An Algorithmic Approach to the Brain Biopsy—Part II

Richard A. Prayson, MD; B. K. Kleinschmidt-DeMasters, MD

Context. —The formulation of appropriate differential diagnoses for a slide is essential to the practice of surgical pathology but can be particularly challenging for residents and fellows. Algorithmic flow charts can help the less experienced pathologist to systematically consider all possible choices and eliminate incorrect diagnoses. They can assist pathologists-in-training in developing orderly, sequential, and logical thinking skills when confronting difficult cases.

Objective.—To present an algorithmic flow chart as an approach to formulating differential diagnoses for lesions seen in surgical neuropathology.

Design.—An algorithmic flow chart to be used in teaching residents.

Results.—Algorithms are not intended to be final diagnostic answers on any given case. Algorithms do not substitute for training received from experienced mentors nor do they substitute for comprehensive reading by trainees of reference textbooks. Algorithmic flow diagrams can, however, direct the viewer to the correct spot in reference texts for further in-depth reading once they hone down their diagnostic choices to a smaller number of entities. The best feature of algorithms is that they remind the user to consider all possibilities on each case, even if they can be quickly eliminated from further consideration.

Conclusions.—In Part II, we assist the resident in arriving at the correct diagnosis for neuropathologic lesions containing granulomatous inflammation, macrophages, or abnormal blood vessels.

(Arch Pathol Lab Med. 2006;130:1639–1648)

The majority of lesions that are the target of a brain biopsy turn out to be neoplastic. Particularly challenging is recognizing the occasional nonneoplastic lesion that may mimic a tumor or be the target of a biopsy. A variety of nonneoplastic lesions are encountered in the routine practice of surgical neuropathology. These often present a considerable diagnostic challenge and can be the source of much confusion and anxiety.

The purpose of this paper is to present a general algorithmic approach to certain commonly encountered pathologic patterns that are suggestive of a nonneoplastic process. Flow-chart style algorithms are provided for this section in Figures 1 and 2. First, a few general comments:

1. The role of intraoperative consultation in the evaluation of these lesions is important. Touch or crush preparations may be particularly useful in this setting to recognize macrophages and avoid confusing them with neoplastic astrocytic cells. If something looks as though it might be infectious, recommendations for culture can be made.

2. Communication with the neurosurgeon is important! Often, the imaging studies and/or clinical history are suggestive of a nonneoplastic process.

3. One does not want to misdiagnose a nonneoplastic lesion as tumor, resulting in overtreatment of the patient. Likewise, one does not want to misdiagnose a tumor as a nonneoplastic lesion. This latter scenario is perhaps less problematic in that if the lesion is really a tumor, it will sooner or later declare itself as such.

4. Suggested reference texts helpful to trainees and nonneuropathologists are provided at the end of this paper.1–8

PART II—APPROACH TO GRANULOMATOUS DISEASE

Is There Known Systemic Disease That Can Cause Granulomatous Inflammation?

A prior history of an immunocompromised state, such as acquired immunodeficiency syndrome, heightens one’s suspicion of infectious processes, including those that may cause granulomatous inflammation (Figure 3, A). A history of previous surgery may suggest a foreign body giant cell reaction; one should look for polarizable material. Sarcoidosis, another cause of granulomatous inflammation, may be seen in approximately 5% of patients with systemic sarcoidosis; in many instances, patients with central nervous system (CNS) disease have known systemic disease (Figure 3, B). Likewise, with the lipogranulomatous disorders, many of these patients have evidence of lipogranulomatous inflammation involving other organ systems, which may already be known. Parasitic diseases such as schistosomiasis or cysticercosis elicit a localized foreign body-like inflammatory response, often accompanied by increased eosinophils.

Is the Inflammation Lipogranulomatous in Nature?

Lipogranulomatous inflammation refers to a nodular focus of granulomatous inflammation associated with in-
An Algorithmic Approach to Granulomatous Inflammation in the CNS

**IS THERE KNOWN SYSTEMIC DISEASE?**

**YES**

**Immunocompetent host?** Consider sarcoidosis, tuberculosis, lipogranulomatous disorders (Erdheim-Chester Disease, systemic lipogranulomatous disease, rheumatoid nodules, metabolic disorders (Farber’s disease)

**NO**

**Immunocompromised host?** Especially AIDS/HIV+ patients and transplant recipients on therapy: Consider fungal or mycobacterial infections

**Previous neurosurgery?** Consider retained suture causing foreign body granulomatous reaction. CAVEAT! always check for polarizable foreign material

**Hemosiderin present?** Consider organizing hemorrhage; prominent multinucleated giant cells and histiocytes may be seen in association with cholesterol clefts. Examples: xanthogranulomatous change in choroid plexus, intracranial cholesterol granulomas

**Keratin present?** Consider ruptured dermoid or epidermoid cysts with foreign body granulomatous reaction

**Amyloid present?** Consider cerebral amyloid angiopathy; rare patients with CAA manifest granulomatous reaction. CAVEAT! Systemic amyloidosis do not involve the CNS but can affect peripheral nervous system

**Eosinophils present?** Consider schistosomiasis, cysticercosis, amebic encephalitis

**SPECIFIC LOCATIONS**

**Pineal or suprasellar?** Consider germ cell tumor with granulomatous reaction

**Dura?** Consider rheumatoid arthritis nodules, Wegener’s granulomatosis, Rosai Dorfman disease

**Choroid plexus?** Consider xanthogranuloma of choroid plexus

**Base of brain?** Tuberculosis versus sarcoidosis. CAVEAT! Rare examples of sarcoidosis are necrotic; rule out TB based on combination of culture, stains (only 50%-60% of AFB/FITE stains are positive), and PCR testing.

Figure 1. An algorithmic flow diagram containing questions to ask oneself when encountering granulomatous inflammation in central nervous system biopsy material, at the time of either frozen or permanent sections. CNS indicates central nervous system; CAA, cerebral amyloid angiopathy; AIDS, acquired immunodeficiency virus; TB, tuberculosis; HIV, human immunodeficiency virus; PCR, polymerase chain reaction.
creased lipid material accumulated within foamy-type macrophages. With cholesterol clefts in an organizing hemorrhage or with keratin debris extravasated from a dermoid or epidermoid cyst (Figure 3, C), this may be a predominant pattern. There are other, fortunately uncommon, conditions that are also associated with predominantly lipogranulomatous inflammation. The histologic appearance of rheumatoid nodules can be similar to that of those seen in soft tissue sites elsewhere in the body. These nodules may be associated with multinucleated giant cells and increased numbers of foamy-type macrophages. Intraventricular xanthogranulomatous inflammation of the choroid plexus may radiographically present as a mass but is a much more common incidental finding at autopsy in aged individuals.

Are the Granulomas Necrotizing or Nonnecrotizing?

In medical school, we were taught that necrotizing granulomas are generally associated with infectious processes and nonnecrotizing granulomas with other conditions such as sarcoidosis (Figure 3, A). In general, this is true; however, in practice, there are always exceptions. Granulomatous inflammation associated with infectious processes such as tuberculosis may involve the formation of both necrotizing and nonnecrotizing granulomas (Figure 3, B). Although granulomas formed in sarcoidosis tend to be nonnecrotizing, small foci of necrosis may occasionally be seen in such granulomas. Both processes preferentially involve the base of the brain and may either involve leptomeninges or parenchyma. Both processes may be associated with a vasculitic component. Sarcoidosis is often considered the diagnosis of exclusion once an infectious etiology has been ruled out. The presence of granulomas at the time of intraoperative consultation, either necrotizing or nonnecrotizing, should prompt recommendation for culture, particularly for mycobacteria and fungi, and rarely, toxoplasma organisms.

Idiopathic hypertrophic cranial pachymeningitis is a rare entity of unknown etiology presenting as a dural mass mimicking a dural-based tumor, such as meningioma. Pathologically, the entity is characterized by chronic leptomeningeal inflammation, nonnecrotizing granulomas, and negative staining for organisms. The diagnosis
Algorithmic Approach to Brain Biopsy: Part II
Prayson & Kleinschmidt-DeMasters

Figure 3. A, A leptomeningeal nonnecrotizing granuloma with associated chronic inflammation in sarcoidosis (hematoxylin-eosin, original magnification ×200). B, Necrotizing granulomatous inflammation in a tuberculoma (hematoxylin-eosin, original magnification ×200). C, A ruptured epidermoid cyst with associated histiocytic and giant cell reaction (hematoxylin-eosin, original magnification ×100). D, Leptomeningeal involvement with venous wall infiltration in the setting of chronic lymphocytic leukemia (hematoxylin-eosin, original magnification ×100). E, Necrotizing vasculitis involving cerebral arteries in polyarteritis nodosa (hematoxylin-eosin, original magnification ×50). F, Atypicality of cells marks a diffuse large B-cell lymphoma (hematoxylin-eosin, original magnification ×400).

is often one of exclusion when other causes of noninfectious, granulomatous leptomeningitis are excluded.

A mass in the pineal gland region associated with granulomas or syncytiotrophoblastic-type giant cells is highly suggestive of germinoma; occasionally in such a scenario, especially in the evaluation of small stereotactic biopsy specimens, one may only sample areas of granulomatous inflammation, and germinoma cells may not be seen.

Are Special Stains for Organisms Positive? If Not, Are Cultures Positive?
The evaluation of granulomatous inflammation with special stains should be almost reflexive. One of the more common causes of infectious, granulomatous inflammation is tuberculosis. Tuberculosis meningitis is far more frequent than focal tuberculomas in the United States.

In most patients, the diagnosis is made by isolation of
the organism on culture. Special stains for acid-fast organisms (Ziehl-Neelsen or Fite stains) yield positive results on tissue sections in only about one half of culture-positive cases. Unfortunately, cultures may require several weeks before being declared positive or negative. Polymerase chain reaction testing has dramatically improved turnaround time in the identification of mycobacterial organisms but is not universally available. Despite the poor yield in tissue sections, organismal stains should be routinely performed. A positive result may facilitate a more timely intervention and peace of mind with regard to the clinical approach. Nevertheless, a negative stain does not necessarily exclude an infectious process.

Remember that infections with fungal organisms manifest their histological features based on the immune status of the host. Infections of the central nervous system by *Aspergillus* species and *Cryptococcus* species may present as focal granulomatous inflammation in immunocompetent patients and as diffuse necrotizing processes with or without a prominent neutrophilic/lymphocytic inflammatory response in immunosuppressed individuals, depending on the degree of immunosuppression. Fungal organisms can usually be readily identified with Gomori methenamine silver stains. Periodic acid–Schiff or mucicarmine stains are often helpful in highlighting cryptococcal organisms.

**Is There Evidence of Vasculitis or Vessel Wall Thickening?**

Granulomas associated with vasculitis imply a differential diagnosis that includes infectious processes and primary or other secondary causes of vasculitis. Again, the distinction often is dependent on one's ability to identify organisms on tissue sections or culture organisms in such cases.

Although the granulomas of sarcoidosis are often associated with vessels, necrotizing vasculitis is not a prominent feature of sarcoidosis in the CNS. Examples of primary granulomatous vasculitis or Wegener-type vasculitis have been rarely described in the CNS. This form of vasculitis is often associated with fibrinoid necrosis and may affect both arteries and veins. Serologic testing for antineutrophil cytoplasmic antibody may be helpful in evaluation for Wegener granulomatosis. Often, patients with Wegener granulomatosis have associated nasal/sinus, pulmonary, or renal involvement. Rare examples of granulomatous inflammation associated with amyloid deposition (amyloid angiopathy) have also been noted.

**Approach to Vascular Inflammation**

Either clinically or by neuroimaging features, the diagnosis of CNS vasculitis continues to remain a challenge. Further complicating the issue is the fact that multiple pathologic conditions can exhibit a vasculitic pattern of injury.

**Is There Truly “Vasculitis” or Is the Inflammatory Infiltrate Perivascular?**

The first question one needs to critically ask when confronted with a biopsy specimen that contains vessel-based inflammation is whether or not vasculitis truly is present (Figure 3, D and E). Vasculitis pathologically is defined as infiltration of the vessel wall by inflammatory cells, often accompanied by some degree of vessel wall injury (Figure 3, E). True vasculitis may either be part of a systemic disease or represent primary angiitis of the CNS. The latter scenario accounts for the minority of cases of vasculitis one encounters in the CNS. In cases of primary vasculitis or vasculitis associated with systemic disease, brain biopsy is often utilized for purposes of diagnosis. In selecting a site for biopsy, it is generally appropriate to select an area that is either clinically or radiographically involved.

An optimal biopsy should include samples from the dura and leptomeninges, cortex, and white matter with the highest yield from sections containing leptomeninges and superficial cortex. Some neurosurgeons will elect to take separate leptomeningeal biopsy specimens to eliminate the possibility that the critical leptomeninges will not “roll off” the cortex and be underrepresented on the pathologist's specimen. Many of these cases require ancillary studies, which may include triaging tissue for cultures, processing tissue for possible electron microscopic evaluation, and keeping tissue frozen for later immunofluorescence or molecular analysis. Since vasculitis is a notoriously localized process, stereotactic biopsies are virtually contraindicated and any tissue received by the pathologist should be submitted in toto and may need to be examined on several leveled sections. A positive biopsy result is often helpful clinically. It is important to remember, however, that a negative biopsy result does not necessarily exclude a diagnosis. Only about two-thirds of attempted biopsies may yield positive results. If the index of suspicion is high and only a perivascular pattern of inflammation is observed, deeper sectioning into paraffin blocks may be warranted. Without evidence of inflammatory cells within the vessel wall, a definite diagnosis of vasculitis should not be rendered. Unfortunately, the term “perivasculitis” has crept into the literature. The term can be misleading; people choose to see the “vasculitis” and forget about the “peri-” prefix. To avoid confusion when communicating with our clinical colleagues, we advocate not using the term “perivasculitis.”

**Are the Inflammatory Cells Atypical?**

In most cases of vasculitis or perivascular inflammation unassociated with a neoplasm, the diagnosis requires ancillary clinical and laboratory correlation. In contrast, in the setting of inflammation associated with tumors, the diagnosis is straightforward, provided adequate volumes of tissue (and tissue fully representative of the lesion) are received by the pathologist. Although primary and metastatic tumors may be associated with chronic, vascular-based inflammation, the biggest differential diagnostic problem often lies in distinguishing lymphomatous, leukemic, or lymphoproliferative processes from true primary or systemic vasculitis (Figure 3, D). This often rests on the recognition of cytologic atypia in the cells involved in the inflammatory infiltrate (Figure 3, F).

Primary CNS lymphoma typically presents as a periventricular mass, with the vast majority of cases being supratentorial in location. Most primary CNS lymphomas are parenchymal-based lesions, in contrast to secondary involvement of the CNS by lymphoma or leukemic processes, which tend to be leptomeningeal based. Lymphomas in the CNS typically have indistinct borders and enhance on neuroimaging studies. At least one half of the patients will present with multiple lesions.

The key to recognizing a lesion as primary CNS lymphoma rests on appreciating the nuclear atypia (Figure 3, F). The majority of primary CNS lymphomas are of the diffuse large cell type (REAL classification [Revised European-American Classification of Lymphoid Neoplasms]).
and have a B-cell immunophenotype. This holds true for both the human immunodeficiency virus–associated lymphomas, many of which appear to be Epstein-Barr virus–associated lesions, as well as the nonhuman immunodeficiency virus–associated lymphomas. Immunocompromised patients are more likely to present with multiple and necrotic lesions, whereas immunocompetent, often elderly, patients are more likely to present with a single mass. Cells tend to be discohesively arranged with large nuclei, marked nuclear irregularities, and sometimes prominent nucleolation. Cells characteristically arrange themselves in a vasculocentric fashion. In more advanced tumors, the infiltrate may be confluent and the vasculo-centric nature not readily apparent. In these latter cases, distinction from metastatic carcinomas, particularly small cell carcinoma, and primary malignant gliomas is an issue. Immunohistochemistry may be helpful in the more difficult cases; in the vast majority of lymphomas, tumor cells stain positively with B-cell immunomarkers such as CD20. Usually admixed with the larger, atypical-appearing B-cells are smaller numbers of tumor-infiltrating lymphocytes that generally have a T-cell immunophenotype. Lesions in which the T-cell population predominates may cause problems in terms of diagnosis, and rare examples of T-cell lymphoma have been documented. In such cases, gene rearrangement studies may be helpful in determining monoclonality in a very small population of cells in the lesion.

Many CNS lymphomas are initially quite responsive to steroid therapy. Remember that administration of steroids prior to biopsy may make diagnosis quite difficult and may result in significant individual tumor cell lysis with a virtual absence of residual B-cell lymphoma cells and may result in significant individual tumor cell lysis with a virtual absence of residual B-cell lymphoma cells and areas of patchy demyelination and tissue damage on subsequent posttreatment biopsy or autopsy.

If the Process Does Not Represent a Malignancy, Does It Represent Primary or Secondary Vasculitis?

This is often a very difficult question to answer, requiring close correlation with clinical history. A number of infectious agents can be associated with a vasculitis. Identifiable organisms, prominent formation of microglial nodules, and appropriate serologies would all support an infectious etiology. Microbiologic culturing should be routine in any case in which infection is suspected. In some cases, ultrastructural examination may be helpful in identifying certain infectious agents that are not readily apparent by light microscopic examination.

Infectious processes with an associated vasculitis tend to be subarachnoid-based lesions. There has been even some suggestion in the literature that certain forms of so-called primary angiitis of the central nervous system may be tied to certain infectious organisms, in particular herpes zoster. All forms of vasculitis may result in vascular wall occlusion and necrosis, which may present with infarct or hemorrhage.

A variety of drugs and toxic agents (such as amphetamines and heroin) have been associated with development of a vasculitic pattern of injury.

Sarcoidosis, which has been previously discussed, can occasionally present with a lymphocytic vasculitis pattern of injury, although granulomas are usually nearby and necrosis is very uncommon. Small numbers of chronic inflammatory cells may be seen in vessels in a variety of atherosclerotic and other diseases that affect the vessel directly. Demyelinating disorders such as acute tumefactive demyelinating disease/multiple sclerosis are more often characterized by intense perivascular chronic inflammation, and lymphocytes can be seen occasionally infiltrating vessels; vessel wall damage is absent, however, and unlike in the overwhelming majority of true vasculitis cases, the inflammation is associated with a demyelination, not infection on hematoxylin-eosin and myelin and axon stains.

If a Primary Vasculitis, What Type?

Once one has excluded obvious causes of secondary vasculitis, including neoplasia, one is often left with a differential diagnosis of systemic vasculitides or primary vasculitis of the CNS. Differentiation of one type from another relies on many of the criteria that are established for other organ systems. Things that one typically looks for include the following: (1) Is the process necrotizing, that is, is there evidence of fibrinoid necrosis involving the vessel wall? (2) Is the process granulomatous or not? (3) Are there prominent numbers of eosinophils associated with the inflammatory cell infiltrate? Widely accepted classifications of systemic vasculitis have not been forthcoming. The precise diagnosis of vasculitis again is often dependent upon a correlation of clinical history with laboratory findings and assays, as well as the histopathology. Vasculitic entities associated with vessel wall necrosis include classic polyarteritis nodosa (Figure 3, E), Wegener granulomatosis, Churg-Strauss vasculitis, and so-called lymphomatoid granulomatosis. Giant cell arteritis typically includes Takayasu arteritis and temporal arteritis.

A diagnosis of primary angiitis of the CNS should be reserved for vasculitis confined to the CNS and confirmed by biopsy. Classically, most of these vessels demonstrate angioinvasive granulomatous inflammation or transmural lymphocytic infiltrates. The majority of lymphocytes involved in the inflammatory response tend to have a T-cell immunophenotype. Treatment makes use of immunosuppressive agents with the goal of preventing disease recurrence.

Approach to Thickened Vessel Walls

Thickened vessel walls are not an uncommon finding in autopsy pathology. The most common cause of vascular wall thickening is related to hypertension, atherosclerosis, and arteriolosclerosis changes. There are, however, other causes of vascular wall thickening that may arise in the scenario of surgical neuropathology (increased age, in the center of remote multiple sclerosis plaque, white matter vessels from temporal lobectomy specimens for chronic epilepsy and in remote infarcts) and thickened blood vessel walls should not be overinterpreted in these situations.

Are the Vessel Walls Thickened?

Routine evaluation of nonneoplastic biopsy material should include an evaluation of vasculature and the caliber of vessels seen in various locations throughout the biopsy specimen. Parenchymal vessels tend to be smaller in size and are normally inconspicuous, particularly in deep white matter. If one can readily identify capillary-sized vessels, this may be indicative of abnormal vascular wall thickening and require further scrutiny of all vessels.

Is There a Prior History of Radiation?

Radiation characteristically results in thickened hyalinized sclerosis of vessel walls. This thickening may be ac-
companied by variable amounts of chronic inflammation, thrombosis, and atherosclerotic changes. In a patient who has received prior radiation, vascular wall thickening is most likely attributable to this etiology.

Is There Amyloid Deposition in the Vessel Wall?
A good general rule of thumb is that if one suspects or even thinks about amyloid deposition, one should perform the necessary staining to evaluate for it (Figure 4, A). A variety of stains can be used to evaluate for amyloid (congo red, crystal violet, fluorescent thioflavin S). Sporadic deposition of amyloid in the CNS is most commonly encountered in a perivascular or vascular distribution (Figure 4, A). Amyloid angiopathy is responsible for anywhere between 5% and 12% of primary nontraumatic intracerebral hemorrhages. Classically, these hemorrhages occur in a nonhypertensive distribution, particularly in elderly, normotensive patients. They are commonly superficially based and may be multifocal, associated with subarachnoid hemorrhage.

Is There Basophilic Granularity in the Vessel Wall?
Once amyloid deposition has been excluded as a diagnostic possibility, careful attention should be paid to whether or not basophilic granularity can be appreciated within the vessel walls (Figure 4, B). Recognition of this finding has been associated with a fairly recently described entity referred to as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy or CADASIL. This arteriopathy is a systemic disorder that has been recently recognized as a cause of stroke and vascular dementia.

Histopathologically, the disorder is characterized by a thickening of vessels, most notably in the white matter and leptomeninges. Vessel walls have a smudged, fibrohyaline appearance that may be accompanied by a sparse perivascular chronic inflammatory cell infiltrate and duplication and fragmentation of the internal elastic lamina. Careful inspection of the vessels frequently shows granular, basophilic osmiophilic material in the vessel wall (Figure 4, B). Perivascular atrophy is a common concomitant finding. Ultrastructurally, this material appears as electron dense, extracellular granular deposits, without filament-like profiles, ranging in size from 0.2 to 0.8 mm. The exact nature of these deposits is not entirely known.

Is There a History of Hypertension?
Hypertension-associated vasculopathy usually assumes 1 of 2 forms: small vessel disease and so-calledBinswanger disease. Development of atherosclerotic thickening of vessel walls secondary to chronic hypertension is a welldescribed phenomenon. Chronic hypertension is a wellknown risk factor for intracerebral hemorrhages. Classically, these hemorrhages occur in a nonhypertensive distribution, particularly in elderly, normotensive patients. They are commonly superficially based and may be multifocal, associated with subarachnoid hemorrhage.

Too Many Blood Vessels
Vascular malformations are a group of lesions that are responsible for a significant number of hemorrhagic strokes seen in the United States each year. They are often diagnosed radiographically, and certain types that are particularly prone to hemorrhage, namely arteriovenous malformations and cavernous angiomas, are often resected. The specimens are frequently submitted to surgical pathology for evaluation (Figure 4, C).

Are There Too Many Blood Vessels?
The brain is a richly vascular structure, supplied by the internal carotid and verteobasilar circulations. In contrast to usual vascular malformations, the vessels are histologically unremarkable. In general, vessels seen in the cortex and white matter tend to be smaller in size and caliber.

Conditions that result in increased number of vessels fall into 1 of 3 categories. One may see increased capillary-type vessels formed as part of granulation tissue associated with abscess or previous trauma. The pattern of granulation tissue formation histologically looks similar to that observed in other organ systems and is generally not problematic for most pathologists. One may also encounter an increased number of vessels as part of a vascular neoplastic process (Figure 4, D). Third, increased vessel number may be part of a malformative lesion such as Sturge-Weber disease or vascular malformation (Figure 4, C).

Are the Increased Vessels Part of a Tumor or a Vascular Malformation?
A number of neoplasms can demonstrate increased vascularity. Most gliomas are hypervascular. This hypervasularity is particularly notable in oligodendrogliomas, which are characterized by readily apparent arcuate, so-called “chicken-wire” capillary vasculature. Certain metastatic lesions, such as renal cell carcinoma and malignant melanoma, are notoriously vascular. Other tumors that are notably hypervascular include lesions such as hemangioblastoma (Figure 4, D), hemangiopericytoma, and pilocytic astrocytoma.

Rarely, angiomatous lesions or hemangiomas may be observed in the dura. These are particularly prevalent in patients with Sturge-Weber syndrome. In this setting, dystrophic mineralization involving gray and white matter vessels with accompanying gliosis is frequently seen.

If Part of a Malformation, What Type?
Once it has been determined that one is dealing with a vascular malformation, there are 2 important histologic features that are helpful in subtyping the lesion. The first of these focuses on the type of vessels that are involved in the malformation. Are the vessels arterial, venous, capillary, or a mixture of several types? Arteriovenous malformations (AVM) characteristically consist of both arteries and veins, but the latter often predominate in surgical specimens the pathologist receives; one should not incorrectly call these “venous angiomas” (Figure 4, C). In general, arterial vessels are not seen as part of the other malformative lesions (except for the mixed types that contain an arteriovenous component). Frequently, the vessels observed within malformations are altered by abnormal blood flow through these lesions. Vascular thrombosis, atherosclerotic changes, calcifications, areas of hemosiderin deposition, and gliosis are frequent concomitant findings. Venous vessels in AVM may acquire an “arterialized” appearance. Despite this, arterialized veins do not develop a smooth muscle layer and do not contain an internal elastic lamina, features that mark larger arterial vessels. Consequently, elastic stains may be helpful in the evaluation of malformations if one is unable to be certain whether or not there is an arterial component to the lesion. Cavernous malformations consist of medium-sized to small-sized, closely juxtaposed, hyalinized vascular chan-
nels that do not usually display features of veins; an arterial component is never present. Venous angiomas consist of smaller venous channels. The varix, considered by some to represent a form of venous angioma, is marked by a single dilated vein. Capillary telangiectasias are usually incidental findings, often located in the pons, that microscopically consist of small-caliber vessels.

Another important factor in the classification of parenchymal-based vascular malformations is whether or not the lesions demonstrate intervening neural parenchyma. Characteristically, the vessels in cavernous malformations are arranged in a back-to-back fashion. All of the other malformations contain intervening parenchyma, which may be gliotic, collagenized, or marked by hemosiderin deposition (as in the case of AVM) or may be fairly normal in appearance (as in the case with most venous angiomas and capillary telangiectasias).

The importance of distinguishing one malformation from the other lies in the risk of hemorrhage and in certain known associations. By far the most important malformation, because it is the one most likely to hemorrhage, is the AVM. The typical AVM is a wedge-shaped lesion with its base oriented towards the leptomeninges and the apex directed towards the center of the brain. Most of these arise over the lateral hemispheric surfaces in the distribution of the middle cerebral artery.

Venous angiomas are marked by a proliferation of venous vessels. The vessel walls in the venous malformations tend to be thicker and the lumens larger than what usually is seen in normal veins. The subarachnoid space of the lower thoracic spinal cord is a favored site of origin. Often there is a draining vein situated in the center of the lesion. A single ectatic venous channel represents a varix. There is generally no need for surgical intervention in venous angiomas; they are frequently incidental findings at autopsy. Capillary telangiectasias consist of multiple dilated capillaries with intervening parenchyma. The typical capillary telangiectasia is usually small, less than 2 cm in greatest dimension. Lesions are typically of little clinical significance and again are often incidental findings at autopsy.

**Approach to Macrophages**

Normally, macrophages are not seen in either gray or white matter tissue. White matter disease with macrophages raises a differential diagnosis primarily focused on differentiating infarct from demyelinating disease. Occasionally, one can encounter white matter macrophages in a variety of other conditions such as radiation-induced necrosis, certain infectious conditions such as Whipple disease, and granulomatous lesions, as previously discussed.

**Is It an Infarct or Demyelinating Disease?**

Characteristically, demyelinating disease is confined to the white matter, whereas infarcts may also involve gray matter. The distinction between these 2 entities may be at times difficult, particularly when one does not have history or when one is dealing with limited biopsy material. The neuroimaging appearance and the distribution of the lesion in the territory of a vascular supply, or not, along with the number of lesions is critical information to obtain. A middle-aged woman with slowly progressive white matter disease more likely has multiple sclerosis than infarct.

Microscopically, macrophages may be seen as early as 24 hours after infarct and may persist for months afterward. Astrocytic proliferation usually develops 7 to 10 days after the infarct and predominates around the perimeter of the lesion (Figure 4, E and F). Similarly, demyelinating lesions are associated with some degree of macrophage infiltration and astrocytosis. Reactive astrocytes in a demyelinating lesion tend to be distributed throughout the entire affected area (Figure 4, G and H). Infarct, because it represents tissue necrosis, will result in destruction of myelin, axons, and usually astrocytes in the epicenter of the lesion (Figure 4, E and F). In most demyelinating diseases, however, there is a relative sparing of axons and preservation of astrocytes, accounting for their presence throughout the lesion (Figure 4, G and H). Ancillary stains are often critical in evaluating potential demyelinating lesions and include the use of myelin stains (Luxol fast blue–periodic acid-Schiff allows characterization of myelin debris as acute [Luxol fast blue–positive] vs subacute or chronic [periodic acid–Schiff positive]). Axons should be evaluated from the same section, utilizing either modified Bielschowsky silver stains or immunostaining for neurofilament protein. Immunostaining for macrophages (CD68, HAM56) and astrocytes (glial fibrillary acidic protein) is also strongly recommended. The finding of prominent numbers of CD20-positive B-cells should always prompt consideration of CNS lymphoma since infarctions, demyelinating disorders, and infections are dominated by reactive T-cells. In addition, identifying causes of infarct, that is, thromboemboli or necrotizing vasculitis, may serve as clues in the differential.

**If Demyelinating Disease, Are There Identifiable Viral Inclusions?**

If one has established that the disorder may represent a demyelinating process, a viral etiology should be considered and a diligent search for viral inclusions should ensue. Tissue should be processed at the time of intraoperative consultation for electron microscopic evaluation,
which may be helpful in identifying or confirming one’s suspicion of certain viral agents. Two viral diseases that preferentially are marked by white matter demyelination are progressive multifocal leukoencephalopathy (PML) and subacute sclerosing panencephalitis. Characteristically, PML presents in immunocompromised patients with acute and subacute sclerosing panencephalitis. Characteristically, suspicion of certain viral agents. Two viral diseases that may be helpful in identifying or confirming one’s history of measles virus infection is noted. Both gray and mental deterioration. In most cases, careful evaluation will demonstrate dense viroacous, intranuclear inclusions involving oligodendroglial cells by JC or SV40 viruses (Figure 4, G). These inclusions typically exhibit a basophilic staining quality. Immunostains exist for these agents, and electron microscopy can be useful in demonstrating viral particles. Another salient feature of many PML cases is the presence of astrocytes, which are large, irregularly shaped, and sometimes multinucleated.

Subacute sclerosing panencephalitis typically presents in the first 2 decades of life, often with behavioral changes or mental deterioration. In most cases, a documented prior history of measles virus infection is noted. Both gray and white matter are typically involved in subacute sclerosing panencephalitis. Microscopically, subacute sclerosing panencephalitis demonstrates variable amounts of perivascular and leptomeningeal chronic inflammation, neuronal loss and gliosis, microglial cell proliferation, and variable numbers of white matter macrophages. Intranuclear inclusions may be identifiable within oligodendroglial and neuronal cell nuclei.

A number of other viral agents have been associated with demyelinating disease. Most notably, human immunodeficiency virus can present as a demyelinating disorder. Diagnosis requires careful clinical correlation. Typically, patients infected with human immunodeficiency virus are not biopsied for demyelinating lesions unless the lesion radiographically or clinically is mimicking lymphoma or PML is a strong consideration.

If Demyelinating Disease, What Type?

If a viral etiology is excluded, one is left with a differential diagnosis of demyelinating disease that includes a variety of disorders. Some of these disorders have characteristic histopathologic features or clinical presentations that allow for diagnosis. Others tend to be more difficult to diagnose, specifically in biopsy specimens alone.

The prototypical demyelinating disease is multiple sclerosis. The disease usually presents in young women, with a waxing and waning clinical history that is slowly progressive over time. The presentation of multiple sclerosis past the age of 60 or 65 years of age is unusual and more typical of disorders such as PML. Characteristically, multiple sclerosis demonstrates multiple, asymptomatically distributed zones of demyelination or plaques that are sharply demarcated from adjacent parenchyma. Plaques are marked histologically by variable numbers of macrophages, reactive astrocytes, and perivascular lymphocytes that have a predominantly T-cell immunophenotype (Figure 4, H).

A number of examples of ‘tumorlike’ presentations of multiple sclerosis have been reported in the literature. In most of these cases, a solitary white matter lesion, similar radiographically to most gliomas, is noted. The major problem comes at the time of intraoperative consultation, when macrophages can be easily confused with neoplastic astrocytes or oligodendrocytes. This confusion can persist at the time of permanent section, when the most common misdiagnosis of these demyelinating lesions is mixed oligoastrocytoma. Intraoperatively, smears or touch preparations are extremely helpful in distinguishing macrophages from either glial cell type. In contrast to demyelinating lesions, tumors are generally hypercellular, demonstrate some degree of astrocytic cell atypia, and may demonstrate focal areas of microcystic degeneration, mitotic activity, or necrosis. As noted previously, immunostaining for macrophages is critical at the time to avoid making this error; macrophages are almost never seen in untreated gliomas.

Another disorder that can histologically look very similar to multiple sclerosis is disseminated encephalitis. Most of these represent postvaccine or postviral demyelinating disorders with a sudden onset 5 to 14 days after viral infection or vaccination. Many of these are presumed to represent immune-mediated processes. Characteristically, the demyelinating pattern tends to preferentially be perivascular in distribution, although with time, these zones of demyelination may become more confluent and indistinguishable from multiple sclerosis. Variable amounts of perivascular chronic inflammation, microglial cell proliferation, and astrocytosis may be seen.

A variety of dysmyelinating disorders are marked by a loss of myelin, frequently in a symmetrical distribution, with an accumulation of abnormal myelin breakdown products. Axonal involvement is often marked in many of these disorders. Many of them are biochemically defined and include such entities as metachromatic leukodystrophy, globoid cell leukodystrophy or Krabbe disease, and adrenoleukodystrophy. These disorders often present early in life. If such a diagnosis is suspected based on clinical presentation, triaging of tissue for electron microscopic evaluation and keeping tissue frozen for possible metabolic evaluation are in order.

The authors thank Ms Denise E. Egleton for expert manuscript preparation.

References