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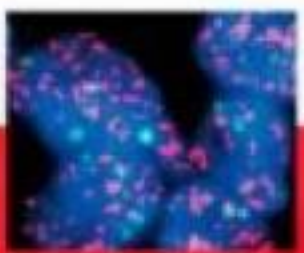
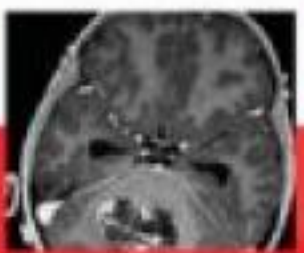
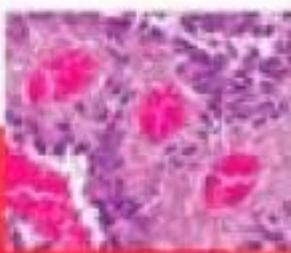
Practical Surgical Neuropathology

A Diagnostic Approach

Arie Perry
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Practical Surgical Neuropathology

A Diagnostic Approach

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Series Preface

It is often stated that anatomic pathologists come in two forms: "Gestalt"-based individuals, who recognize visual scenes as a whole, matching them unconsciously with memorialized archives; and criterion-oriented people, who work through images systematically in segments, tabulating the results—internally, mentally, and quickly—as they go along in examining a visual target. These approaches can be equally effective, and they are probably not as dissimilar as their descriptions would suggest. In reality, even "Gestaltists" subliminally examine details of an image, and, if asked specifically about particular features of it, they are able to say whether one characteristic or another is important diagnostically.

In accordance with these concepts, in 2004 we published a textbook entitled *Practical Pulmonary Pathology: A Diagnostic Approach* (PPPDA). That monograph was designed around a *pattern-based* method, wherein diseases of the lung were divided into six categories on the basis of their general image profiles. Using that technique, one can successfully segregate pathologic conditions into diagnostically and clinically useful groupings.

The merits of such a procedure have been validated empirically by the enthusiastic feedback we have received from users of our book. In addition, following the old adage that "imitation is the sincerest form of flattery," since our book came out other publications and presentations have appeared in our specialty with the same approach.

After publication of the PPPDA text, representatives at Elsevier, most notably William Schmitt, were enthusiastic about building a *series* of texts around pattern-based diagnosis in pathology. To this end we have recruited a distinguished group of authors and editors to accomplish that task. Because a panoply of patterns is difficult to approach mentally from a practical perspective, we have asked our contributors to be complete and yet to discuss only principal interpretative images. Our goal is eventually to provide a series of monographs which, in combination with one another, will allow trainees and practitioners in pathology to use salient morphological patterns to reach with confidence final diagnoses in all organ systems.

As stated in the introduction to the PPPDA text, the evaluation of dominant patterns is aided secondarily by the analysis of cellular composition and other distinctive findings. Therefore, within the context of each pattern, editors have been asked to use such data to refer the reader to appropriate specific chapters in their respective texts.

We have also stated previously that some overlap is expected between pathologic patterns in any given anatomic site; in addition, specific disease states may potentially manifest themselves with more than one pattern. At first, those facts may seem to militate against the value of pattern-based interpretation. However, pragmatically, they do not. One often can narrow diagnostic possibilities to a very few entities using the pattern method, and sometimes a single interpretation will be obvious. Both of those outcomes are useful to clinical physicians caring for a given patient.

It is hoped that the expertise of our authors and editors, together with the high quality of morphologic images they present in this Elsevier series, will be beneficial to our reader-colleagues.

Kevin O. Leslie, MD
Mark R. Wick, MD

Preface

When Kevin Leslie and Mark Wick approached us a few years ago to write a new neuropathology textbook for a patterns-oriented organ-based series, it was with some trepidation that we ultimately accepted. After all, there are already some excellent texts available on this topic, and we have both contributed chapters to some of these in the past. However, the *patterns approach* used in the Leslie and Wick *Practical Pulmonary Pathology* book is somewhat novel, and we were not aware of others placing a major emphasis on this tactic toward neuropathology diagnosis. As our work progressed, we found additional ways of enhancing the reader's experience and we are quite excited about the final product! Our primary target audience is the general surgical pathologist and pathology trainees. However, while we focused most on common issues of surgical neuropathology, rarer entities and clinicopathologic correlations are also well covered and illustrated. Therefore, we believe that this book will also be useful to neuropathologists and clinical colleagues from related medical specialties such as neurosurgery, neurology, neuroradiology, neuro-oncology, and pediatrics. In order to readdress the important question of why one should buy yet another neuropathology textbook, we provide the following list of strengths.

- **Patterns-based diagnostic approaches:** In addition to offering the traditional *disease-based approach* to nervous system pathology (Chapters 5 through 25), this book provides instructive algorithms based on *8 major (scanning magnification) patterns* (immediately following the introduction) and *20 minor (higher magnification) patterns* (Chapter 1). This material can be particularly helpful to less experienced morphologists who may feel lost or overwhelmed by the myriad diagnostic possibilities. After the reader obtains an appropriately focused differential, he or she can quickly turn to more detailed discussions of specific entities in later chapters of the book. Alternatively, one can start with basic *clinicoradiologic patterns* combining patient age, location, and neuroimaging features to create a differential diagnosis (Table 1-1). In fact, these two approaches are easily combined to further narrow the differential. To further enhance this strategy, the key clinicopathologic features for *21 common differentials* and the *immunoprofiles for 26 common tumors* are summarized in Tables 1-3 and 1-4, respectively. Major *neuroimaging patterns* are listed in Box 4-1.
- **Background data:** The nervous system is particularly challenging because of its remarkable anatomic and cellular complexity. For instance, the histology changes completely from one area to another, engendering diverse diagnostic differentials depending on the site of involvement. Therefore, a review of basic *neuroanatomy* and *histopathology* may help (Chapter 2). In addition, the use of *ancillary techniques* is rapidly evolving, and therefore an overview of immunohistochemistry, electron microscopy, and molecular diagnostics is provided in Chapter 1.
- **Intraoperative consultation and optimal processing:** Nothing seems to provoke a panic attack more reliably than the "neuro frozen," yet there is often little practical guidance available for this common setting. Furthermore, *artifacts* induced by frozen sections and many other procedures implemented by either the neurosurgeon or the pathologist can present serious pitfalls and may preclude an accurate diagnosis. These important topics are discussed in Chapter 3.
- **Neuroradiology:** As will be mentioned several times in this book, neuroradiology increasingly provides the most relevant *gross pathology* for nervous system biopsy interpretation, particularly when the tissue sample is small. In this context the pathologist must become at least an amateur neuroradiologist so that important radiologic-pathologic correlations are not missed. This critical topic is summarized and illustrated in Chapter 4.
- **The authors:** In addition to being international authorities on their topics, the authors were carefully selected for their clarity and *enthusiasm for teaching*. They are highly sought conference speakers, writers, and recipients of teaching awards. One is also known for a somewhat unconventional but highly popular teaching method. Dr. Perry's innovative use of "neuropathology songs" to help medical students remember key features of neurological disorders has been the topic of several newspaper and radio reports. By the time this book is published, a CD recording should be complete and readers interested in a fun approach to musically reinforcing their knowledge base should visit www.neuropathsongs.com.

- **The images:** One can scarcely find a more visually oriented medical specialty than pathology. Therefore, if the average picture is worth 1000 words, then the average pathology picture must be worth at least 10,000. With this in mind, we took great care to find the best images possible, making sure that the text is *amply illustrated with generously sized high-quality figures*. Given the focus of this book on surgical neuropathology, most of the "gross photos" are naturally magnetic resonance images. Nonetheless, we did not hesitate to utilize some postmortem photos and discussions when these clearly enhanced the reader's understanding. This was particularly true for the infectious/inflammatory, vascular, and neurodegenerative disorders covered in Chapters 21, 24, and 25, respectively.
- **The text:** In order to highlight the most salient features of each disorder, *italics* are used throughout the text for quick reference, as are helpful *summary tables* and *boxes*.

We have endeavored to create a practical guide for those who work with biopsies of the nervous system and the patients from whom they were derived. We sincerely hope that you find it useful and enjoyable.

Arie Perry, MD
Daniel J. Brat, MD, PhD

Acknowledgments

As with any project of this magnitude, it simply can't be done alone. I am extremely grateful to my talented coeditor, Dan Brat, and to all my wonderful coauthors for injecting countless hours of additional time and effort into their already busy schedules in order to create an exceptional product. For any diagnostic prowess I may possess, I owe an incredible debt to my surgical neuropathology mentor, Bernd Scheithauer of the Mayo Clinic, as most of my "pearls of wisdom" are easily traced back to him. I was particularly thrilled that he agreed to contribute two chapters on topics for which he is clearly one of the world's authorities: pituitary pathology and peripheral nerve sheath tumors. For autopsy neuropathology, Joe Parisi was an equally outstanding mentor. In addition, I would especially like to thank Robert Schmidt for being such a remarkably supportive "boss" and close friend over my 12 years at Washington University in St. Louis. I particularly enjoyed our cordial competitions over who could shoot (and improve with Adobe Photoshop) the best photomicrographs (Bob: I think I won!). Particularly useful for this book was our practice of sharing with one another images from interesting cases as they came through our clinical service. A number of Bob's masterpieces are sprinkled throughout several chapters and perhaps a few of mine have snuck into his chapter. Special thanks also go to Franz ("Jay") Wippold of the Mallinckrodt Institute for Radiology with whom I've coauthored several review articles for a series entitled "Neuropathology for the Neuroradiologist." It seems only fitting that he now offers his remarkable expertise to teach us some basic "neuroradiology for the neuropathologist." In broader terms, I'd like to thank my parents, Gabriel and Bathsheba, for their incredible support and for giving me an innate desire to excel. My brother Ron similarly supported me through some challenging times. Lastly, I'm eternally grateful to my wife, Andrea, and my kids, Ryan and Jaclyn, for putting up with me and my long hours at work over the last few years.

Arie Perry, MD

The writing and editing of a comprehensive and authoritative textbook should not be entertained by the impatient or the faint of heart. Because of his wealth of knowledge, high standards, persistence, and overall good nature, I can think of no better collaborator on such an effort than Arie Perry. I look forward to updated editions as well as new neuropathology songs in the years to come. The collection of authors that we were able to gently persuade to contribute to this text is truly impressive. They deserve our deepest appreciation for allowing us to tap into their hard-earned expertise for this project. For their efforts, I hope this text will be widely acknowledged for the excellence it brings to the field of neuropathology. My own abilities to assist in this effort are directly attributed to those who drew me into neuropathology and to those who trained me both in person and at a distance. Joe Parisi and Bernd Scheithauer were larger than life figures that attracted a young medical student at the Mayo Clinic into the field of neuropathology and have continued to be role models. Peter Burger provided mentorship and enormous opportunity during residency and fellowship at Johns Hopkins Hospital and is most responsible for any academic successes I have had or will have. Finally, the family of Brats has always been a source of stability, inspiration, and thorough entertainment. Thanks to Paul, Dave, Jim, and Nancy Elaine.

Daniel J. Brat, MD, PhD

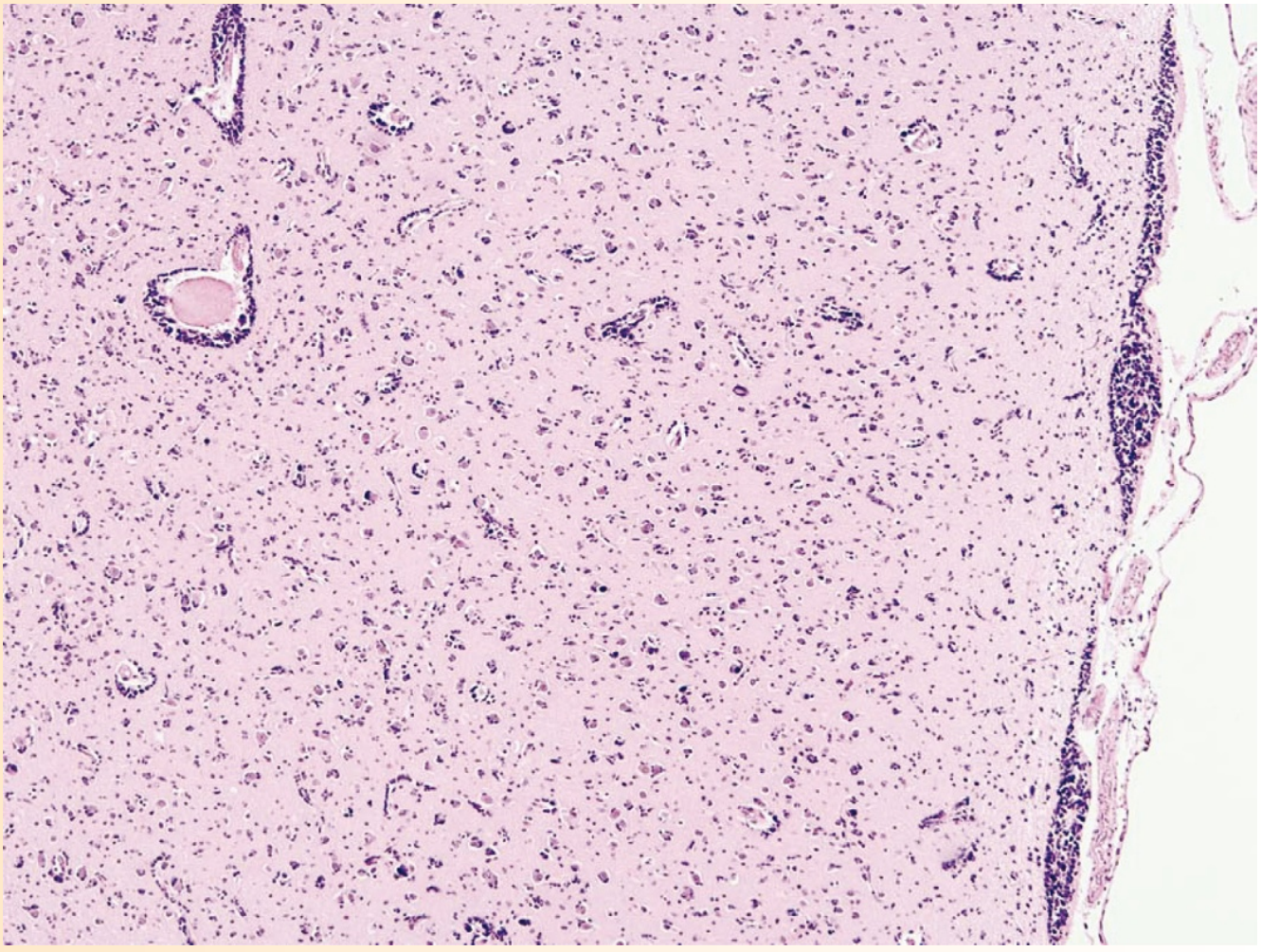
Practical Surgical Neuropathology Major Patterns

Pattern	Diseases to Be Considered
Parenchymal infiltrate with hypercellularity	Diffuse glioma CNS lymphoma Infections Active demyelinating disease Cerebral infarct Reactive gliosis
Solid mass (pure)	Metastasis Ependymoma Subependymoma Subependymal giant-cell astrocytoma (SEGA) Central or extraventricular neurocytoma Pineocytoma Embryonal tumor (e.g., AT/RT) Choroid plexus papilloma Hemangioblastoma Paraganglioma Pituitary adenoma
Solid and infiltrative process	Pilocytic astrocytoma Pleomorphic xanthoastrocytoma Glioblastoma/gliosarcoma (and other high grade gliomas) Ganglioglioma Dysembryoplastic neuroepithelial tumor (DNT) Embryonal tumor (e.g., medulloblastoma/CNS PNET) Choroid plexus carcinoma Germ cell tumors Craniopharyngioma CNS lymphoma Sarcoma Histiocytic disorders Abscess and other forms of infection

Pattern	Diseases to Be Considered
Vasculocentric process	CNS lymphoma Intravascular lymphoma Angiocentric glioma Ependymoma Vasculitis Meningioangiomatosis Active demyelinating disease Amyloid angiopathy Arteriolosclerosis Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) Vascular malformations Infections (e.g., aspergillosis) Neurosarcoidosis Thromboembolic disease
Extra-axial mass	Meningioma Hemangiopericytoma Solitary fibrous tumor Hemangioblastoma Sarcomas Schwannoma and other nerve sheath tumors Metastasis Melanoma or melanocytoma Secondary lymphoma or leukemia Paraganglioma Pituitary adenoma Neurosarcoidosis Granulomatous infections Inflammatory pseudotumors Calcifying pseudotumor of the neuraxis Primary bone tumors (e.g., chordoma) Histiocytic disorders (e.g., Rosai-Dorfman disease)
Meningeal infiltrate	Meningeal carcinomatosis, gliomatosis, melanosis, melanomatosis, sarcomatosis, or hemangioblastomatosis Metastatic medulloblastoma/CNS PNET Secondary lymphoma or leukemia Histiocytic disorders Meningitis Neurosarcoidosis Infectious granulomatous diseases Collagen vascular disorders Sturge-Weber syndrome

Pattern	Diseases to Be Considered
Destructive/necrotic process	Cerebral infarct Radiation necrosis or treatment effects Infections Vasculitis CNS lymphoma in an immunosuppressed patient Intravascular lymphoma CADASIL Severe demyelinating disease Metabolic/toxic disease
Subtle pathology or near-normal biopsy	Nonrepresentative biopsy specimen Subtle diffuse glioma (WHO grade II) Hypothalamic hamartoma Cortical dysplasia or tuber Mesial temporal sclerosis Intravascular lymphoma Meningioangiomatosis Mild encephalitis Cerebral malaria Ischemic disease Neurodegenerative diseases Benign cysts Metabolic or toxic disorder Reactive gliosis or "glial scar"

Pattern 1 Parenchymal infiltrate with hypercellularity

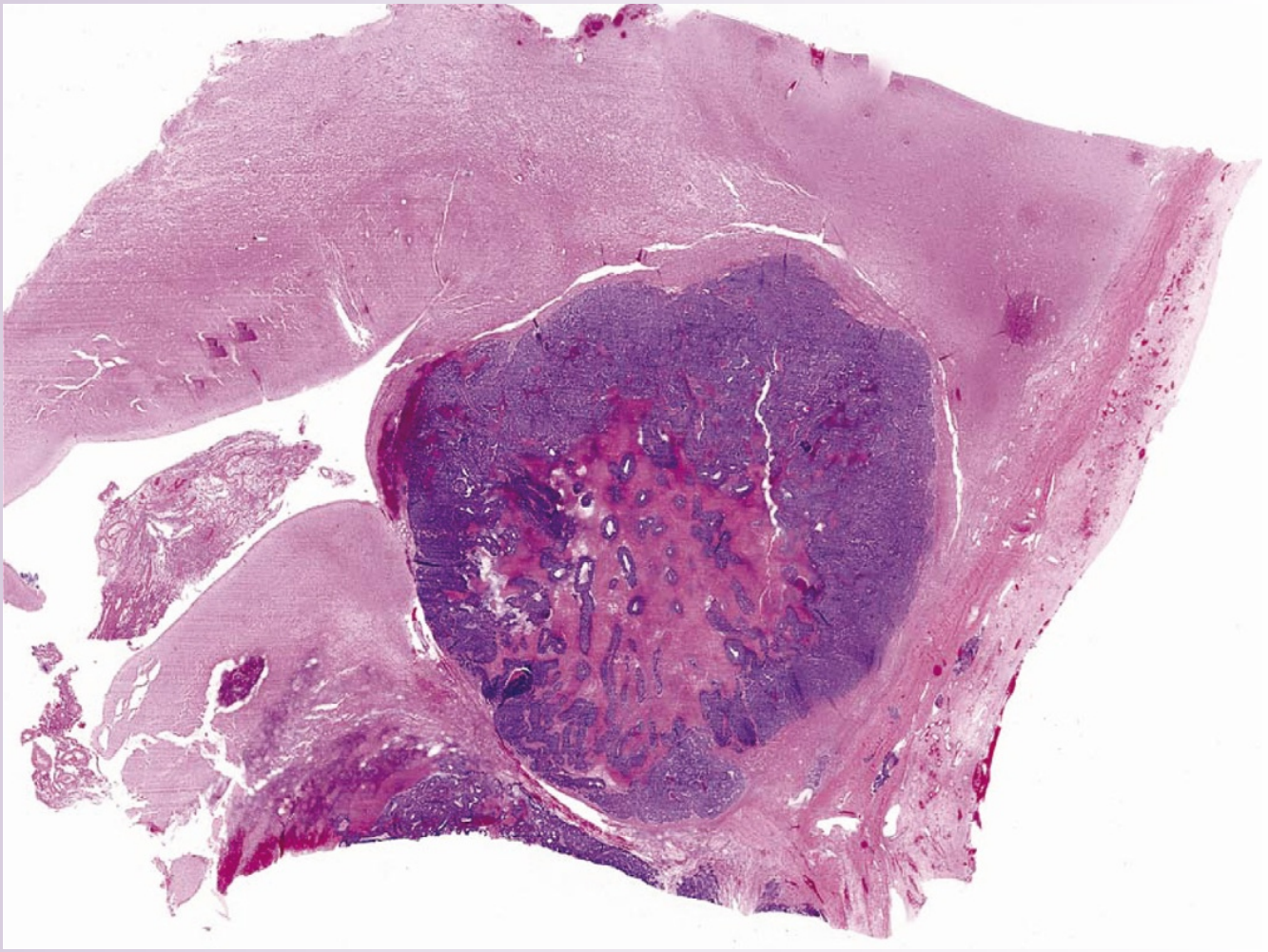


Elements of the pattern: The brain biopsy specimen shows intact cortical architecture, but a hypercellular infiltrate is evident at scanning magnification. In this particular example, an additional finding is *secondary structure* formation, with subpial condensation, perivascular aggregates, and perineuronal satellitosis. This growth pattern is most common in diffuse gliomas.

Pattern 1 Parenchymal infiltrate with hypercellularity

Additional Findings	Diagnostic Considerations	Chapter:page
Secondary structures of Scherer	Diffuse gliomas	**Ch. 5:63**
Extensive bilateral cerebral involvement	Gliomatosis cerebri Lymphomatosis cerebri	**Ch. 5:71, 80** **Ch. 14:316**
Angiocentric pattern	CNS lymphoma Angiocentric glioma Meningoencephalitis/Infections Active demyelinating disease	**Ch. 14:315** **Ch. 17:361** **Ch. 21:468** **Ch. 22:485**
Microcystic pattern	Diffuse gliomas	**Ch. 5:63**
Pleomorphism	Astrocytoma/glioblastoma Infections, especially PML	**Ch. 5:63** **Ch. 21:470**
Monomorphism	Oligodendroglioma Some lymphomas	**Ch. 5:93** **Ch. 14:315**
Lymphocytic infiltrate	Gemistocytic astrocytoma CNS lymphoma Meningoencephalitis/Infections Active demyelinating disease	**Ch. 5:70** **Ch. 14:315** **Ch. 21:468** **Ch. 22:485**
Foamy histiocytes	CNS lymphoma Active demyelinating disease Cerebral infarct	**Ch. 14:315** **Ch. 22:485** **Ch. 24:528**
Cytologic atypia or anaplasia	Diffuse gliomas CNS lymphoma	**Ch. 5:63** **Ch. 14:315**
Viral inclusions or organisms	Meningoencephalitis/Infections	**Ch. 21:468**
None	Reactive gliosis	**Ch. 1:8, Ch. 5:74**

Pattern 2 Solid mass (pure)

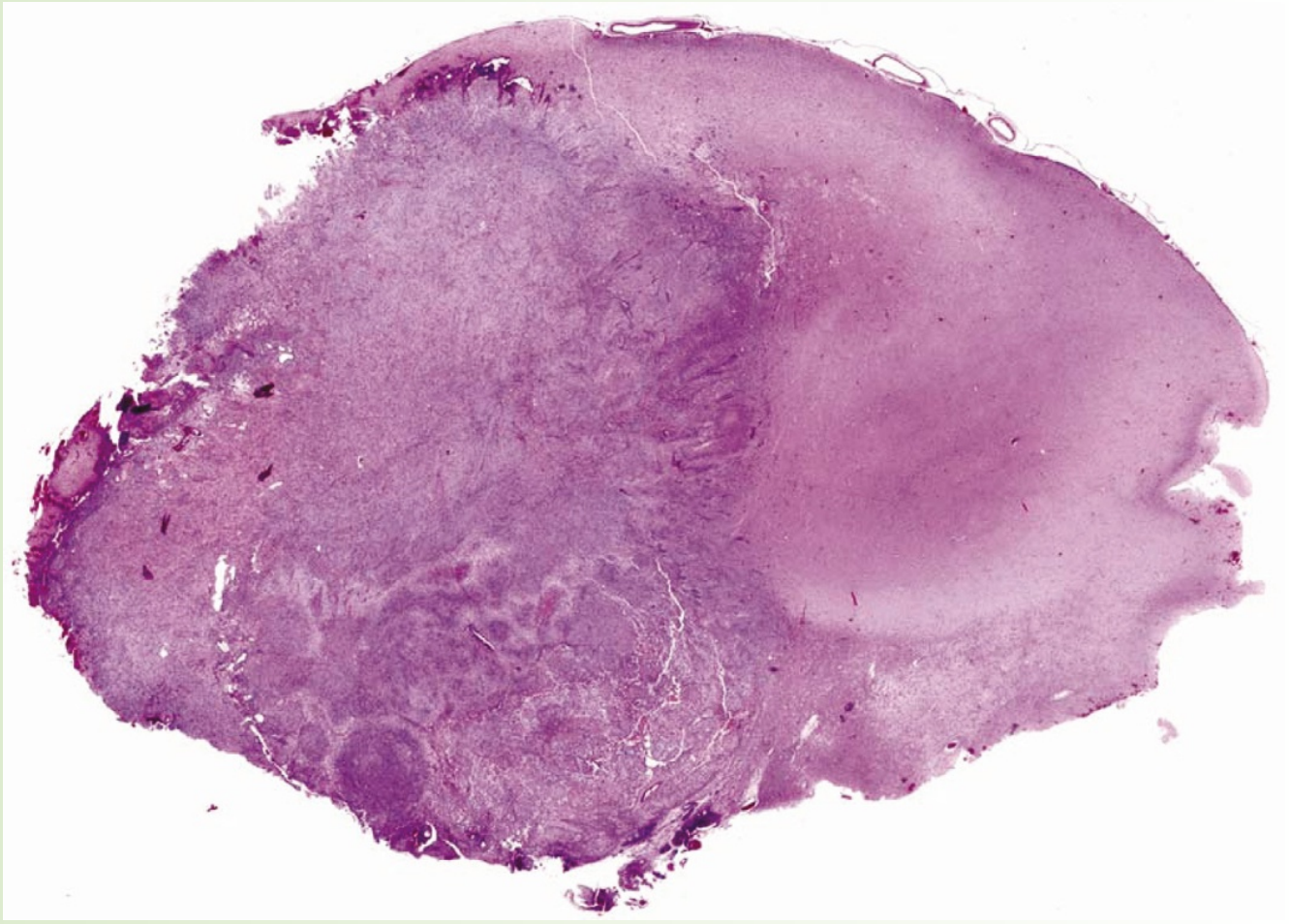


Elements of the pattern: The biopsy specimen shows a very sharply demarcated intracerebral mass. The increased cellularity imparts a blue color to the tumor, whereas foci of central necrosis appear pink. An additional finding was gland formation, consistent with metastatic adenocarcinoma.

Pattern 2 Solid mass (pure)

Additional Findings	Diagnostic Considerations	Chapter:page
Mucin-filled glands	Metastatic adenocarcinoma	**Ch. 13:287**
Perivascular pseudorosettes	Subependymal giant-cell astrocytoma	**Ch. 5:88**
	Ependymoma	**Ch. 6:103**
	Central or extraventricular neurocytoma	**Ch. 7:135**
	Pineocytoma	**Ch. 8:152**
	Metastasis (neuroendocrine)	**Ch. 13:287**
	Paraganglioma	**Ch. 13:296**
	Pituitary adenoma	**Ch. 18:372**
Nodularity	Subependymoma	**Ch. 6:104**
	Metastasis (neuroendocrine)	**Ch. 13:287**
	Paraganglioma	**Ch. 13:296**
	Pituitary adenoma	**Ch. 18:372**
Gliofibrillary processes	Subependymal giant-cell astrocytoma	**Ch. 5:88**
	Ependymoma	**Ch. 6:103**
	Subependymoma	**Ch. 6:104**
Papillary pattern	Choroid plexus papilloma	**Ch. 6:113**
	Papillary ependymoma	**Ch. 6:106, 109**
	Metastatic carcinoma	**Ch. 13:287**
	Pituitary adenoma	**Ch. 18:372**
Hypervascularity	Choroid plexus papilloma	**Ch. 6:113**
	Hemangioblastoma	**Ch. 20:440**
Neuropil/neuronal rosettes	Central or extraventricular neurocytoma	**Ch. 7:135**
	Pineocytoma	**Ch. 8:152**
Adjacent piloid gliosis	Craniopharyngioma	**Ch. 18:402**
	Hemangioblastoma	**Ch. 20:440**
Epithelioid cytology	Choroid plexus papilloma	**Ch. 6:113**
	Metastatic carcinoma	**Ch. 13:287**
Small primitive cells	Embryonal tumor (AT/RT)	**Ch. 9:165, 179**
	Metastatic carcinoma (small cell)	**Ch. 13:287**
Melanin pigment	Melanoma (usually metastatic)	**Ch. 13:291, Ch. 6:353**
Clear cells	Clear cell ependymoma	**Ch. 6:107**
	Central or extraventricular neurocytoma	**Ch. 7:135**
	Pineocytoma	**Ch. 8:152**
	Hemangioblastoma	**Ch. 20:440**
	Metastatic carcinoma	**Ch. 13:287**
Cytologic anaplasia	Embryonal tumor (AT/RT)	**Ch. 9:165, 179**
	Metastatic carcinoma	**Ch. 13:287**

Pattern 3 Solid and infiltrative process

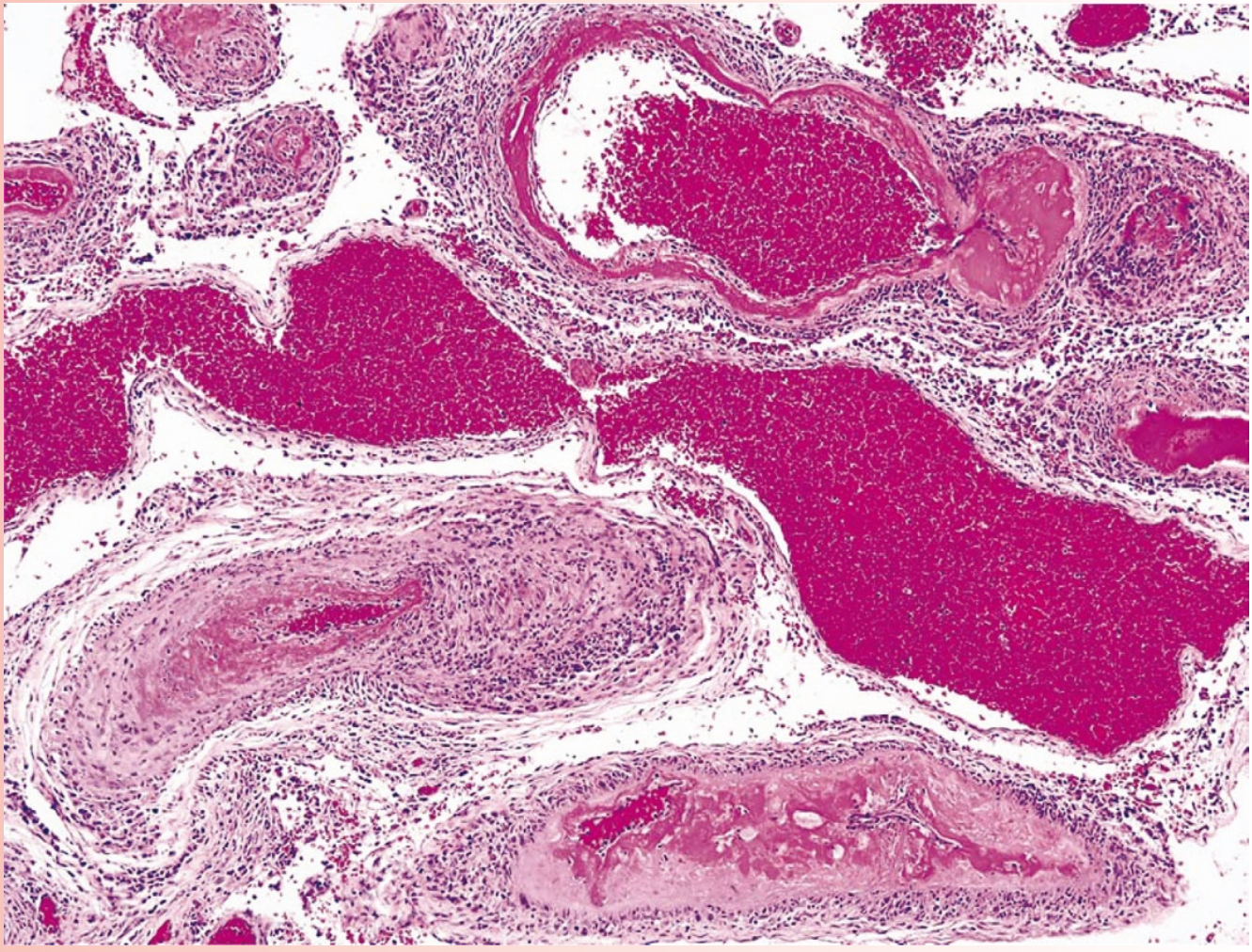


Elements of the pattern: The biopsy specimen shows a mostly solid-appearing neoplasm (*left half*), but has fuzzy or ill-defined margins with the adjacent brain parenchyma, consistent with at least a partially infiltrative component as well (*right half*, especially in white matter). Additional findings in this case were reticulin-rich spindled elements, GFAP-positive glial elements, and pseudopalisading necrosis, consistent with gliosarcoma.

Pattern 3 Solid and infiltrative process

Additional Findings	Diagnostic Considerations	Chapter:page
Biphasic growth (compact and microcystic), EGBs, Rosenthal fibers	Pilocytic astrocytoma Pleomorphic xanthoastrocytoma Ganglioglioma Dysembryoplastic neuroepithelial tumor	**Ch. 5:82** **Ch. 5:91** **Ch. 7:125** **Ch. 7:140**
Pseudopalisading necrosis	Glioblastoma or gliosarcoma	**Ch. 5:63, 66**
Nodularity	Anaplastic oligodendroglioma Dysembryoplastic neuroepithelial tumor Ganglioglioma Desmoplastic or nodular medulloblastoma Germinoma or germ cell tumors	**Ch. 5:93** **Ch. 7:140** **Ch. 7:125** **Ch. 9:169** **Ch. 15:336**
Angiocentric pattern	CNS lymphoma Infections	**Ch. 14:315** **Ch. 21:477**
Fascicles of spindled cells	Gliosarcoma Pleomorphic xanthoastrocytoma Primary CNS sarcoma (rare)	**Ch. 5:70** **Ch. 5:91** **Ch. 11:219**
Inflammation-rich	Pleomorphic xanthoastrocytoma Ganglioglioma CNS lymphoma Germinoma or germ cell tumors Abscess and other infections	**Ch. 5:91** **Ch. 7:125** **Ch. 14:315** **Ch. 15:336** **Ch. 21:477**
Adjacent piloid gliosis	Pleomorphic xanthoastrocytoma Craniopharyngioma	**Ch. 5:91** **Ch. 18:402**
Glial cytology	Pilocytic astrocytoma Pleomorphic xanthoastrocytoma Glioblastoma or gliosarcoma Ganglioglioma Dysembryoplastic neuroepithelial tumor	**Ch. 5:82** **Ch. 5:91** **Ch. 5:63, 66** **Ch. 7:125** **Ch. 7:140**
Large ganglioid cells with vesicular nuclei and large nucleoli	Pleomorphic xanthoastrocytoma Ganglioglioma Dysembryoplastic neuroepithelial tumor CNS lymphoma (anaplastic large cell) Germinoma	**Ch. 5:91** **Ch. 7:125** **Ch. 7:140** **Ch. 14:330** **Ch. 15:336**
Epithelioid cytology	Choroid plexus carcinoma Germ cell tumors Craniopharyngioma	**Ch. 6:113** **Ch. 15:333** **Ch. 18:402**
Small primitive cells	Choroid plexus carcinoma Medulloblastoma/CNS PNET CNS lymphoma	**Ch. 6:113** **Ch. 9:165, 175** **Ch. 14:315**
Foamy cells	Pleomorphic xanthoastrocytoma Glioblastoma (occasionally) Histiocytic disorders Infections	**Ch. 5:91** **Ch. 5:63, 66** **Ch. 14:326** **Ch. 21:455**

Pattern 4 Vasculocentric process

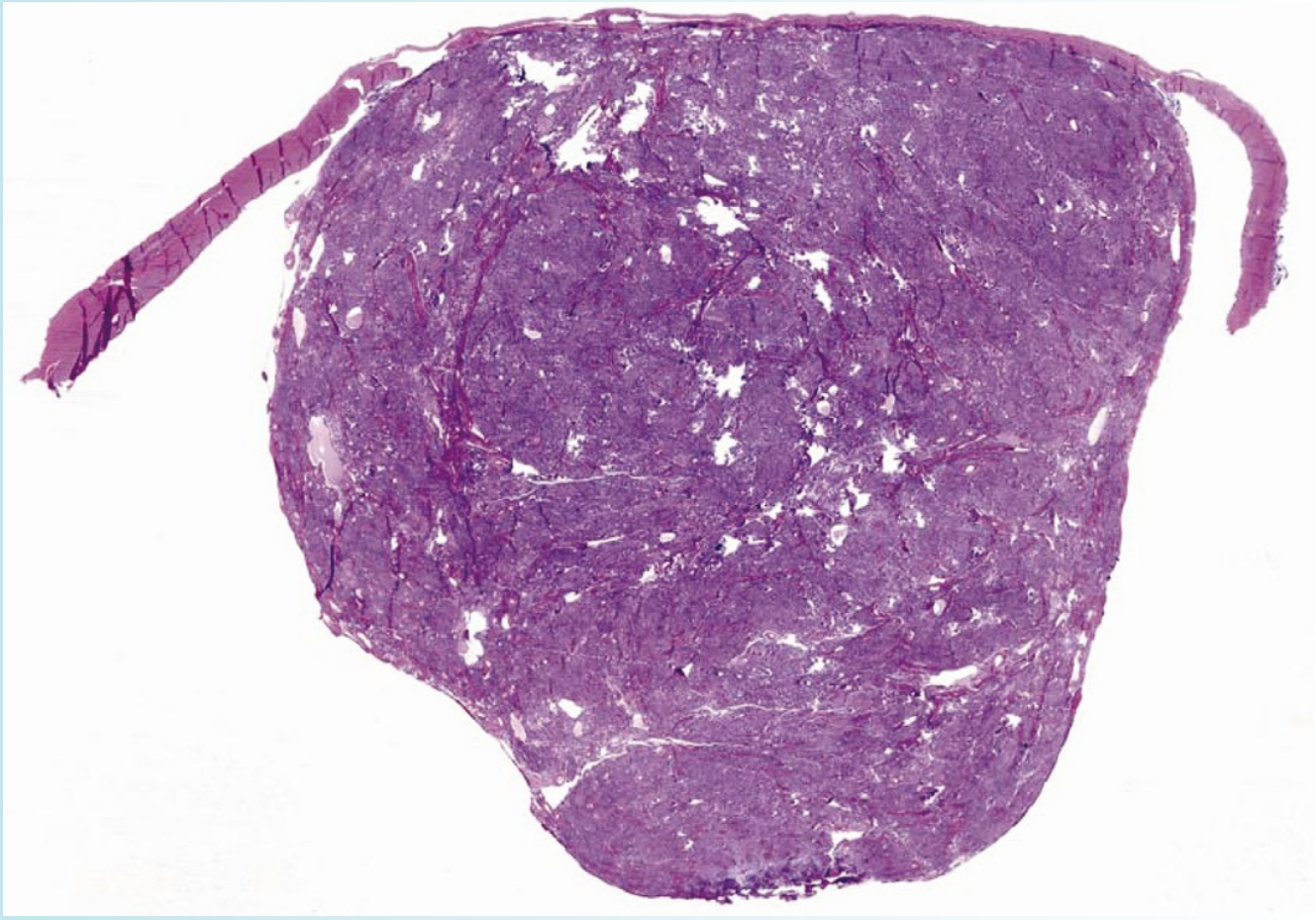


Elements of the pattern: The biopsy specimen shows a disease process that is clearly centered on blood vessels. Additional findings in this case were foci of angionecrosis and vascular or perivascular inflammation, consistent with vasculitis.

Pattern 4 Vasculocentric process

Additional Findings	Diagnostic Considerations	Chapter:page
Perivascular or intravascular infiltrate	CNS lymphoma	**Ch. 14:315**
	Meningoencephalitis/infection	**Ch. 21:468**
	Neurosarcoidosis	**Ch. 21:481**
	Active demyelinating disease	**Ch. 22:485**
	Vasculitis	**Ch. 24:537**
	Amyloid angiopathy with vasculitis	**Ch. 24:535**
Intraluminal atypical cells	Intravascular lymphoma	**Ch. 14:319**
Perivascular glial or spindled cells	Ependymoma	**Ch. 6:103**
	Angiocentric glioma	**Ch. 17:361**
	Meningioangiomatosis	**Ch. 20:433**
Angionecrosis	Infections (aspergillosis)	**Ch. 21:464**
	Vasculitis	**Ch. 24:537**
	Thromboembolic disease	**Ch. 24:528**
Vascular hyalinization	Meningioangiomatosis	**Ch. 20:433**
	Amyloid angiopathy	**Ch. 24:535**
	CADASIL	**Ch. 24:546**
	Arteriolosclerosis	**Ch. 24:533**
	Vasculitis	**Ch. 24:537**
	Vascular malformations	**Ch. 24:542**
Granular vascular deposits	CADASIL	**Ch. 24:546**
Granulomas or giant cells	Infections	**Ch. 21:455**
	Neurosarcoidosis	**Ch. 21:481**
	Vasculitis	**Ch. 24:537**
	Amyloid angiopathy with vasculitis	**Ch. 24:535**
Cerebral hemorrhage	Infections (aspergillosis)	**Ch. 21:464**
	Amyloid angiopathy	**Ch. 24:535**
	Vascular malformations	**Ch. 24:542**
Cerebral infarcts or microinfarcts	Intravascular lymphoma	**Ch. 14:319**
	Infections	**Ch. 21:455**
	Neurosarcoidosis	**Ch. 21:481**
	Vasculitis	**Ch. 24:537**
	Amyloid angiopahty	**Ch. 24:535**
	CADASIL	**Ch. 24:546**
	Arteriolosclerosis	**Ch. 24:533**
	Thromboembolic disease	**Ch. 24:528**
Disorganized, irregular blood vessels	Meningioangiomatosis	**Ch. 20:433**
	Vascular malformations	**Ch. 24:542**

Pattern 5 Extra-axial mass



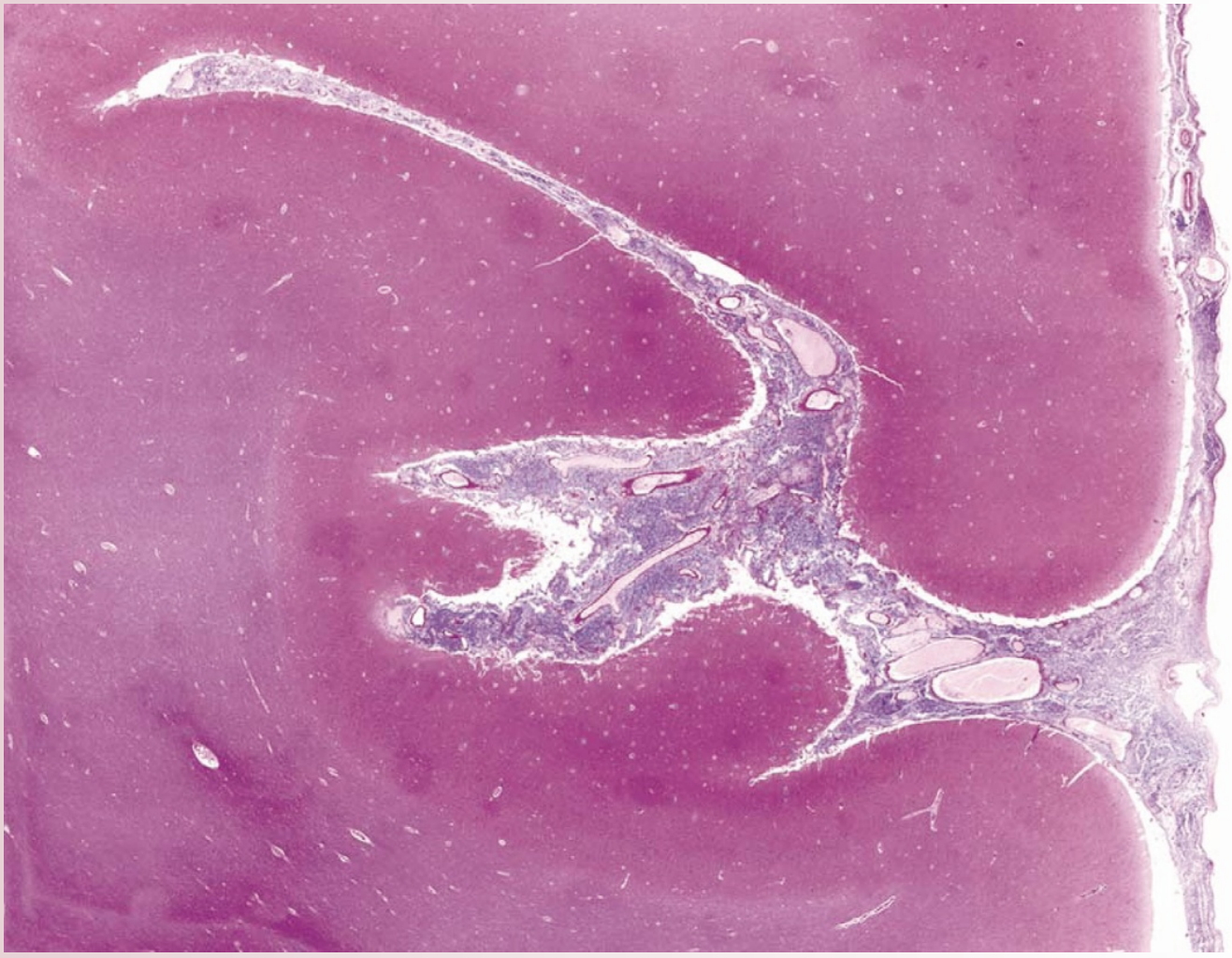
Elements of the pattern: The biopsy specimen shows a solid mass attached to a strip of dura in the upper portion of the image. Additional findings in this case were whorls of epithelioid cells and scattered psammoma bodies, consistent with meningioma.

Additional Findings	Diagnostic Considerations	Chapter:page
Whorls or nests	Meningioma	**Ch. 10:185**
	Chordoma	**Ch. 11:231**
	Schwannoma (occasionally)	**Ch. 12:240**
	Metastatic carcinoma	**Ch. 13:287**
	Paraganglioma	**Ch. 13:296**
	Melanocytoma	**Ch. 16:353**
Psammoma bodies	Meningioma	**Ch. 10:185**
	Psammomatous melanotic schwannoma	**Ch. 12:251**
	Metastatic carcinoma (rare)	**Ch. 13:287**
Peripheral or cranial nerve involvement	Pilocytic astrocytoma (optic pathway)	**Ch. 5:82**
	Orbital meningioma	**Ch. 10:185**
	Orbital sarcoma (rhabdomyosarcoma)	**Ch. 11:226**
	Schwannoma	**Ch. 12:240**
	Neurofibroma	**Ch. 12:251**
	Perineurioma	**Ch. 12:260**
	MPNST	**Ch. 12:272**
	Neurolymphomatosis	**Ch. 14:315**

Pattern 5 Extra-axial mass

Additional Findings	Diagnostic Considerations	Chapter:page
Biphasic (compact and loose) pattern with Verocay bodies	Meningioma (rare) Schwannoma	**Ch. 10:185** **Ch. 12:240**
Hypervascular	Angiomatous meningioma Hemangiopericytoma Hemangioblastoma	**Ch. 10:194** **Ch. 11:220** **Ch. 20:440**
Gaping "staghorn" blood vessels	Meningioma (rare) Hemangiopericytoma Solitary fibrous tumor	**Ch. 10:185** **Ch. 11:220** **Ch. 11:220**
Alternating "dark and light" regions	Hemangiopericytoma Solitary fibrous tumor	**Ch. 11:220** **Ch. 11:220**
Dense bundles of eosinophilic collagen	Clear cell meningioma Solitary fibrous tumor	**Ch. 10:200** **Ch. 11:220**
Inflammatory infiltrate	Lymphoplasmacyte-rich meningioma Inflammatory myofibroblastic tumor Secondary lymphoma/leukemia Infections Neurosarcoidosis Collagen vascular disorders	**Ch. 10:198** **Ch. 11:221** **Ch. 14:321** **Ch. 21:455** **Ch. 21:481** **Ch. 21:481**
Fibrillar to amorphous basophilic material	Calcifying pseudoneoplasm of the neuraxis	**Ch. 10:211**
Small primitive cells	Hemangiopericytoma Other sarcomas (EWS/pPNET) Metastatic carcinoma (small cell) Secondary lymphomas/leukemias	**Ch. 11:220** **Ch. 11:233** **Ch. 13:287** **Ch. 14:321**
Large anaplastic cells	Anaplastic meningioma Metastatic carcinoma Anaplastic large cell lymphoma Myeloid sarcoma Melanoma	**Ch. 10:192, 203** **Ch. 13:287** **Ch. 14:320** **Ch. 14:322** **Ch. 16:353**
Epithelioid cells	Meningioma Metastatic carcinoma Paraganglioma Melanoma Pituitary adenoma	**Ch. 10:185** **Ch. 13:287** **Ch. 13:296** **Ch. 16:353** **Ch. 18:372**
Clear cells	Clear cell meningioma Hemangiopericytoma Other sarcomas (leiomyosarcoma) Metastatic carcinoma Paraganglioma Histiocytic disorders Hemangioblastoma	**Ch. 10:200** **Ch. 11:220** **Ch. 11:225** **Ch. 13:287** **Ch. 13:296** **Ch. 14:326** **Ch. 20:440**
Foamy cells	Angiomatous meningioma Schwannoma (histiocytes) Histiocytic disorders Hemangioblastoma	**Ch. 10:194** **Ch. 12:240** **Ch. 14:326** **Ch. 20:440**
Granulomas or giant cells	Infections (TB, fungal meningitis) Neurosarcoidosis Collagen vascular disorders	**Ch. 21:455** **Ch. 21:481** **Ch. 21:481**

Pattern 6 Meningeal infiltrate

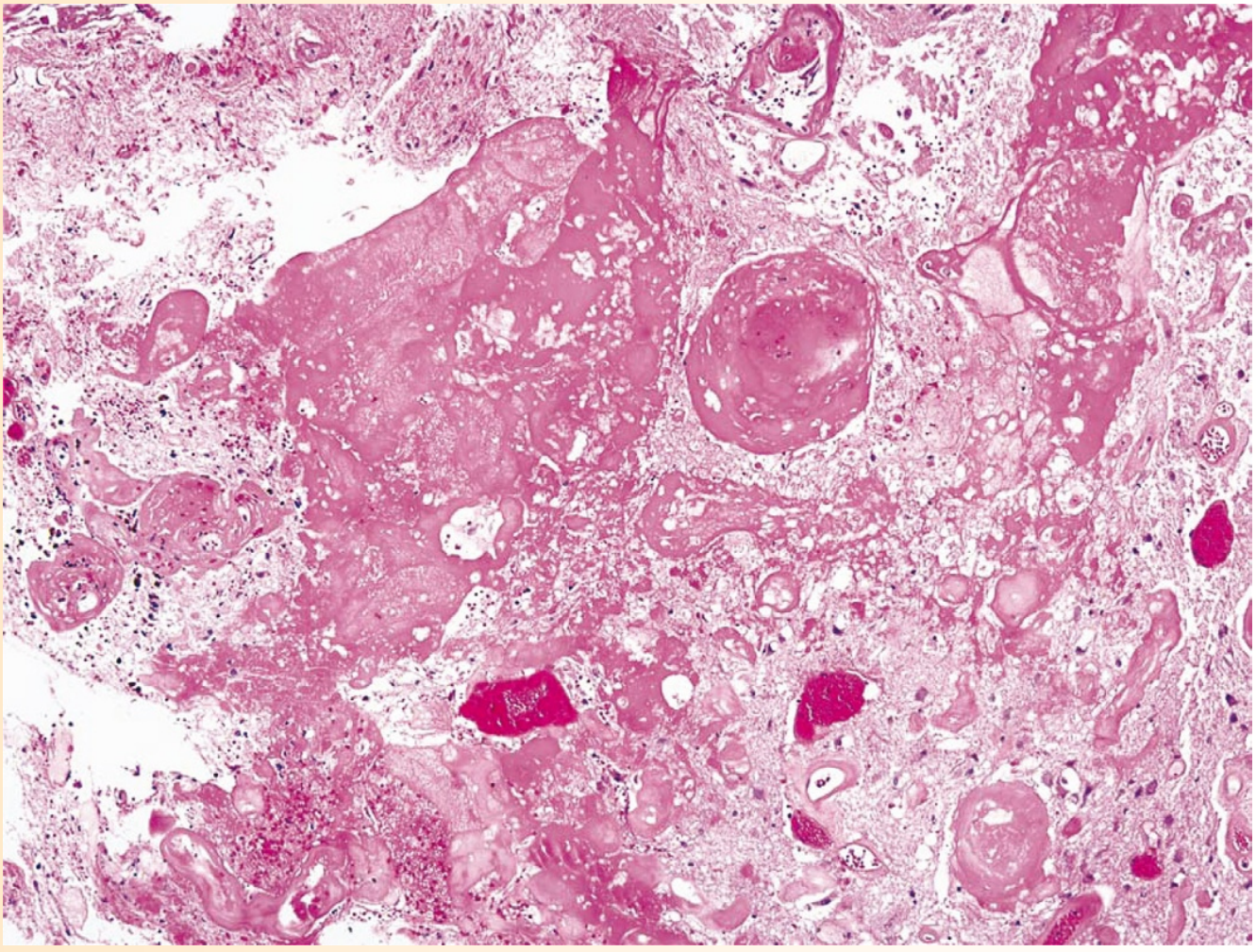


Elements of the pattern: The whole-mount brain section shows a markedly expanded subarachnoid space filled with blue cells. At higher magnification, the infiltrate consisted predominantly of neutrophils, consistent with acute meningitis.

Pattern 6 Meningeal infiltrate

Additional Findings	Diagnostic Considerations	Chapter:page
Neoplastic cells	Metastatic medulloblastoma/CNS PNET	**Ch. 9:165, 175**
	Meningeal sarcomatosis	**Ch. 11:220**
	Meningeal carcinomatosis	**Ch. 13:287**
	Secondary lymphoma/leukemia	**Ch. 14:321**
	Meningeal melanosis/melanomatosis	**Ch. 16:353, 357**
	Meningeal gliomatosis	**Ch. 21: 465**
Venous malformation	Sturge-Weber syndrome	**Ch. 20:451**
Neutrophil-rich infiltrate	Acute bacterial meningitis	**Ch. 21:456**
Lymphoplasmacytic infiltrate	Infectious meningitis	**Ch. 21:456**
	Chemical meningitis	**Ch. 21:465**
	Neurosarcoidosis	**Ch. 21:481**
	Collagen vascular disorder	**Ch. 21:481**
Granulomas/giant cells	Infectious meningitis (TB, fungal)	**Ch. 21:456**
	Neurosarcoidosis	**Ch. 21:481**
	Collagen vascular disorder	**Ch. 21:481**
Clear to foamy cells	Meningeal carcinomatosis	**Ch. 13:287**
	Histiocytic disorders	**Ch. 14:326**

Pattern 7 Destructive or necrotic process

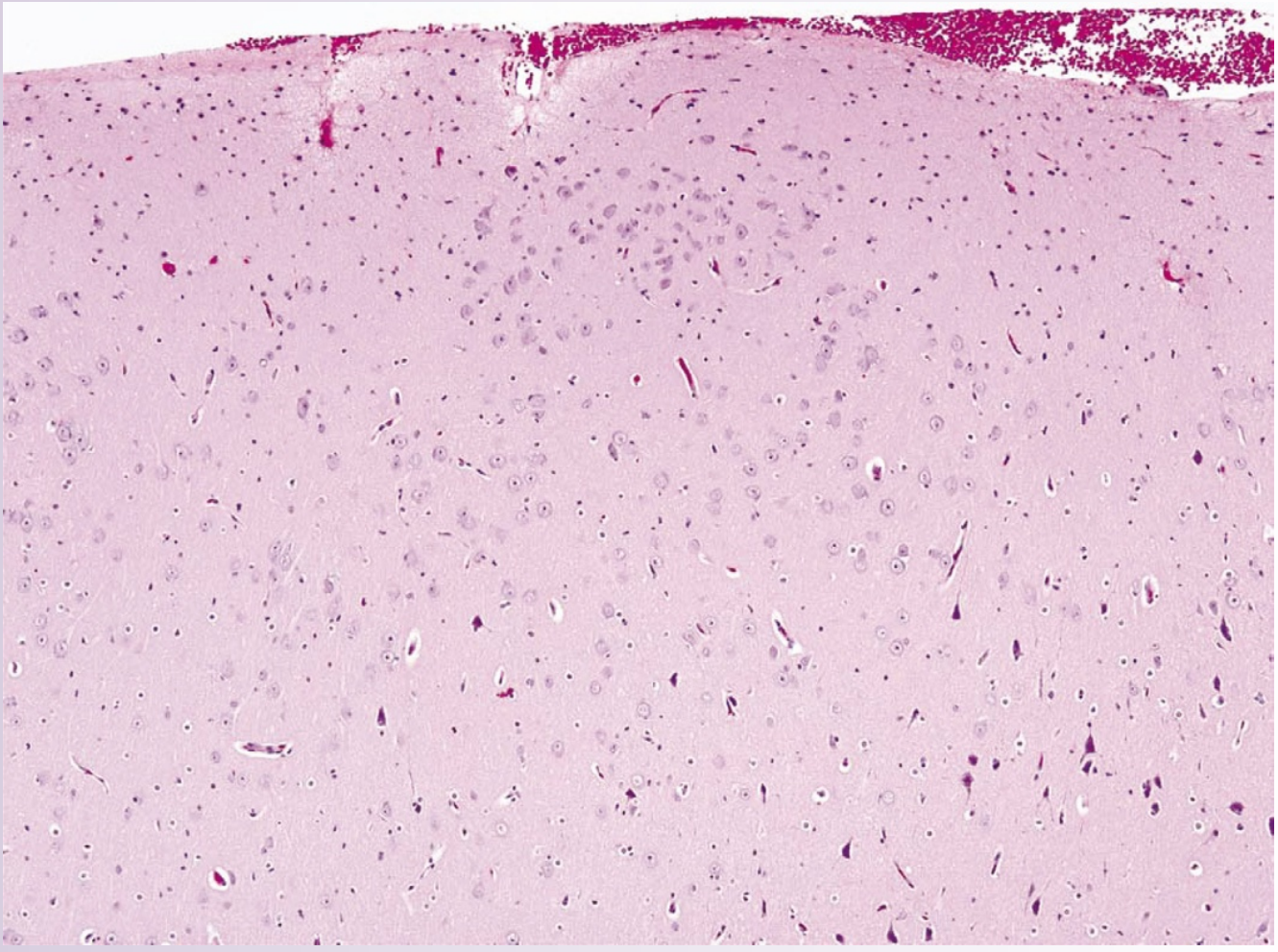


Elements of the pattern: The brain biopsy specimen from a patient with known glioma shows extensive fibrinoid parenchymal and vascular necrosis, consistent with radiation necrosis.

Pattern 7 Destructive or necrotic process

Additional Findings	Diagnostic Considerations	Chapter:page
Fibrinoid brain necrosis, vascular hyalinization, telangiectasias	Radiation necrosis or treatment effects	**Ch. 19:417**
Angionecrosis	Radiation necrosis or treatment effects Infection (toxoplasmosis) Vasculitis	**Ch. 19:417** **Ch. 21:476** **Ch. 24:537**
Vascular or perivascular inflammation	Lymphoma (immunosuppressed host) Severe demyelinating disease (rare) Vasculitis	**Ch. 14:316** **Ch. 22:485** **Ch. 24:537**
Intraluminal infiltrate	Intravascular lymphoma	**Ch. 14:319**
Granular vascular deposits	CADASIL	**Ch. 24:546**
Eosinophilic necrotic neurons	Acute cerebral infarct	**Ch. 24:528**
Neutrophil-rich infiltrate	Infection (abscess) Acute cerebral infract (rare)	**Ch. 21:478** **Ch. 24:528**
Macrophage-rich infiltrate	Severe demyelinating disease (rare) Metabolic or toxic disorders Cerebral infarct	**Ch. 22:485** **Ch. 22:506, 510** **Ch. 24:528**
Granulomas or giant cells	Infections (TB, fungal) Vasculitis	**Ch. 21:456** **Ch. 24:537**
Viral inclusions	Encephalitis (HSV)	**Ch. 21:468**

Pattern 8 Subtle pathology or near-normal biopsy specimen



Elements of the pattern: The brain biopsy specimen from a patient with chronic seizure disorder shows a nearly normal cortex. However, there is a subtle disarray of the laminar architecture and clustering of large superficial neurons in the center. Leptomeningeal gray matter heterotopia was also seen in other regions of the biopsy. This constellation of findings is consistent with a malformation of cortical development (i.e., cortical dysplasia).

Pattern 8 Subtle pathology or near-normal biopsy specimen

Additional Findings	Diagnostic Considerations	Chapter:page
Reactive gliosis or cerebral edema	Nonrepresentative biopsy	**Chs. 3–5**
	Subtle diffuse glioma	**Ch. 5:63**
	Hypothalamic hamartoma	**Ch. 7:146**
	Pineal cyst	**Ch. 8:157**
	Arachnoid cyst	**Ch. 13:309**
	Other developmental cyst	**Ch. 13:303**
	Metabolic or toxic disorders	**Ch. 22:506, 510**
	Nonanatomic cause of epilepsy	**Ch. 23:515**
	Subtle form of cortical dysplasia	**Ch. 23:515**
Glial atypia, clustering, or secondary structuring	Diffuse glioma	**Ch. 5:63**
Intraluminal atypical cells	Intravascular lymphoma	**Ch. 14:319**
Neuronal clustering and mild dysmorphism	Hypothalamic hamartoma	**Ch. 7:146**
	Subtle form of cortical dysplasia	**Ch. 23:515**
Balloon cells	Focal cortical dysplasia, type IIb	**Ch. 23:518**
	Tuber	**Ch. 23:516, 518**
Neuronal loss in hippocampus (CAI, CA4)	Mesial temporal sclerosis/hippocampal sclerosis	**Ch. 23:520**
Microglial nodules/scant perivascular inflammation	Encephalitis (infectious, paraneoplastic)	**Ch. 21:469**
	Rasmussen encephalitis	**Ch. 23:523**
Intravascular pigment	Cerebral malaria	**Ch. 21:474**
Red necrotic neurons	Acute cerebral infarct	**Ch. 24:528**
Vascular hyalinization	Radiation effects	**Ch. 19:417**
	Meningioangiomatosis	**Ch. 20:433**
	Amyloid angiopathy	**Ch. 24:535**
	CADASIL	**Ch. 24:546**
	Arteriolosclerosis	**Ch. 24:533**
Granular vascular deposits	CADASIL	**Ch. 24:546**
Hemorrhage/hemosiderin	Epileptogenic "glial scar"	**Ch. 23:515**
	Amyloid angiopathy	**Ch. 24:535**
	Small cavernous angioma	**Ch. 24:545**
Neurofibrillary tangles or neuritic plaques	Alzheimer disease	**Ch. 25:553**
Spongiform changes in gray matter	Cerebral infarct	**Ch. 24:528**
	Creutzfeldt-Jakob disease (CJD)	**Ch. 25:566**
	Other neurodegenerative disorders (usually superficial spongiosis)	**Ch. 25:559**

For additional histopathology algorithms, see "Minor Histopathologic Patterns of Nervous System Tumors" in the next chapter.

1

Neuropathology Patterns and Introduction

Arie Perry and Daniel J. Brat

Central Nervous System Tumor Classification Schemes and Additional "Neuropathology Patterns"

The first comprehensive classification of nervous system tumors, formulated by Percival Bailey and Harvey Cushing in 1926, was founded on presumed parallels between embryologic and neoplastic cells.[1] In large part, this histogenetic "cell of origin" model still forms the basis for today's nomenclature, although much of the terminology has changed considerably. Renewed interest in the role of developmental pathways in tumorigenesis has led to more recent studies focusing on cancer stem cells and progenitor cells.[2,3] In 1949, however, as a means of enhancing the clinical utility of tumor classification, Kernohan contributed a tumor-grading system focusing on correlations with patient prognosis.[4] As progress was made over time, Russell and Rubinstein continued to modify and update the Bailey and Cushing system from the 1960s through the 1980s. Nonetheless, considerable variability in diagnostic practice existed on both sides of the Atlantic. In order to enhance consistency, an experts' consensus scheme known as the *World Health Organization (WHO) classification scheme* was first completed in 1979 and then revised in 1993, 2000, and 2007.[5] This scheme is currently the most widely utilized by neuropathologists for typing and grading tumors.

The 2007 WHO "blue book" currently lists over 100 types of nervous system tumors and their variants.[5] This level of complexity can be daunting; therefore, an organized approach or algorithm is required. As a first step, consideration of clinical and radiologic characteristics is a critical way to narrow the differential diagnosis, often to a few fairly common entities. In fact, the combination of *patient age* and *neuroimaging features* (including tumor location) provides some of the most powerful diagnostic clues before any tissue is even sampled or examined under the microscope. For example, the differential varies considerably for supratentorial versus infratentorial, pediatric versus adult, and enhancing versus nonenhancing tumors. The most common diagnostic considerations are summarized by age, location, and imaging features in Table 1-1, with each specific entity discussed in greater detail in subsequent chapters. Also, for a much more detailed background on the use of neuroimaging, the reader is referred to Chapter 4. This is a particularly critical topic in surgical neuropathology, since brain and spinal cord biopsy specimens are often small and the neuroimaging essentially provides the "gross pathology."

The next set of clues is naturally provided by histopathology. The *eight major patterns* provided at the beginning of this textbook narrow the differential diagnosis considerably based purely on the overall low-magnification appearance, and the subheadings of additional findings provides a useful diagnostic algorithm. When presented with a challenging biopsy specimen, the pathologist can start with either the clinical or morphology-based approaches but is encouraged to incorporate all available data before making a final diagnosis. In the vast majority of cases, the clinical, radiologic, and pathologic features are all consistent with one another; if not, the pathologist should carefully reexamine the specimen to be sure that all appropriate possibilities have been considered and if necessary, excluded with ancillary studies. The use of common ancillary diagnostic techniques is briefly summarized in this chapter, with many more examples provided in the subsequent topic-specific chapters. As useful secondary algorithms, the major differential diagnosis based on an additional 20 *minor histologic patterns* is presented in Table 1-2, with helpful clinicopathologic features summarized for 21 common differential diagnoses in Table 1-3.

Electron Microscopy

Although electron microscopy (EM) has historically been vital in defining a number of diagnostic entities, its everyday use in surgical neuropathology is generally labor-intensive, time-consuming,

(*Text continues on page 7*)