Mass Lesions of the Brain: A Differential Diagnostic Approach

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Though not as common as lung cancer, breast cancer, or others, 70,000 new cases of primary brain tumors are diagnosed annually in the USA. There are nearly 700,000 people in the USA living with a brain tumor. Meningiomas represent 34 % of all primary brain tumors, and their prevalence at autopsy is approximately 1 % making them the most common primary brain tumor. Gliomas represent 30 % of all primary brain tumors and 80 % of all primary malignant tumors. There are more than 120 types of brain tumors. Approximately 50 % of solitary tumors discovered in the brain relate to metastatic disease; when multiple tumors are found, metastatic disease is easier to suspect. Finally, there are many disease entities in the brain that simulate the morphology of a neoplasm yet are caused by infection, stroke, demyelination, etc.

Needless to say, the choice of an imaging modality, and particularly the specific algorithms within an imaging modality that are used, greatly influences not just detection of masses in the brain but their characterization which helps to lead the radiologist toward a concise differential diagnosis. Patient history, objective clinical findings, and the demographics are always useful in that effort.

The clinical presentation of brain tumors varies widely. Headache is a frequent symptom; however the widespread prevalence of headaches in the general population makes it an extremely nonspecific one. Many tumors discovered on imaging for headaches are really incidentally found, the headache only occasionally being associated with the tumor. More worrisome patient complaints suggesting the presence of an underlying tumor are the onset of a seizure beyond the age of 15, progressive sensory or motor disturbance of a subacute or subtle nature, progressive alteration of cognition or mental status in a young or middle-aged adult, or slow onset of visual change. Imbalance, nausea and vomiting, and hearing loss can herald the presence of a posterior fossa mass or increased intracranial pressure from tumor-induced obstructive hydrocephalus.

The development of CT scanning greatly improved the ability to detect intracranial neoplasms. Iodinated contrast agents help characterize them in terms of vascularity and loss of the integrity of the blood-brain barrier, a marker of greater degrees of malignancy. However, CT suffers from beam-hardening artifacts in the region of the middle and posterior fossa, and its ability to delineate subtle alteration of tissue in the form of differential x-ray attenuation detracts from its sensitivity. Physics that rely on changes in electron density for differentiation of normal and abnormal tissue are not as robust as the physics of the hydrogen relaxation parameters, magnetic susceptibility of intrinsic tissue constituents, restriction in the diffusion of water molecules, etc., that are the hallmarks of the greater tissue differentiation capability of magnetic resonance imaging, improving its sensitivity. Only the presence of calcification is arguably more sensitive with CT as compared to MRI on routine imaging studies.

Once detected, the location of tumors to a specific compartment aids the differential diagnosis from a purely anatomic perspective. Allocating the origin or location of a tumor into either the intra-axial or the extra-axial space is the first basic step. Localizing to the intraventricular, subarachnoid, and extra leptomeningeal spaces likewise helps further differentiation. Although special allocation sounds simple, especially when the tumor is well within the brain substance, the distinction may be difficult when the mass is in the periphery of the brain or in such regions as the cerebellopontine angle, the skull base, and even the anterior fossa. The angle between the mass and the adjacent cranium, presence of displaced vessels, and menisci in the spinal fluid space help this distinction.

Certain general locations narrow the differential diagnosis. For instance, lesions in the cerebellopontine angle have a

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relatively limited differential which includes acoustic neuroma, meningioma, aneurysm of the vertebral artery branches, and neuromas of the various cranial nerves at the level of the foramen magnum but also less common lesions such as lipomas and arachnoid cysts. A lesion in the region of the pineal gland creates another category of differential diagnoses, which includes benign pinealomas and the more malignant pineoblastomas, germ cell layer tumors such as germinomas and teratomas, and also glial tumors given the proximity of glial cells to the pineal region. In fact, ependymomas, even meningiomas, can occasionally stimulate the pineal gland as the originating cell types are found in the vicinity. Intraventricular tumors again have a more specific differential, including ependymoma and meningioma, in children tumors related to congenital syndromes such as giant cell astrocytoma. In older adults, intraventricular neurocytomas can be found, as can paraventricular neurocytomas. Masses around the pituitary fossa can be better analyzed by first determining if the normal pituitary gland can be identified, as large tumors of the pituitary (craniopharyngiomas, nonfunctioning giant adenomas) can simulate intra-axial brain tumors.

As magnetic resonance has become the staple for characterizing brain tumors, the basic parameters of T1 and T2 relaxation, magnetic susceptibility characteristics of inherent constituents [1], and the diffusion of water molecules in the microarchitecture help tumor characterization. Additional parameters that can be used with MR include perfusion imaging with its components of blood volume and contrast transit time, as well as spectroscopy. Though as a general rule, T2 high signal connotes malignancy, certain tumors such as lymphoma and mucinous carcinoma exhibit relatively low T2-weighted signal features due to the presence of specific components such as free radicals and mucin, respectively, although hemorrhagic components of tumors can likewise lower T2 relaxation and demonstrate low signal on T2-weighted images. Melanoma is a tumor which can lower T2 weighting due to both blood by-products (it is frequently hemorrhagic) or intrinsic components such as free radicals and even melanin itself. High T1 signal is also associated with blood by-products, particularly methemoglobin due to a component of subacute hemorrhage within the tumor, but occasionally follicular calcification can produce T1 shortening of hydrogen nuclei at the surface of such microcalcific foci, mimicking hemorrhagic components.

A hallmark of several subtypes of low-grade astrocytomas (e.g., protoplasmic astrocytoma) is the low T1-weighted signal intensity of a well-circumscribed lesion without surrounding edema, while the bubbly appearance of a localized lesion in the gray matter convolutions in a youngster with seizures should raise the consideration of a dysembryoplastic neuroepithelial tumor to a low-grade lesion with a very good prognosis. Cystic components can be seen with relatively benign tumors such as craniopharyngiomas (the cysts highly variable in signal depending on protein concentration within) and pilocytic astrocytomas which have highly enhancing solid components, but are well circumscribed with little or no edema. Also demonstrating necrotic cysts, but showing ill-defined borders and varying degrees of surrounding edema, are the malignant gliomas and the medulloblastomas of childhood which tend to be midline in the posterior fossa.

Two other features that help in the differential diagnosis are the presence of multiple foci, most often associated with metastatic disease, but sometimes due to nonneoplastic conditions such as infection, vasculitis, demyelinating disease, and others. One must remember, however, that there is multifocality seen in glial primary brain tumors, with gliomatosis cerebri and multicentric glioblastomas being the most notable examples. When a single lesion presents on both sides of the brain midline, particularly by spread through the corpus callosum, the differential diagnosis becomes significantly limited to such infiltrating lesions as malignant gliomas, lymphomas, and epidermoids (which cross the midline through the subarachnoid space) and dural tumors such as meningiomas and metastatic lesions to the dura of the interhemispheric falcine structure. Epidermoids can simulate expanded spinal fluid spaces, but FLAIR and diffusion sequences clearly separate the two.

Paramagnetic contrast agents provide considerable support for the diagnostic capability of MRI, making the diagnosis of blood-brain barrier disruption demonstrable, as well as physiologic evaluation of perfusion and blood volume parameters. It is notable that certain chemotherapeutic agents may actually mistake reduction in vascularity and blood volume for tumor remission (e.g., Avastin). However, overall, cerebral blood volume and contrast permeability analysis can help distinguish degrees of malignancy and thus help monitor disease treatment. Recent advances with MRI include the development of PET MRI capability [2], which has been found helpful in distinguishing radiation necrosis from recurrent tumor. Spectroscopy helps in this type of differential as well, as it allows for specific analysis of various metabolites within brain tissue. Tumors, especially primary brain tumors, show elevation of choline (a marker of cell membrane turnover) and loss of an N-acetylaspartate (a neuronal marker). However, it should be noted that MR spectroscopy, like perfusion analysis, is not totally specific. Any rapidly evolving process which produces membrane breakdown or turnover, including demyelinating disease, can show elevation of choline (although the decrease in an acetylaspartate is not as prominent in demyelinating disease).

Diffusion imaging can be specifically used for tractography, allowing surgical planning in certain cases where involvement of important white matter tracts is questioned,

but the most common use of diffusion imaging is to demonstrate restricted diffusion and resulting high signal on appropriately reconstructed images in highly cellular tumors such as lymphoma and in differentiating abscesses from brain tumors (the former almost always demonstrate diffusion restriction). This is particularly pertinent in separating necrotic tumor cavities from infected ones. Any significant increases of membranes in the micro environment can also restrict diffusion, so hypercellular tumors in addition to demyelination can show high signal on diffusion images, but the finding is not tumor specific. Even hematomas will demonstrate diffusion restriction, despite no underlying neoplasms.

Despite our advanced technology, it is still challenging to specifically differentiate certain lesions in terms of a non-neoplastic versus neoplastic histology. Masses such as tumefactive multiple sclerosis, certain fungal infections (e.g., toxoplasmosis), encephalitides, congenital dysplasias such as migrational disorders, and even hematomas can simulate neoplasms. Careful attention to the numerous MR parameters as expressed on specific pulse sequences of a given lesion can usually solve the quandary, but occasionally full specificity in this distinction will evade us. Any unexplained hematoma should be followed until resolution to exclude a possible underlying pathology, including malignancy.

Once detection of localization and characterization of neoplasms is determined, MRI can help considerably in treatment planning. Its three-dimensional capability, and other characterization capabilities, allows much better delineation of tumor extent and relationships to eloquent brain structures. For instance, we have been using the combination of FLAIR imaging and MR spectroscopy to better delineate stereotactic radiation of infiltrating gliomas, treating the "leading edge" of the tumor as determined on multivoxel spectroscopy applied to FLAIR images. Further, surface contours which can easily be created with 3D techniques, inherent in modern MRI instruments, help couple the data to intraoperative navigation techniques creating a "virtual reality" for the neurosurgeon, aiding more accurate resection. We have found such techniques useful in helping prolong the median survival time of infiltrating gliomas, suggesting a survival advantage using such gamma knife radiosurgery for patients with glioblastomas and other malignant gliomas [3].

Given this very broad overview and in summary, the radiologist now has available extremely advanced imaging capabilities that aids in the detection of brain tumors at much earlier stages and to a greater degree of accuracy. The availability of multiple instruments, some melded into one (as in the case of PET/MR and MR/CT) [2], the ability to fuse images from one modality with another, and the various algorithms greatly help characterization of lesions as well as monitoring of therapy. A concise differential in a newly referred patient starts with lesion localization, then its characterization. The patient's age, gender, clinical history and objective signs are always important.

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