The Use of Neuroimaging to Guide the Histologic Diagnosis of Central Nervous System Lesions

Cristina Vincentelli, MD, Scott N. Hwang, MD, PhD,†*
*Chad A. Holder, MD,† and Daniel J. Brat, MD, PhD**

Abstract: Recent advances in neuroimaging techniques, particularly in magnetic resonance imaging, have led to substantially improved spatial anatomic resolution such that subtle or small central nervous system lesions, which could go undetected on gross examination of brain sections, are now readily identified on imaging. Although neuroimaging is generally considered the surrogate of gross neuropathology, it is still not a substitute for tissue diagnosis. Rather, it can be a valuable tool for the surgical pathologist in the process of formulating a differential diagnosis based on location and imaging features, as well as in identifying radiologic/pathologic discordance, such as the possible undersampling of a heterogenous glioma, which could lead to underestimation of the tumor grade. The following review focuses on the application of neuroimaging techniques, mainly magnetic resonance imaging, to the histologic diagnosis of central nervous system lesions, and the correlation of imaging features of infiltrative gliomas with histologic findings pertinent to tumor grading. The use of advanced functional magnetic resonance methods, specifically diffusion-weighted imaging, perfusion-weighted imaging, and magnetic resonance spectroscopy is also discussed, as well as the common pitfalls in imaging interpretation.

Key Words: neuroimaging, central nervous system lesions, glioma grading

(*Adv Anat Pathol* 2012;19:97–107)

When formulating a histopathologic diagnosis in general surgical pathology, the integration of macroscopic and microscopic findings is of extreme importance. Therefore, nearly everyone would agree that a thorough gross inspection, description, and interpretation of the specimen are necessary for the generation of an accurate final diagnosis. In the practice of surgical neuropathology, the macroscopic characteristics of a lesion provide equal, if not greater, insight to the disease process. However, the vast majority of brain and spinal cord specimens consist of small fragments and the gross lesion is rarely seen in the context of its anatomic setting within the tissue.

For these reasons, neuroimaging takes on a greater significance and is generally considered the surrogate of gross neuropathology.[1] Recent advances in neuroimaging techniques, particularly in magnetic resonance imaging (MRI), have led to substantially improved spatial anatomic resolution such that subtle or small central nervous system (CNS) lesions, which could go undetected on gross examination of brain sections, are now readily identified on imaging. With the advent of physiology-based magnetic resonance techniques [functional magnetic resonance (MR)], further characterization of CNS lesions is possible including their molecular, physiological, and metabolic features, both at their initial presentation and at follow-up, which may include changes resulting from treatment.[2]

As advanced as neuroimaging may be, it is still not a substitute for tissue diagnosis. Rather, it can be a valuable tool for the surgical pathologist in the process of formulating a differential diagnosis based on clinical and imaging features. It is surprising how the most modest combination of patient age, lesion location, and imaging characteristics can dramatically narrow the scope of the differential diagnosis from formidable to manageable. In addition, review of the imaging features allows the identification of any radiologic/pathologic discordance in a case, such as the possible undersampling of heterogeneous gliomas, which could lead to underestimation of the tumor grade. Because of this, clinicoradiologic information should be obtained by the pathologist before frozen section and final diagnosis.

The following review focuses on the application of neuroimaging techniques, mainly MRI, to the histologic diagnosis of CNS lesions, and the correlation of imaging features of infiltrative gliomas with histologic findings pertinent to tumor grading. The use of advanced functional MR methods, specifically diffusion-weighted imaging (DWI), perfusion-weighted imaging (PWI), and magnetic resonance spectroscopy (MRS) is also discussed, as well as the common pitfalls in imaging interpretation.

NEUROIMAGING TECHNIQUES

Magnetic Resonance Imaging and Computed Tomography

In 2003 Paul C. Lauterbur and Sir Peter Mansfield shared the Noble Prize in Physiology or Medicine "*for their discoveries concerning magnetic resonance imaging*."[3] MRI, along with computed tomography (CT), has become the imaging technique of choice for the evaluation of intracranial lesions. Both techniques show the brain anatomy in a tomographic or "slice" format. MRI uses a magnetic field measured in Tesla (T), as opposed to CT which relies on ionizing radiation. In MRI, a magnetic field, together with finely tuned radio waves, produces cross-sectional images. Because of its abundance in body water, hydrogen nuclei are usually targeted. A powerful magnetic field aligns the hydrogen protons before radio waves emitted by the scanner excite the hydrogen nuclei, which subsequently "relax" or return to baseline by releasing energy, also in the form of radio waves. The released energy is detected by a surface

From the *Departments of Pathology and Laboratory Medicine; and †Radiology and Imaging Science, Emory University School of Medicine, Atlanta, GA.
The authors have no funding or conflicts of interest to disclose.
Reprints: Cristina Vincentelli, MD, Department of Pathology and Laboratory Medicine, Emory University Hospital, G-167, 1364 Clifton Rd. NE, Atlanta, GA 30322 (e-mail: cvince3@emory.edu).

coil or antenna placed on or around the anatomic area being studied. Relaxation consists of T1 and T2 components, and the images can be adjusted to emphasize either of their T1 or T2 properties. The generated image will be T1 or T2 weighted based on the time interval between each exciting radio wave delivered, and the time interval of collection of the emitted radio waves by the protons during relaxation. These time intervals are known as "time to repetition" and "time to echo," respectively.[4] The basic MRI scans usually include T1-weighted, T2-weighted, and T2-weighted fluid attenuated inversion recovery (T2-FLAIR) images. The signal intensities on T1, T2, and T2-FLAIR relate to specific tissue characteristics (Table 1). T1-weighted images are excellent for displaying anatomic features, whereas T2-weighted and T2-FLAIR images highlight free water changes in pathologic conditions. Water, such as cerebrospinal fluid and edema, tend to be hypointense (dark) on T1-weighted images and hyperintense (bright) on T2-weighted images (Fig. 1).

The use of contrast agents modulates image intensity by improving the visibility of blood vessels and allowing the evaluation of the integrity of the blood-brain barrier. These agents are usually administered intravenously. Gadolinium (a heavy metal) is used in MRI, typically in the setting of T1-weighted images. Iodinated compounds analogously modulate density in CT scans. Pathologic conditions in which there is increased permeability of the blood-brain barrier allow the contrast agent to leak into the extravascular space resulting in increased intensity or "enhancement" of the lesion (Fig. 1). The contrast agent also accumulates normally in anatomic structures where the blood-brain barrier is anatomically absent such as in the infundibulum, adenohypophysis, and choroid plexus.[4]

Although MR is the imaging modality preferred for the detection and characterization of brain neoplasms, CT is still considered superior in the evaluation of bone pathology and in the detection of calcifications. Recent data has shown that MRI is as sensitive as CT in the setting of acute intracranial hemorrhage[5]; however, CT is a faster technique and therefore favored in emergency situations. The advantages and disadvantages of each imaging modality are listed in Table 2.

Advanced Noninvasive Magnetic Resonance Imaging Techniques

Current neuroimaging techniques allow characterization of morphologic and biological alterations to facilitate the diagnosis and grading of brain tumors and to monitor and assess treatment response and patient prognosis.[6] The clinical application of these physiology-based MRI methods is discussed below.

Diffusion-weighted Magnetic Resonance Imaging

DWI exploits the mobility of water molecules in living tissue to produce images that provide information not provided by conventional MRI. Processes that decrease the diffusivity of water in the brain produce a hyperintense region in the scan. This technique is currently used for estimating tumor cellularity and grade, analyzing peritumoral edema, evaluation of postsurgical injury, and in white matter tracking.[6,7]

The apparent diffusion coefficient (ADC) is a value that describes microscopic water diffusion in the presence of factors that restrict diffusion within tissues.[8] The greater the density of structures impeding water mobility, the lower the ADC.[2] This principle is applied to assess tumor cellularity, and therefore, to estimate the grade of gliomas. Because cells constitute a relative barrier to water diffusion compared with the extracellular space, it would be expected that the higher the tumor cellularity, the lower the ADC.[6,8]

Although some studies have shown the usefulness of this inverse correlation in the grading of gliomas, others have not.[6,8,9] There is a considerable overlap between the ADC values among high and low-grade gliomas, which is most likely a result of the inherent heterogeneity of gliomas across different grades, within the same grade and even within a single tumor.[6] DWI is most valuable in distinguishing tumor types that substantially differ in their cell densities, as in the case of posterior fossa tumors in children. Medulloblastomas and atypical teratoid/rhabdoid tumors typically show low ADC, ependymomas have intermediate ADC, and pilocytic astrocytomas display the highest ADC.[10]

Variations in water diffusivity can also be used to analyze peritumoral edema and to help determine the presence of cellular infiltration. Vasogenic edema is a reversible process in which there is an increase in vascular permeability resulting in an increase in the extracellular space, and therefore in the ADC. In metastatic brain tumors and noninfiltrative primary tumors the peritumoral edema is vasogenic, facilitating diffusion and leading to an increase in ADC values.[2,6]

In the case of infiltrative gliomas, however, the peritumoral edema represents both vasogenic edema and infiltrating tumor cells. Infiltrating gliomas may restrict diffusion due to hypercellularity within the vasogenic edema.[7] Restricted diffusion is most frequently used to detect acute infarction, which results in acute cellular damage leading to intracellular swelling and reduction of the extracellular space (Fig. 2). Similar changes can also be seen postsurgically, and should be interpreted carefully within this context.

A variation of DWI known as diffusion tensor imaging allows the evaluation of peritumoral white matter tracts

TABLE 1. Signal Intensity of White Matter, CSF, Edema, and Fat Relative to Gray Matter

	T1 Weighted	T2 Weighted	FLAIR (T2 Weighted)
Gray matter	"Gray"	"Gray"	"Gray"
White matter	Brighter than gray	Darker than gray	Darker than gray
CSF	Darkest	Brightest	Darkest
Edema	Same or darker than gray	Bright	Bright
Fat	Brightest	Bright	Bright

CSF indicates cerebrospinal fluid.

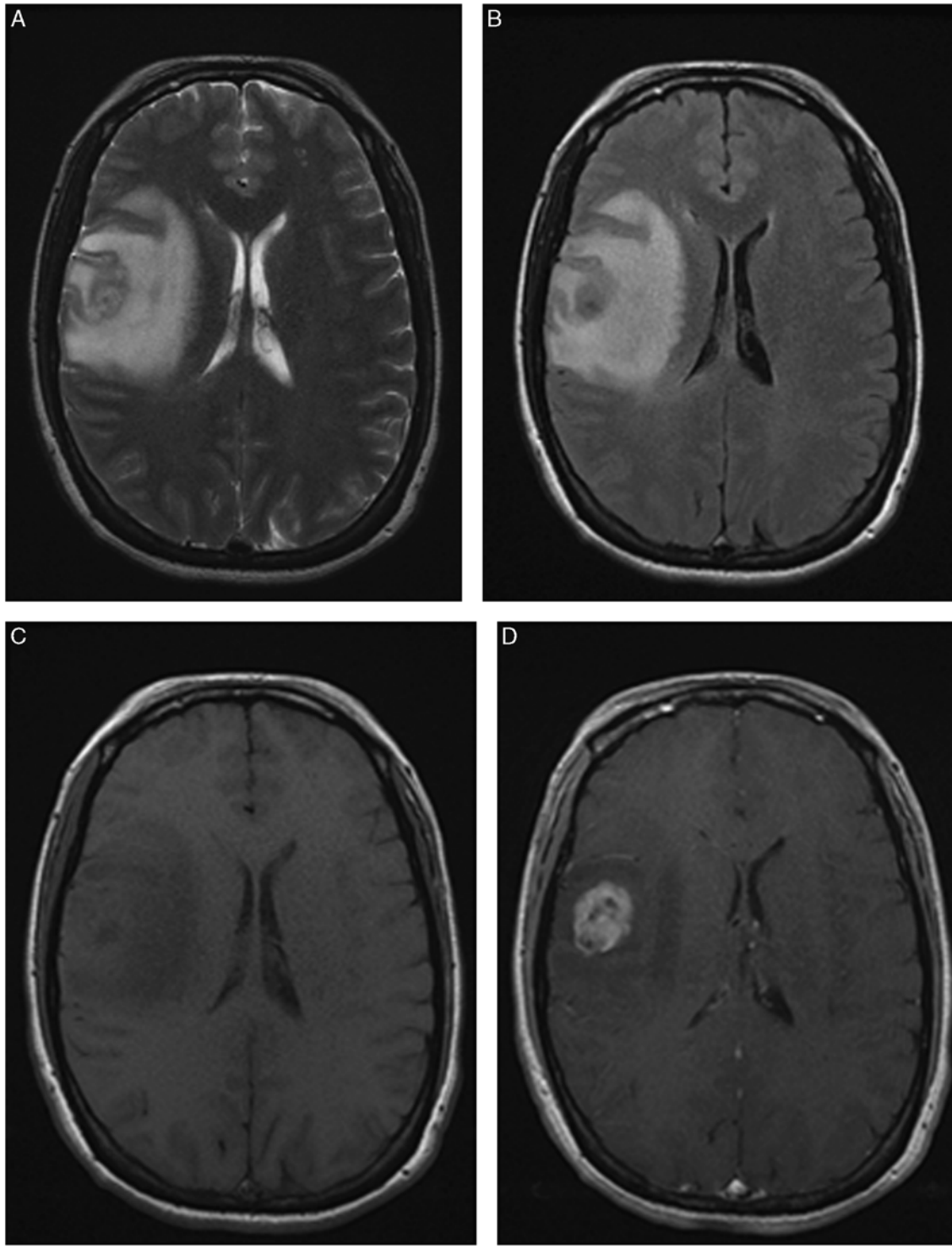

FIGURE 1. Basic magnetic resonance imaging sequences in a case of glioblastoma. Axial T2-weighted image (A) and fluid attenuated inversion recovery (FLAIR) image (B) showing a large area of tumoral edema in the right cerebral hemisphere, primarily in the white matter. On the T2-weighted image, cerebrospinal fluid (CSF) is hyperintense (bright, white), whereas on the FLAIR image, CSF is suppressed (hypointense, dark). On both the T2-weighted and FLAIR images, white matter is hypointense to (darker than) gray matter. The tumoral edema is hyperintense to both gray and white matter. On the axial precontrast T1-weighted image (C), white matter is hyperintense to gray matter, and CSF is hypointense to both white and gray matter. The tumoral edema is less conspicuous than on the T2-weighted and FLAIR images and is hypointense to both normal white matter and gray matter, but hyperintense to CSF. Subcutaneous fat is hyperintense to both brain and CSF. On the postcontrast T1-weighted image (D), there is an irregularly enhancing mass in the right cerebral hemisphere, within the region of tumoral edema, with central nonenhancing areas that are compatible with necrosis.

TABLE 2. Advantages and Disadvantages of MRI and CT

	Advantages	Disadvantages
MRI	Better discrimination between different soft tissues, such as the gray and white matter	Often contraindicated in patients with electrical medical devices or metallic implants
	Provides multiple imaging planes without changing the patient's position	Claustrophobia (reduced in open MRI devices)
	Higher safety margin of gadolinium compared with iodinated contrast	
CT	Rapid scanning speed, thus less susceptible to patient motion artifact	Poor distinction between tissues with similar densities
	Detailed evaluation of osseous structures	Toxicity risk of the iodinated contrast agent
	Detection of calcifications	Use of ionizing radiation

CT indicates computed tomography; MRI, magnetic resonance imaging.

due to its sensitivity to anisotropic or directionally dependent diffusion. Diffusion tensor imaging tractography is a valuable tool in neurosurgery as a noninvasive guide to avoid injuring critical white matter tracts, such as the corticospinal tract, while achieving gross total tumor resection.[6,11] This technique is also helpful in differentiating gliomas that infiltrate along the axons, which will cause an inherent change in anisotropy, from noninfiltrative tumors, which displace rather than infiltrate white matter tracts.[11]

Finally, a potential application of DWI is the assessment of response of solid tumors to therapy. Studies in patients with brain tumors have shown that increases in water diffusion generally indicate a positive response to therapy.[8] Increasing ADC values suggest therapy-induced necrosis, while decreasing ADC values suggest tumor progression.[11]

Perfusion Magnetic Resonance Imaging or Perfusion-weighted Imaging

Perfusion MRI methods have been developed to provide noninvasive and robust surrogate markers of tumor angiogenesis and capillary permeability.[6] The variable measured in PWI is the relative cerebral blood volume (rCBV), which has shown to correlate with catheter angiography assessment of tumor hypervascularity, as well as with histopathologic measurements of tumor neovascularity and mitotic activity in 1 study of gliomas with diverse histologies and grades (Fig. 3).[11,12] Similarly, rCBV has also shown a strong positive correlation with tumor grade in diffuse astrocytomas, as well as with vascular endothelial growth factor expression for World Health Organization (WHO) grade II and III astrocytomas.[13] PWI may also be predictive of clinical behavior within a given tumor grade. For example, in a recent multi-institutional study, rCBV measurements correlated well with time to progression or death in patients with low-grade gliomas.[14] Despite these promising advances, it remains essential to interpret PWI in conjunction with conventional images and the histopathology as some biologically benign tumors, such as pilocytic astrocytoma, may show prominent vascularity (Fig. 4A).[11]

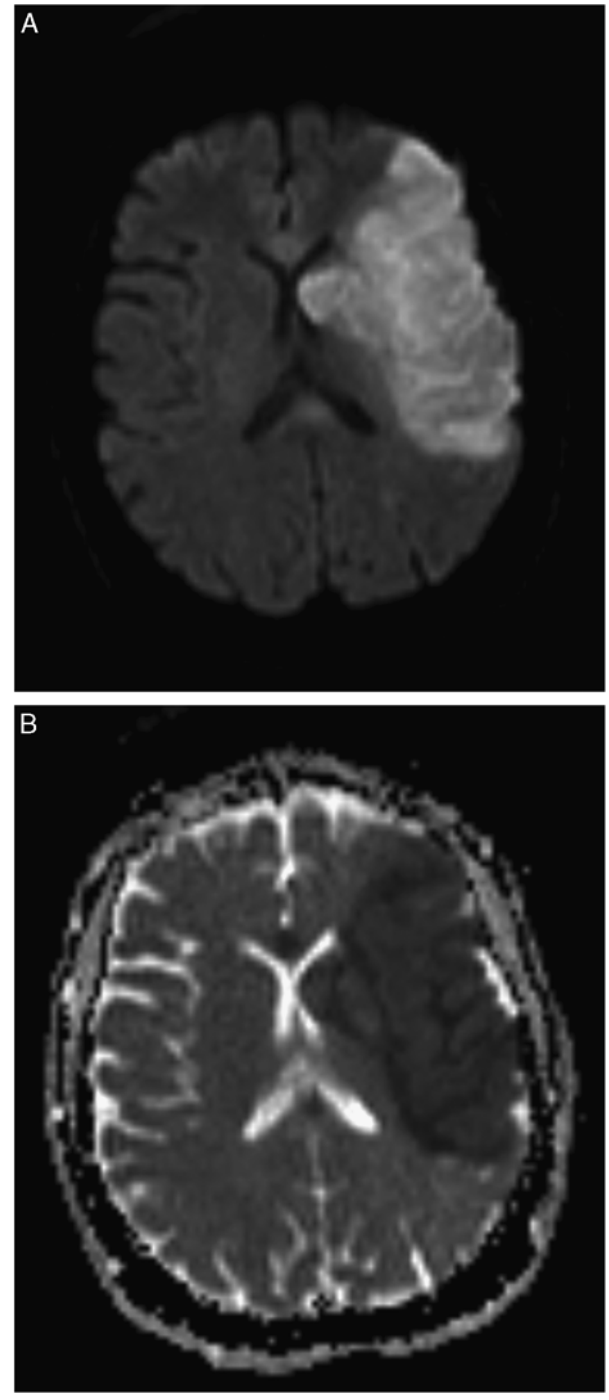

FIGURE 2. Diffusion-weighted image (DWI) and apparent diffusion coefficient (ADC) map in acute infarction. A, DWI showing a geographic area of abnormal hyperintense signal in the left middle cerebral artery territory, involving both gray and white matter and extending to the cortical surface. B, The corresponding ADC map shows low ADC (abnormally restricted diffusion) due to cytotoxic edema.

Magnetic Resonance Spectroscopy

MRS is a noninvasive technique that can be used to complement other brain-imaging studies due to its ability to reveal additional information on cell membrane metabolism,

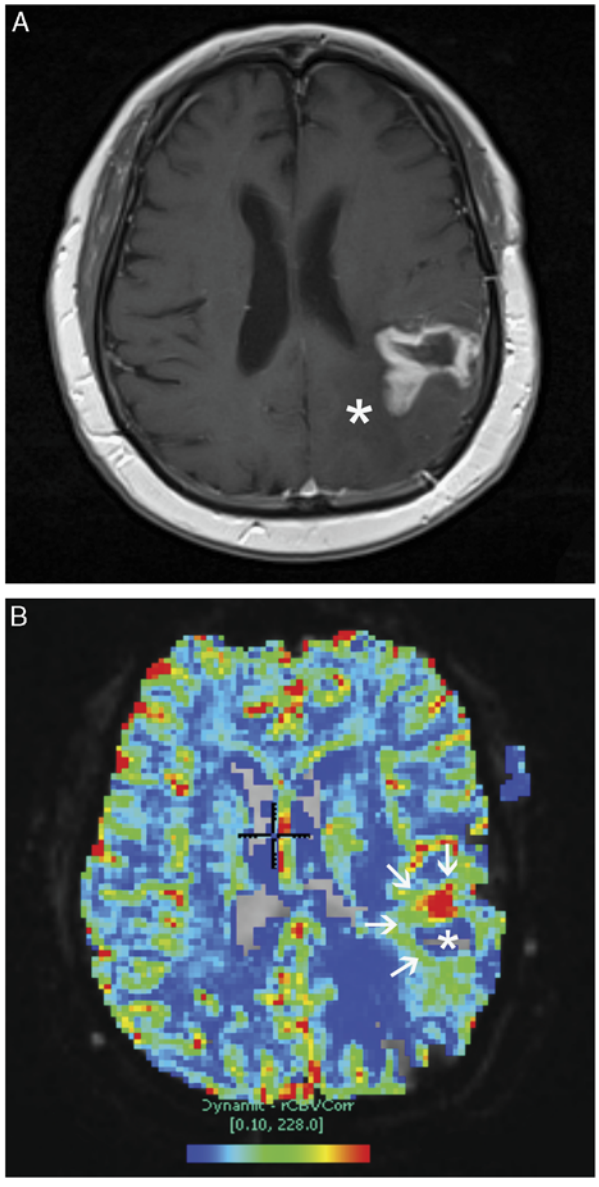

FIGURE 3. Perfusion-weighted imaging in a case of glioblastoma. A, Postcontrast T1-weighted image showing a partially ring-enhancing mass centered in the left parietal lobe, with central necrosis and surrounding nonenhancing tumoral edema, particularly medial to the ring-enhancing component. B, Corresponding relative cerebral blood volume (rCBV) map, obtained using dynamic susceptibility contrast technique, showing abnormally elevated rCBV (arrows) in the region of contrast enhancement. This correlates histologically with increased microvascular density, consistent with neoangiogenesis. The central necrotic region (small asterisk) and the surrounding nonenhancing tumoral edema (large asterisk) show decreased rCBV.

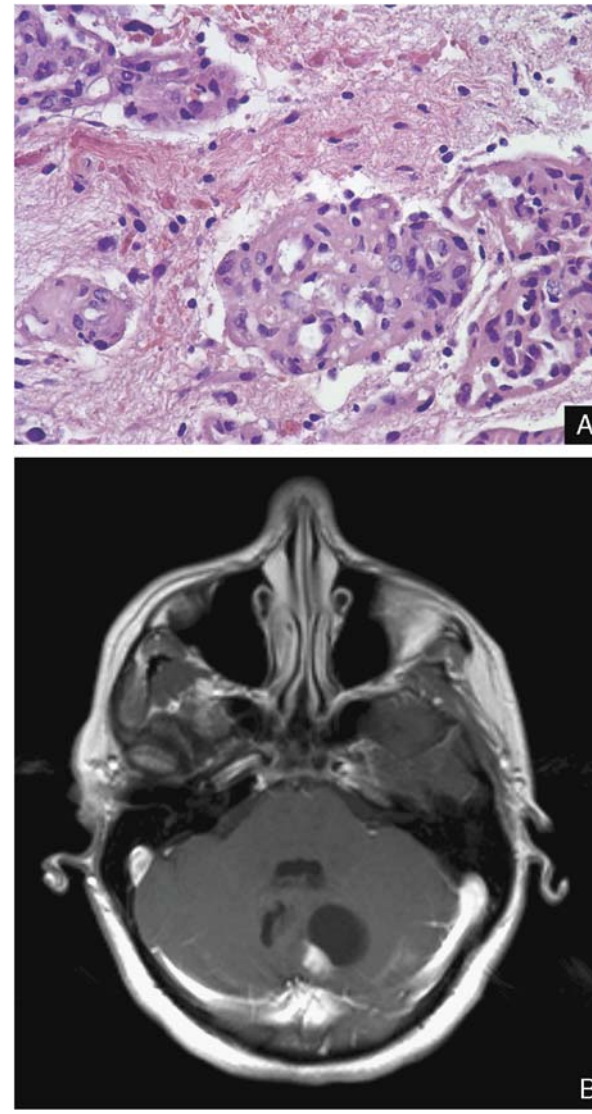

FIGURE 4. Pilocytic astrocytoma. A, Histologic section of a pilocytic astrocytoma showing the florid microvascular hyperplasia that contributes to the avid contrast enhancement in these lesions. B, Postcontrast axial T1-weighted image showing an enhancing lesion in the left cerebellar hemisphere with a "cyst with mural nodule" configuration.

neuronal integrity, and energy metabolism.[15] MRS measures and graphically displays the presence and relative amount of various metabolites based on their spectroscopic properties (Fig. 5). Among the metabolites most relevant to neuro-oncology are choline, N-acetyl aspartate (NAA), lactate, creatine, and mobile lipids. Choline is abundant in cell membranes where it is found in the head groups of phospholipids, and therefore is considered a marker for phospholipid turnover. An increase in choline values has been associated with a higher glioma grade and expression of the proliferation marker Ki-67 (MIB-1).[15,16] NAA is a neuronal molecule which typically decreases with increased glioma infiltration as a result of displacement or destruction of neurons.[16] Measurement of the choline:NAA ratio reveals a significant difference between grade II and grade III gliomas.[16,17] High concentrations of lactate, the end product of hypoxia-induced nonoxidative glycolysis, and mobile lipids are associated with high-grade gliomas.[6,15] High lactate levels may correlate with hypoxic but viable areas of the tumor, whereas mobile lipids may represent necrotic portions of the tumor where there is cell membrane destruction.[6] Creatine is helpful in the distinction of gliomas versus metastasis, as this

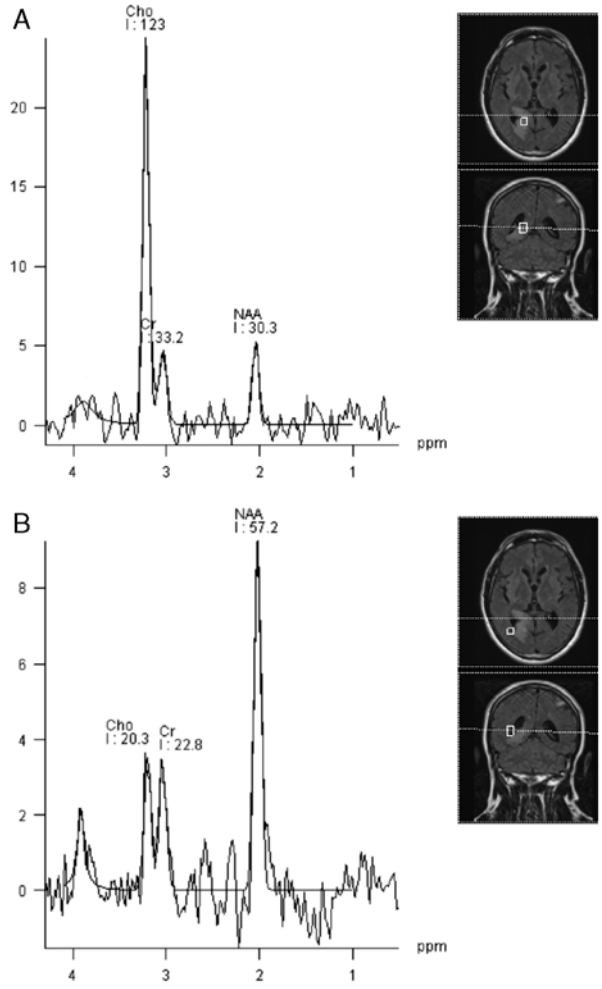

FIGURE 5. Magnetic resonance spectroscopy in a case of anaplastic astrocytoma, World Health Organization grade III. A, Proton magnetic resonance spectrum obtained from a voxel (white squares) placed in the intra-axial lesion in the right occipital lobe, shown on the axial and coronal fluid attenuated inversion recovery reference images (top right). The MR spectrum shows markedly elevated choline (Cho) peak and decreased N-acetyl aspartate (NAA) peak. Note: the creatine (Cr) peak is used as the internal control. B, Normal proton MR spectrum obtained from non-neoplastic brain.

metabolite is nearly absent in the latter.[15] In summary, high-grade gliomas typically show an increased choline, decreased NAA, decreased creatine, and the presence of lipids and lactate. However, these findings are not entirely specific, as metastases and lymphoma may show similar spectra.[11]

Interpretation of Intracranial Lesions on Magnetic Resonance Imaging

When an intracranial lesion is identified on MRI, the initial step for the radiologist is to determine whether the mass arises from the brain parenchyma itself (intra-axial) or from the surrounding anatomic structures (extra-axial), such as the skull, meninges, or nerves (Fig. 6). After an accurate localization of the mass, the examination of other imaging features or "signal" characteristics, a differential diagnosis based on clinical and imaging findings can be generated.[11]

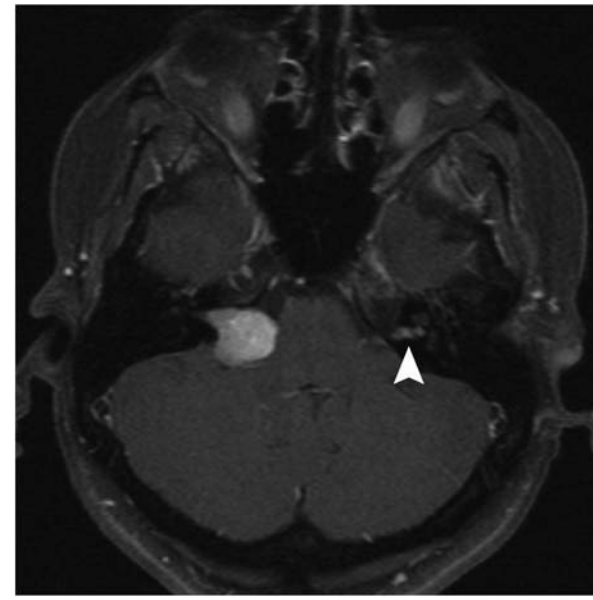

FIGURE 6. Extra-axial lesion: cerebellopontine angle (CPA) schwannoma. Postcontrast axial T1-weighted image showing a homogenously enhancing extra-axial mass arising from the right internal auditory canal (IAC) and extending into the right CPA cistern. Note also the small enhancing lesion in the left IAC (arrowhead). This patient has neurofibromatosis type 2. The most frequent differential diagnosis is a CPA meningioma.

Intrinsically T1-hyperintense Lesions

The presence of specific elements in CNS lesions may lead to areas of T1-hyperintensity in the absence of a contrast agent. Some of these elements and corresponding examples of CNS lesions are the following: hemorrhage (hematoma, infarct, primary, or metastatic neoplasms), protein (colloid cyst of the third ventricle, craniopharyngioma), fat (lipoma, dermoid cyst), melanin (metastatic melanoma, leptomeningeal melanosis), and calcium and other minerals.[18] As mentioned above, calcium is best detected by CT scans as areas of hyperdensity, whereas in MRI it usually has an isointense or hypointense appearance in both T1 and T2-weighted images. However, when present as calcium salts or in association with other cations, such as iron and manganese, it may produce a hyperintensity in T1.[18]

After surgical resection of a glioma, there may be T1-hyperintense signal in or near the surgical resection site due to procedural bleeding. Thus, the postcontrast image will need to be compared with the precontrast image to determine if there is truly residual contrast-enhancing tumor, or if the bright signal is due to hemorrhage. Once the hemorrhage has resolved, the presence of residual or recurrent glioma on contrast enhanced images is more straightforward.

Although hemorrhage within a neoplasm is a nonspecific finding, the nature of the hemorrhagic pattern may be telling. For example, a hemorrhagic mass near the gray-white junction is most typical of a metastasis. Moreover, tumoral hemorrhages are poorly organized and tend to recur, producing blood products of various ages on imaging.[7]

In addition, hemorrhage within a neoplasm may obscure the visualization or presence of contrast enhancement. Although dating hemorrhagic lesions is beyond the

scope of this review, it is important to note that the signal intensity characteristics in MRI will vary depending on the age of the bleed.

T2 and T2-fluid Attenuated Inversion Recovery Hyperintense Lesions

Vasogenic cerebral edema can be demonstrated on MRI as an area of hyperintensity on T2 or T2-FLAIR–weighted images. Although the presence of cerebral edema attests to the presence of a pathologic process, it provides no guarantee that the lesion is neoplastic and may not provide insight into the type of disease.[4] Indeed, T2 signal hyperintensity is characteristic of many non-neoplastic processes such as cerebral ischemia, encephalitis, demyelinating disease, and vasculitis, as well as edema that surrounds abscesses or metastatic lesions.

The degree of T2-weighted signal associated with a neoplasm or the relative amount of edema to tumor size may provide insight into its rate of growth, with large amounts of edema associated with rapidly growing tumors. For example, metastatic neoplasms are known for the large amount of surrounding edema they generate compared with their size.

In contrast, slowly growing neoplasms such as pilocytic astrocytoma and well-differentiated meningioma may grow to extremely large sizes without substantial surrounding edema.

T2-weighted images and FLAIR demonstrate characteristic findings in low-grade and intermediate-grade infiltrative gliomas. Among astrocytomas, grade II lesions show hyperintense T2-weighted (or FLAIR) signal abnormalities, reflecting vasogenic edema generated in response to diffuse infiltration by individual tumor cells (Fig. 7).[19] Histologically, these lesions show a moderate increase in brain cellularity due to the infiltrating neoplastic cells with enlarged hyperchromatic nuclei with irregular contours (Fig. 7C). Grade III astrocytomas (anaplastic astrocytomas) have higher cellular density and greater nuclear atypia than grade II astrocytomas, and also show mitotic activity (Fig. 7F).[20] Although many grade III astrocytomas do not show contrast enhancement, a subset may show subtle or patchy enhancement (but no rim enhancement) and these will generally behave in a more clinically aggressive manner.

Low-grade oligodendrogliomas are also T2/T2-FLAIR bright, and their diagnosis is usually favored by neuroimaging when calcifications are identified or if the lesion shows predominantly peripheral (cortical) involvement. Microscopically, oligodendrogliomas consist of diffusely infiltrating monomorphic cells with uniform round nuclei, rather than the oblong nuclei characteristic of astrocytomas. Perinuclear halos can be seen in paraffin sections, as well as branching capillaries and microcalcifications.[20]

In general, WHO grade I CNS neoplasms are noninfiltrative and do not cause significant cerebral edema. Peritumoral edema can also be considerably reduced or absent in patients treated with steroids.[4]

Contrast-enhancing Lesions

Normal CNS blood vessels allow only limited diffusion through their walls due to a highly restrictive blood-brain barrier, which is formed primarily by endothelial tight junctions, but also by astrocytic foot plates, extracellular matrix and endothelial-pericytic interactions.[19] In pathologic conditions in which there is increased permeability of the blood-brain barrier, the contrast agent can leak into the extravascular space resulting in increased intensity or "enhancement" of the lesion. The presence of vascular leakiness can be attributed to native vessels of the brain becoming physically distorted, dilated or hypertrophied in response to a pathologic process. In addition, the new vessels that form in neoplastic diseases do not have the same blood-brain barrier function as normal brain vessels and are associated with contrast enhancement. These new vessels may be a component of low-grade or high-grade brain tumors, with the pattern of enhancement serving as a guide to distinguish tumor type. Grade I lesions that have induced their own blood supply within a compact, discrete mass, such as pilocytic astrocytoma, ganglioglioma, pleomorphic xanthoastrocytoma, hemangioblastoma, and others, will show a solid, homogenous pattern of enhancement, often associated with a cyst (Fig. 4B). It is important to recognize that contrast enhancement is not specific to neoplasia and that the blood-brain barrier can be leaky in non-neoplastic conditions, such as demyelinating disease, infarcts and infection, or as a result of therapeutic intervention. As mentioned before, the contrast agent will also accumulate in areas where the blood-brain barrier is anatomically absent. For this reason, extra-axial lesions such as meningiomas and schwannomas will also avidly enhance.

The pattern of enhancement is also helpful in distinguishing between CNS lesions. Some common examples of lesions with "homogenous" or uninterrupted enhancement are lymphoma, metastasis, and extra-axial lesions. "Nonhomogenous" enhancement can be seen in a patchy pattern or in a "ring" pattern. In the case of infiltrating gliomas, enhancement of this sort usually heralds the onset of vascular pathology and the beginning of the angiogenic process, both of which reflect a higher grade of malignancy. Not surprisingly, the presence of preoperative contrast enhancement in anaplastic astrocytomas was recently shown to be independently associated with decreased survival and increased recurrence, most likely because these tumors were more advanced in their progression to glioblastoma.[21]

"Ring" or rim-enhancing lesions may represent nonneoplastic lesions, metastatic disease, or high-grade gliomas, classically glioblastoma (WHO grade IV). The ring-like pattern is due to an area of central necrosis that is T1 hypointense and nonenhancing, surrounded by neoplastic regions containing a high density of newly forming and pathologic vessels, accounting for the intense contrast enhancement of the surrounding rim. The histopathologic features that distinguish glioblastoma from lower grade astrocytomas are found near this contrast-enhancing rim and include foci of necrosis, usually with evidence of surrounding cellular pseudopalisades (pseudopalisading necrosis), and microvascular hyperplasia or proliferation, representing angiogenesis (Fig. 8).[19]

Astrocytomas may show significant microscopic heterogeneity in terms of cellularity, pleomorphism, and in the case of glioblastoma, the distribution of necrosis.[22] For these reasons, it is important to be aware of the neuroimaging findings and their interpretation so that the pathologic findings can be correlated and discrepancies can be addressed. A common occurrence is the pathologic diagnosis of a grade II or III glioma in the setting of a rim-enhancing lesion. This is most often due to the undersampling of neoplasm, leading to an absence of necrosis or vascular proliferation within the tissue sections. Neuroimaging tools are now available that enable stereotactically guided biopsies to provide a representative sample from the most malignant component of the lesion, allowing more accurate grading of gliomas.[15]

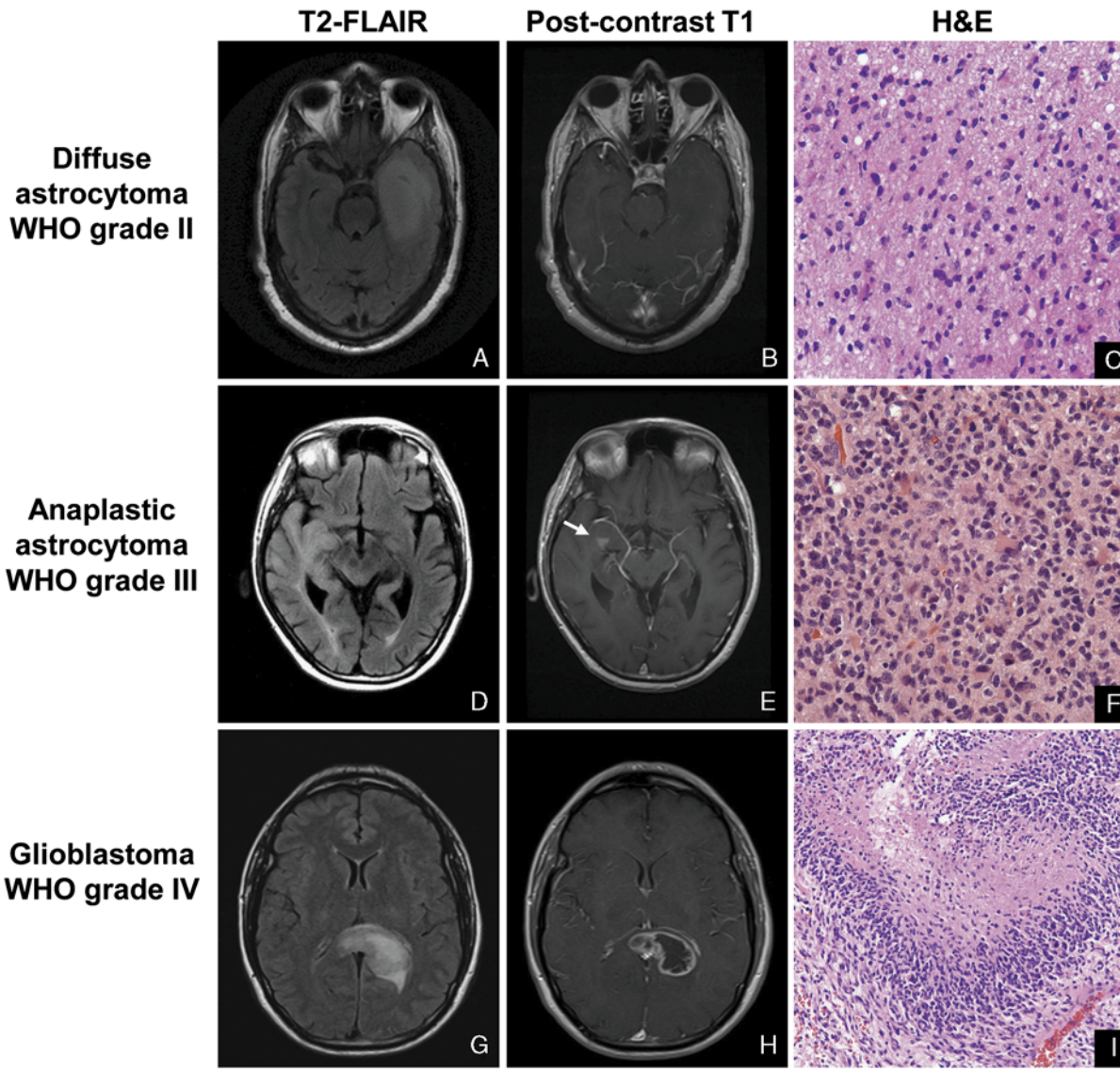

FIGURE 7. Correlation of magnetic resonance imaging findings with histologic features pertinent to the grading of infiltrative astrocytomas. Infiltrative (diffuse) astrocytoma, World Health Organization (WHO) grade II: (A) Axial fluid attenuated inversion recovery (FLAIR) image showing abnormal T2-hyperintense signal and mild mass effect in the left temporal lobe. B, Postcontrast axial T1-weighted image shows no tumor enhancement. C, Tissue sections show an infiltrative astrocytoma consisted of individual neoplastic cells at low cellular density invading through the central nervous system neuropil, generating vasogenic edema that can be seen histologically as microscopic vacuolization. Anaplastic astrocytoma, WHO grade III: (D) Axial FLAIR image showing poorly marginated abnormal T2-hyperintense signal and mild mass effect centered in the right temporal lobe. The abnormal signal also extends into the anterior right occipital lobe and the right cerebral peduncle. E, Postcontrast axial T1-weighted image showing a small triangular area of enhancement (arrow) in the medial right temporal lobe. F, Anaplastic astrocytomas have a higher cell density and are mitotically active. The vessels can be hypertrophic, which may correlate with modest contrast enhancement on neuroimaging but do not show multilayering of endothelial cells. Glioblastoma, WHO grade IV: (G) Axial FLAIR image showing a T2-hyperintense mass expanding the splenium of the corpus callosum. H, Postcontrast axial T1-weighted image showing irregular ring enhancement with central nonenhancement, consistent with necrosis. I, Glioblastomas are typically hypercellular and contain foci of necrosis, often with surrounding pseudopalisading cells as shown here, as well as microvascular hyperplasia.

Potential Pitfalls: Central Nervous System Pseudoneoplasms

Awareness of the common mimickers of neoplasia in neuroimaging is of extreme importance not only to the radiologist but also to the surgical pathologist. Both the misinterpretation of non-neoplastic disease as malignancy and its reverse can lead to significant clinical mismanagement. With regard to neuroimaging, it is not uncommon to encounter within the same radiologic family of diagnoses, or "gamuts," a variety of CNS lesions that include neoplastic and non-neoplastic processes. Many non-neoplastic diseases may present as space-occupying lesions, whereas neoplastic lesions can present without mass effect, particularly in early stages of diffuse gliomas when they infiltrate

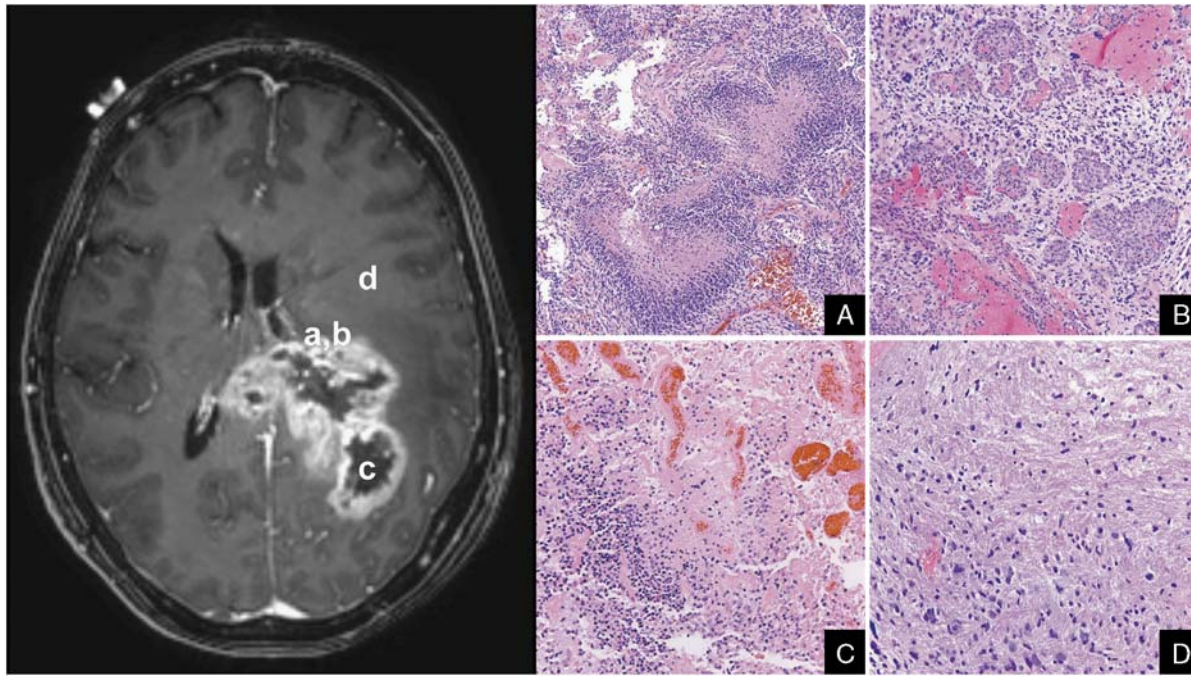

FIGURE 8. Glioblastoma, postcontrast axial T1-weighted image showing irregular ring-enhancing mass. Histologic correlates of magnetic resonance imaging findings listed (a–d) on left include, respectively: (A) pseudopalisading necrosis seen at the leading edge of the rim enhancement; (B) florid microvascular hyperplasia often noted in the region of rim enhancement, adjacent to regions of pseudopalisading necrosis; (C) necrosis and necrobiotic material within the hypointense center of glioblastoma; and (D) infiltrating astrocytoma cells, displaying a gradient of decreasing cell density with increasing distance from the center, are seen within the peripheral white matter.

normal brain tissue but are not expansive.[23] Oftentimes it is the patient's clinical presentation that may raise suspicion of a potential mimicker. Therefore, as in any other pathology subspecialty, knowledge of the clinical scenario in addition to the neuroimaging should be strongly pursued. In addition, non-neoplastic lesions such as stroke, demyelinating diseases, and infectious processes may be associated with increased perfusion and hypermetabolism decreasing the discriminating power of advanced MRI techniques.[23] Examples of non-neoplastic diseases presenting as tumefactive lesions are listed in Table 3, some of which are discussed below.

Brain abscesses may present as rim-enhancing lesions on MRI simulating glioblastoma or metastasis. However, the rim is usually thinner, more uniform and T2 dark, as opposed to the rims of glioblastoma and metastasis which are typically T2 bright (Fig. 9A).[24] DWI can also be useful in this scenario: pus often shows hyperintense signals on DWI and reduced ADC values due to its high viscosity; necrotic centers of neoplasms, on the other hand, are less viscous and therefore iso or hypointense on DWI with increased ADC.[23] A clinical history of fever, recent dental procedures, or head and neck infections can also provide a valuable clue to favor a pyogenic abscess over a neoplasm.

Demyelinating disease is well recognized as a mimic of neoplasia not only histologically but also on neuroimaging, especially when it presents as a solitary tumefactive process (Fig. 9B). Biopsy is unusual when multiple sclerosis presents with classic relapsing remitting clinical symptoms, along with characteristic MRI findings. The latter includes the presence of multiple periventricular white matter lesions that are FLAIR and T2 hyperintense and T1 hypointense, sharp border with gray-matter structures, a defined base on the ependymal surface, and variable contrast enhancement. However, tumefactive multiple sclerosis may simulate a high-grade glioma on MRI when it presents as a single white matter lesion that is T2 and FLAIR hyperintense. The presence of contrast enhancement and mass effect add to the tumor-like picture. The specific pattern of enhancement can raise the suspicion of a tumefactive demyelinating process when it consists of an open ring, or "horseshoe-shaped," with the open end oriented toward the gray matter.[23,24] Still, other patterns of enhancement (including closed rings) have been described.[25] Microscopic examination can also be misleading. The presence of numerous macrophages should lead the pathologist to consider a non-neoplastic process. However,

TABLE 3. Non-neoplastic Diseases that Can Mimic Central Nervous System Neoplasms*

Inflammatory	Multiple sclerosis
	Neurosarcoidosis
	Neurologic Behçet disease
Infectious	Pyogenic abscess
	Toxoplasmosis
	Tuberculosis
	Neurocysticercosis
	Fungal infections
	Syphilitic gumma
Cerebrovascular disease	Subacute ischemic stroke
	Hemorrhagic stroke
	Vascular malformation

*On the basis of review article by Omuro et al.[23]

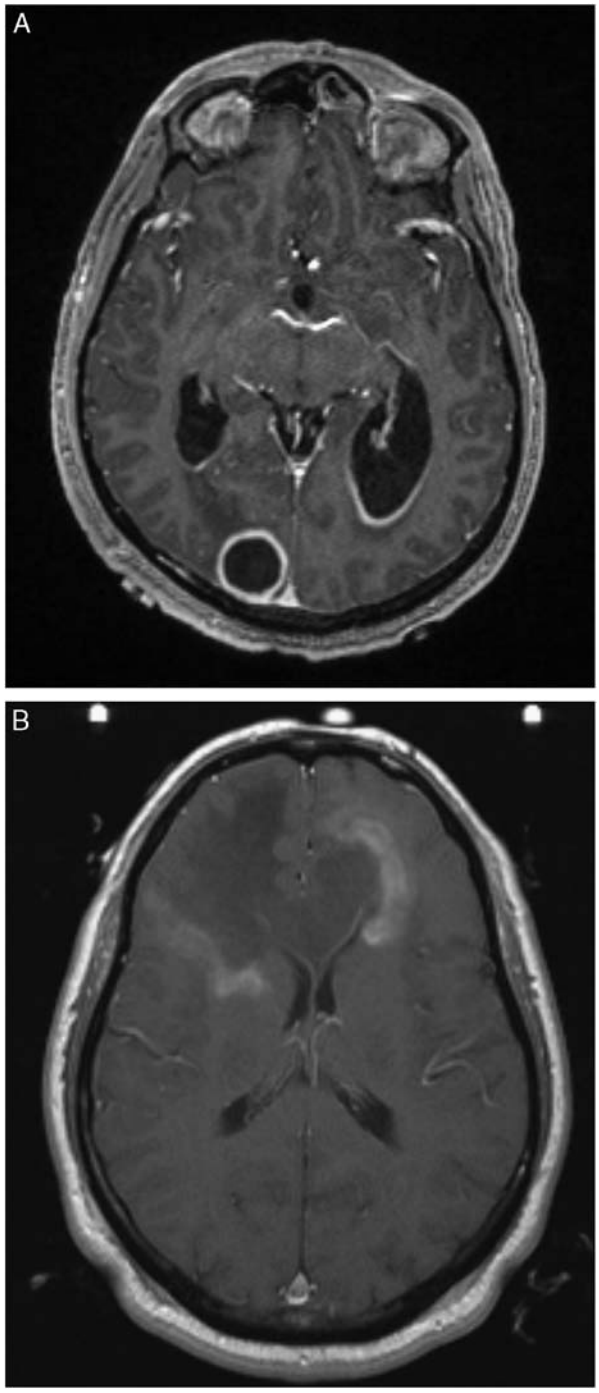

FIGURE 9. Mimics of central nervous system neoplasms, post-contrast axial T1-weighted images. A, Abscess: well-defined ring-enhancing lesion in the right occipital lobe. In addition, note the ependymal enhancement in the left lateral ventricle due to ventriculitis. B, Tumefactive demyelinating lesion (multiple sclerosis): large lesion in the right frontal lobe extending through the corpus callosum into the left frontal lobe showing enhancement along the margin of the lesion, consistent with a "leading edge" of active demyelination.

the hypercellularity of the process, together with the presence of reactive astrocytes with variable nuclear atypia, can mimic an infiltrative glioma.[26]

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of the CNS caused by a polyomavirus, the JC virus. It is seen in immunosuppressed patients, especially in those with human immunodeficiency virus. The white matter lesions on MRI are typically multiple and bilateral, T1 hypointense, FLAIR hyperintense, and nonenhancing. Occasionally, PML may present as a single large lesion and the diagnosis of a low-grade glioma may find its way to the top of the differential diagnosis.[26] Because of the high degree of viral-induced atypia seen in infected oligodendroglial cells and astrocytes, this entity can also be mistaken for a glioma histologically. The recognition of white matter restriction, macrophages, and the nuclear cytopathic changes of glia in histologic sections should rule out a neoplastic process and prompt a consideration of PML. Immunohistochemistry for detection of JC virus-associated proteins aids the diagnosis.

Cerebral ischemic infarcts, generally in the subacute phase, can present as enhancing lesions subsequently leading to a biopsy; however, the absence of mass effect in association with the enhancing lesion should prompt consideration of subacute infarction as a diagnostic possibility. A gyriform pattern of enhancement can be a valuable clue to the diagnosis of stroke.[24] MRS revealing a decreased choline to creatinine ratio will favor the diagnosis of stroke.[23]

CONCLUSIONS

Basic understanding of current neuroimaging techniques, along with the interpretation of common imaging patterns of intracranial lesions, can aid the surgical pathologist by narrowing the differential diagnosis when challenged by a neurosurgical specimen. Of equal importance is the review of neuroimaging findings to address potential radiologic/pathologic discordance. Knowledge of the common mimics of CNS neoplasms and their distinguishing neuroimaging features can minimize the potential for misdiagnosis.

ACKNOWLEDGMENT

The authors would like to acknowledge the contribution of Donna M. Martin, Director of Pathology IT Resources and Development, in the production of the images.

REFERENCES

1. Perry A, Brat DJ. Neuropathology patterns and introduction. In: Perry A, Brat DJ, eds. *Practical Surgical Neuropathology. A Diagnostic Approach*. Philadelphia: Churchill Livingstone; 2010:114.
2. Lemort M, Canizares-Perez AC, Van der Stappen A, et al. Progress in magnetic resonance imaging of brain tumours. *Curr Opin Oncol*. 2007;19:616–622.
3. "The Nobel Prize in Physiology or Medicine 2003". Nobelprize.org. Available at: http://nobelprize.org/nobel_prizes/medicine/laureates/2003/. Accessed July, 21 2011.
4. Burger PC, Nelson JS, Boyko OB. Diagnostic synergy in radiology and surgical neuropathology: neuroimaging techniques and general interpretive guidelines. *Arch Pathol Lab Med*. 1998;122:609–619.
5. Kidwell CS, Wintermark M. Imaging of intracranial haemorrhage. *Lancet Neurol*. 2008;7:256–267.
6. Cha S. Update on brain tumor imaging: from anatomy to physiology. *AJNR Am J Neuroradiol*. 2006;27:475–487.
7. Wippold FJ. Neuroradiology: the surrogate of gross neuropathology. In: Perry A, Brat DJ, eds. *Practical Surgical Neuropathology. A Diagnostic Approach*. Philadelphia: Churchill Livingstone; 2010:47–62.

8. Provenzale JM, Mukundan S, Barboriak DP. Diffusion-weighted and perfusion MR imaging for brain tumor characterization and assessment of treatment response. *Radiology*. 2006;239:632–649.
9. Higano S, Yun X, Kumabe T, et al. Malignant astrocytic tumors: clinical importance of apparent diffusion coefficient in prediction of grade and prognosis. *Radiology*. 2006;241:839–846.
10. Rumboldt Z, Camacho DL, Lake D, et al. Apparent diffusion coefficients for differentiation of cerebellar tumors in children. *Am J Neuroradiol*. 2006;27:1362–1369.
11. Young RJ, Knopp EA. Brain MRI: tumor evaluation. *J Magn Reson Imaging*. 2006;24:709–724.
12. Sadeghi N, Salmon I, Decaestecker C, et al. Stereotactic comparison among cerebral blood volume, methionine uptake, and histopathology in brain glioma. *AJNR Am J Neuroradiol*. 2007;28:455–461.
13. Maia AC Jr, Malheiros SM, da Rocha AJ, et al. MR cerebral blood volume maps correlated with vascular endothelial growth factor expression and tumor grade in nonenhancing gliomas. *AJNR Am J Neuroradiol*. 2005;26:777–783.
14. Caseiras GB, Chheang S, Babb J, et al. Relative cerebral blood volume measurements of low-grade gliomas predict patient outcome in a multi-institution setting. *Eur J Radiol*. 2010; 73:215–220.
15. Ullrich RT, Kracht LW, Jacobs AH. Neuroimaging in patients with gliomas. *Semin Neurol*. 2008;28:484–494.
16. Stadlbauer A, Gruber S, Nimsky C, et al. Preoperative grading of gliomas by using metabolite quantification with high-spatial-resolution proton MR spectroscopic imaging. *Radiology*. 2006;238:958–969.
17. Zeng Q, Liu H, Zhang K, et al. Noninvasive evaluation of cerebral glioma grade by using multivoxel 3D proton MR spectroscopy. *Magn Reson Imaging*. 2011;29:25–31.
18. Cakirer S, Karaarslan E, Arslan A. Spontaneously T1-hyperintense lesions of the brain on MRI: a pictorial review. *Curr Probl Diagn Radiol*. 2003;32:194–217.
19. Rong Y, Durden DL, Van Meir EG, et al. 'Pseudopalisading' necrosis in glioblastoma: a familiar morphologic feature that links vascular pathology, hypoxia, and angiogenesis. *J Neuropathol Exp Neurol*. 2006;65:529–539.
20. Louis DN, Ohgaki H, Wiestler OD, et al. *WHO Classification of Tumours of the Central Nervous System*. Lyon: International Agency for Research; 2007.
21. Chaichana KL, Kosztowski T, Niranjan A, et al. Prognostic significance of contrast-enhancing anaplastic astrocytomas in adults. *J Neurosurg*. 2010;113:286–292.
22. Dean BL, Drayer BP, Bird CR, et al. Gliomas: classification with MR imaging. *Radiology*. 1990;174:411–415.
23. Omuro AM, Leite CC, Mokhtari K, et al. Pitfalls in the diagnosis of brain tumours. *Lancet Neurol*. 2006;5:937–948.
24. Burger PC, Nelson JS, Boyko OB. Diagnostic synergy in radiology and surgical neuropathology: radiographic findings of specific pathologic entities. *Arch Pathol Lab Med*. 1998; 122:620–632.
25. Lucchinetti CF, Gavrilova RH, Metz I, et al. Clinical and radiographic spectrum of pathologically confirmed tumefactive multiple sclerosis. *Brain*. 2008;131(Pt 7):1759–1775.
26. Donev K, Scheithauer BW. Pseudoneoplasms of the nervous system. *Arch Pathol Lab Med*. 2010;134:404–416.

