoma
Pleomorphic xanthoastrocytoma
Subependymal giant cell astrocytoma
Desmoplastic cerebral astrocytoma of infancy
Chordoid glioma of the third ventricle
Circumscribed and dorsally exophytic brain stem gliomas
Myxopapillary ependymoma
Subependymoma
Dysplastic gangliocytoma of the cerebellum
Central neurocytoma
Cerebellar liponeurocytoma
Paraganglioma of the filum terminale
Ganglioglioma
Dysembryoplastic neuroepithelial tumor
Hemangioblastoma
Papillary tumor of the pineal region

features of each of these types of circumscribed tumor, the details of
which are provided in the sources listed in Suggested Readings.

Another source of diagnostic error is mistaking a nonneoplastic disease
for a tumor. Mass lesions such as demyelinating pseudotumors, abscesses,
infarcts, and other rare lesions can mimic neoplasms on neuroimaging
scans and tissue sections. The most deceptive of these is the demyelinating
pseudotumor. The principal morphologic hallmark of demyelinating

disease on H&E-stained tissue sections is the presence of macrophages. The identity of these cells may not always be readily apparent because infiltrating macrophages can mimic infiltrating glioma cells. A cytologic squash preparation performed at the time of intraoperative biopsy sample consultation will usually unmask the presence of macrophages. If doubt remains, one of several commercially available immunostains for macrophages, such as anti-CD68 or anti-HAM56 antibody, may be ordered.

A third common diagnostic pitfall is nonrepresentative biopsy sampling of a high-grade diffuse glioma. By definition, diffuse gliomas infiltrate brain parenchyma and exhibit a gradient of cellularity and key diagnostic features, such as necrosis and microvascular proliferation. The latter 2 features often present only in the densely cellular areas of the tumor and are absent in the peripheral areas of sparse glioma cell infiltration. Biopsy of the latter areas will give the misleading impression of a low-grade glioma. This pitfall may be avoided by simply checking the preoperative MR images for contrast enhancement, which excludes a diagnosis of diffuse low-grade glioma. In addition, low-grade gliomas are very unusual in patients aged 60 years or older. Histologic features of low-grade glioma in a biopsy sample of an older patient, particularly in the setting of a contrast-enhanced lesion on MR images, strongly suggest that the tumor was undersampled (i.e., that the biopsy was taken from an area of the lesion that was not fully representative).

A final frequently encountered clinical scenario is a new contrast-enhanced mass lesion seen in a patient who has had a high-grade brain tumor surgically resected and who has also undergone radiotherapy. The differential diagnosis in this situation may include recurrent tumor, radiation necrosis, textiloma (i.e., gossypiboma), and postoperative abscess. These principal entities are not mutually exclusive. Glioma and radiation necrosis of brain parenchyma may coexist, or one may be overwhelmingly predominant. Textiloma is a form of pseudotumor in which there is a marked inflammatory reaction to resorbable hemostatic agents. This reaction results in striking contrast enhancement on MR images and often in clinical symptoms secondary to inflammation-related edema; all of these features mimic recurrent glioma. In modern neurosurgical practice, postoperative abscess is uncommon.

CONCLUSION

The role of the neuropathologist has expanded as discoveries of new ways of classifying brain tumors, on both the molecular and microscopic levels, have multiplied. A brain tumor is best assigned a diagnosis by a specialized pathologist who is trained in neuropathology and is familiar with the nuances of such classification.

KEY PRACTICE POINTS

- Because brain tumor pathology is a rapidly evolving field—new tumor types, diagnostic antibodies, and molecular diagnostic tests are constantly emerging—frequent continuing medical education in this area is essential.

- The foundation of competent histopathologic tumor diagnosis rests on knowledge of normal morphology, disease morphology, and the patient's clinical information.

- The approach to brain tumor diagnosis begins with a review of the major aspects of the patient's clinical information, including anatomic location of the lesion, preoperative neuroimaging features of the lesion, type and duration of the presenting symptoms, patient age, and relevant medical history.

- During consultation of intraoperative biopsy samples, cytologic preparations (touch, squash, scrape, or drag) can provide morphologic information that complements that provided by frozen tissue sections.

- If possible, the entire tissue specimen should not be submitted for frozen section. Some representative tissue should be saved for permanent formalin-fixed sections, which will be free of freezing artifact.

- In certain clinical situations, such as small spinal cord biopsy samples (in which astrocytomas and ependymomas cannot be distinguished with certainty on H&E-stained tissue sections), glutaraldehyde fixation and ultrastructural evaluation by electron microscopy may be required. If glutaraldehyde fixation is not available, some tumor tissue can be saved in formalin for subsequent postfixing.

- Immunohistochemical analysis, electron microscopy, fluorescence in situ hybridization, and molecular biologic studies may be required to develop a definitive diagnosis.

- The presence of histologic features of low-grade glioma in a biopsy sample from a patient aged 60 years or older, particularly in the setting of a contrast-enhanced lesion on MR images, strongly suggests undersampling of the tumor.

- If a confident diagnosis cannot be reached, a board-certified oncologic neuropathologist should be consulted.

- When expert consultation on difficult cases is being solicited, if at all possible, a compact disc with the preoperative MR images (or at least the preoperative radiology report) and a representative paraffin block or 6 to 10 unstained slides should be sent. These measures will facilitate rapid review and mitigate potential delays in consultation.

- When a patient is referred to M. D. Anderson, the tissue section slides, surgical pathology report, and preoperative neuroimaging studies with reports should be forwarded by registered postal courier well in advance of the patient's appointment.

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