NEUROLOGICAL SURGERY

THIRD EDITION

VOL

5

VOLUME FIVE

NEUROLOGICAL SURGERY

A Comprehensive Reference Guide to the Diagnosis and Management of Neurosurgical Problems

THIRD EDITION

Edited by

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Contents

volume 5

chapter 103

Classification and biology of brain tumors

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The major objective of the study of the pathology of a brain tumor is to provide information about the biological behavior of the lesion and to indicate the extent to which the behavior of any residual tumor can be modified. For these purposes, a system of communication is necessary so that the pathological findings can be synthesized into a diagnostic "entity" to which, when appropriate, a histological grade can be assigned. Any classification system that attempts to categorize a group so complicated and so often interrelated as brain tumors is necessarily arbitrary and artificial. However, existing systems have generally served their purposes and provided useful prognostic information. These classifications and systems of grading were done largely on the basis of morphological criteria with increasing help from the field of immunohistochemistry. They are continually being refined and will be increasingly supplemented, and perhaps even eventually replaced, by more molecular approaches. Although the present discussion is based on morphological features, new diagnostic techniques of promise are also explored.

Regardless of the methods used for analysis, the degree to which a diagnosis and grade of a specific entity are prognostically reliable depends on the extent and the means by which the lesion under question is sampled and studied. For example, in the frequent case of an astrocytic lesion with areas of both high and low degrees of differentiation, a limited biopsy specimen from the better-differentiated area will contain tissue that gives the falsely reassuring hope of a long clinical course. On the other hand, a minute, poorly handled specimen from the most malignant area may be impossible to study at all. In other cases the potentially valuable information obtained from newer methods may be lost if the specimen is fixed and embedded in the traditional manner. It is therefore appropriate to review the potential methods by which tissues may be obtained and examined.

Methods for Tissue Sampling and Study

Open Biopsy. For lesions that are favorably situated, open cerebral resection can provide a true total resection of the tumor for which classification and grading are of academic interest. If this is not possible, as is the case for most gliomas, obtaining a large specimen will maximize the chance that the excised tissue is similar to that remaining in the patient. The problems of sampling may be minimized in this instance by the examination of multiple tissue blocks, recognizing, however, that, by definition, residual tumor is never studied. In addition, such specimens may make it easier for the pathologist to evaluate the diagnostically important relation of the lesion to the surrounding brain. As much tissue as possible should always be submitted for pathological study, even though a definitive diagnosis may have been made intraoperatively by frozen section.

Needle Biopsy. The size of such specimens ranges from small fragments or only scattered cells when a thin needle is used to more substantial tissue fragments when a large, hollow core needle with a cutting side port is employed.[18] In either case, the size of the specimen is the major disadvantage of this technique. Paradoxically, the significant advantage of needle biopsies is their superior sampling. Thus, the precise source of a specimen can be determined by reference to the computed tomographic scan used to determine target points. It must be emphasized that the optimal interpretation of needle biopsy specimens requires close cooperation *in the operating room* between the neurosurgeon and the pathologist and an understanding by both parties of the significance of the radiographic images of the suspected lesions under study. Thus, in the presence of a contrast-enhancing lesion in an adult, the pathological diagnosis of gliosis or a well-differentiated fibrillary astrocytic neoplasm is generally inappropriate and suggests that the needle, if aimed at the contrast-enhancing area, has missed its target.

Frozen Section. Frozen sections of open or needle biopsy specimens provide a means to ensure that adequate material is obtained or to establish a specific histological diagnosis.[28] They are also useful for anticipating the need for special procedures such as electron microscopy or the immunohistochemical markers that must be done on unfixed tissue. Frozen sections are usually examined after staining with hematoxylin and eosin, although other histological methods can be employed. The concurrent use of touch and squash preparations is strongly recommended.[21] Immunostaining can be used but is not commonly done. The freezing process unfortunately produces many artifacts, such as ice crystals and nuclear deformation, so that the features of lesions in the frozen section may deviate significantly from those seen later in permanent sections. The optimal interpretation of frozen sections therefore requires minimizing these artifacts as well as experience on the part of the pathologist in reading what is to a certain extent a different morphological "language," than that used with paraffin sections.

Open communication with the surgeon is again essential, and it is unfortunate that many operating suites are designed in the interest of sterility to separate the Pathology Department from the operating rooms. The necessary transfer of specimens through tubes or windows is a poor substitute for direct surgeon-pathologist contact, especially when only limited clinical information is supplied. Such a system almost guarantees that an "unexpected" pathological diagnosis will be received and that an unfortunate adversarial relationship can develop between the surgeon and the pathologist. In any setting, it is essential that any uncertainties on the part of the pathologist about the nature of the lesion are clearly understood by the surgeon. These are often conveyed by the pathologist's sotto voce equivocations, such as "consistent with," "suggestive of," "could be," or "probably is," which are often incorrectly interpreted by the surgeon as "diagnostic of."

Immunohistochemistry. As it has for pathological diagnoses for other organ systems, immunohistochemistry has had a major impact on operative pathology of the nervous system.[14,85] This technique is employed to recognize antigens on or within neoplastic cells either by immunofluorescence or, more commonly, by the immunoperoxidase method, which can be used on paraffin-embedded material. New antibodies will continue to be produced and used in diagnosis and classification. The most widely employed antibody for diagnosis is that for glial fibrillary acidic protein, a fibrillar protein occurring within astrocytes but found also in neoplastic oligodendroglia, ependyma, or choroid plexus. In light of this diversity and the fact that normal and reactive astrocytes are strongly positive, positive staining does not necessarily establish a lesion as either astrocytic or neoplastic but does establish a glial, and therefore primary, nature. S-100 is a soluble protein found within the cytoplasm of cells of the central and peripheral nervous system. It is expressed strongly in Schwann cells and is useful in establishing this cellular origin for acoustic and spinal schwannomas. The strong S-100 staining of melanocytes is also helpful in identifying amelanotic metastatic malignant melanomas. Other applications of immunohistochemistry include the characterization of the germ cell neoplasm in the pineal region, characterization of the hormones produced by pituitary adenomas, differentiation in a medulloblastoma, and localization of polypeptides within certain ganglion cell neoplasms.[13,23,48]

At present, there are no tumor-specific antibodies, although their production is a field of great endeavor.

Electron Microscopy. Transmission electron microscopy is valuable in selected cases but is time consuming, expensive, and not available in many medium or small institutions. In addition, the chances are generally small that electron microscopy will provide a specific diagnosis not obtained by other methods, particularly immunohistochemistry studies.[119] As a diagnostic technique, the latter has encroached significantly on the former.

Cytology. Because of the continuity of the intracranial and spinal subarachnoid spaces, the flow of cerebrospinal fluid may disseminate neoplastic cells to sites where they may be captured and investigated concerning their origins and behavior.[11] This is particularly true for malignant lesions such as the medulloblastomas and glioblastomas and for intraventricular lesions such as choroid plexus neoplasms, but is less so for intrinsic and more cohesive lesions such as the better-differentiated astrocytomas. Previously, this method focused largely on the nuclear features in order to determine the normal, reactive, or neoplastic nature of the vagrant cells. The ability of antibodies to recognize a cell type by the latter's cytoplasmic antigens now makes more specific identification of the nature of tumor cells possible and therefore augments, and in certain cases supplants, tissue biopsy.[122]

Chromosome Studies. There is increasing interest in the chromosomal abnormalities of human neoplasms because of the possibility that such changes are related etiologically to the neoplasms by means of expression or overexpression of certain oncogenes.[10,116] In addition, the prognostic value of chromosomal abnormalities in lesions such as chronic granulocytic leukemia suggests that karyotyping of brain tumors could provide valuable prognostic information about these tumors as well. As is discussed later, the meningioma and the malignant gliomas have received the most attention in this regard.

Quantitation of Cell Proliferation. The estimate of a neoplasm's proliferative potential is generally done inferentially by study of the cytological characteristics of the cells or more directly by determination of a mitotic index. Since mitoses reflect cell proliferation, they are valuable features, but their absence cannot be taken as evidence that the lesion is biologically "benign." Very few mitoses can be found, for example, in some glioblastomas. Thus, autoradiography has been employed to determine the percentages of cells in the S, or DNA synthesis, phase of the cell cycle. The label is introduced by immersing the excised tumor in tritiated thymidine or by injecting patients preoperatively with this same isotope. Autoradiography is then used to determine the labeling index or percentage of labeled cells.[63,79] Bromodeoxyuridine has also been utilized to determine the percentage of proliferating cells.[60–62] This method also requires preoperative injection of the compound, which is then detected by immunohistochemistry techniques as the incorporated product in the nuclear DNA. Both bromodeoxyuridine and the autoradiographic methods have obvious limitations of time, technique, or preoperative patient selection. Recently, a monoclonal antibody has been developed that can identify proliferating cells in operatively excised tissues without preoperative injection.[43–45] It holds promise that this or similar antibodies can be applied to diagnostic material and can quantitate the proliferative potential of a neoplasm.[26]

Clinicopathological Entities

FIBROUS DYSPLASIA

Fibrous dysplasia is a disorder of unknown etiology that usually is manifested as an enlargement of the bones in and about the orbit. Occasionally, more discrete lesions appear as isolated osteolytic areas in the cranial vault. The enlarging facial bones can impinge symptomatically upon nerves passing through the cranial foramina, but the signs and symptoms of fibrous dysplasia are usually more cosmetic than neurological.[29]

Histologically, the non-neoplastic lesion is formed of gritty tissue in which multiple small irregular spicules of immature bone abound. This finding, referred to as "woven bone," resembles embryonic membranous bone because of the disordered nature of the spicules, the paucity of calcium, and the absence of mature lamellae.[29]

The natural history of fibrous dysplasia has not been studied in detail; many lesions stabilize in adolescence.

CHORDOMA

The chordoma is a destructive neoplasm generally arising at either end of the axial skeleton, i.e., the clivus or the sacrum.[109] There is convincing evidence that the lesion originates from notochordal nests, which are frequently observed in the clivus, although it is not clear why these neoplasms are not more common along the thoracic and lumbar spine, where these same nests are frequently encountered in the center of the intervertebral discs. Chordomas in the clivus are often situated somewhat off the midline and can produce unilateral cranial nerve deficits.

Microscopically, the lesion is a lobulated, often translucent, expansile, and destructive mass that displaces rather than invades nervous system structures. Some lesions bleed profusely when incised. Microscopically, chordomas assume a variety of histological patterns, although most contain characteristic markedly vacuolated physaliphorous cells.

The lesion is a low-grade malignancy whose position, especially in the clivus, often prevents a total resection. Late metastases are occasionally noted, especially from the sacral chordoma.

HISTIOCYTOSIS X

Histiocytosis X is a uni- or multifocal disorder of bone or soft tissue, or both, that most often comes to neurosurgical attention as a lytic lesion of the skull. Although there can be considerable morbidity if multiple bone and soft-tissue lesions are present and fatalities can occur with extensive involvement of soft tissue, the disorder is not considered a neoplasm. It is attributed to a non-neoplastic aberration of the immune system expressed as the proliferation of a normal member of the macrophage family, the Langerhans' cell.[40,104] The common solitary lesion of the skull is known as an eosinophilic granuloma, whereas multiple lesions of the skull that are often associated with diabetes insipidus are part of the Hand-Schüller-Christian syndrome (Fig. 103–1). Extensive involvement of soft tissue characterizes the historical but ill-defined entity of Letterer-Siwe disease.

The cranial lesions of histiocytosis X are markedly osteolytic and erode bone cleanly. Thus, they are not delineated peripherally by the sclerotic rim of the epidermoid cyst or the irregular margin of many metastatic neoplasms. The soft lesions vary from red to yellow and may be attached to, but not generally invasive of, the dura. Only a rare lesion is found within the central nervous system. Histologically, the lesions are distinctive because of the mixture of histiocytes (Langerhans' cells), lymphocytes, and eosinophils (Fig. 103–2). In some cases, the histiocytes are engorged with fat and the lesions are macroscopically yellow. The Langerhans' cells have markedly convoluted nuclei and, by electron microscopy, contain the distinctive Birbeck granule diagnostic of this cell type (Fig. 103–3).[29,40,104]

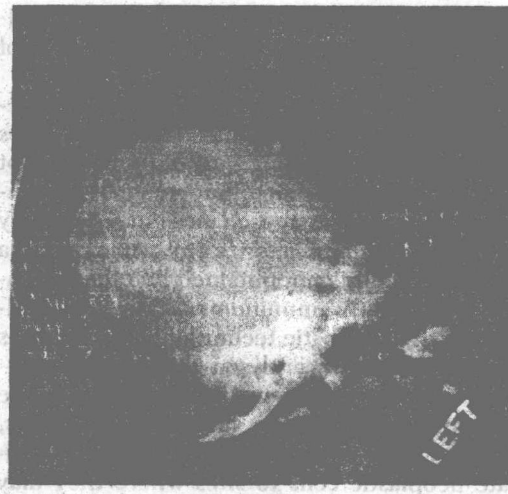

Figure 103–1. **Histiocytosis X. As in this skull roentgenogram from a 2-year-old child with diabetes insipidus, histiocytosis X presents with strikingly lytic lesions of the skull. In the age group of this patient, multiple lytic lesions are common (Hand-Schüller-Christian disease), whereas in older individuals the lesions are more likely to be solitary and confined to bone (eosinophilic granuloma).**

The common solitary lesion of bone is a benign condition responding to radiation therapy. The multifocal lesions of the base of the skull are in many cases also cured by irradiation, although they may be associated with variable morbidity.

CRANIOPHARYNGIOMA

The craniopharyngioma is a radiographically discrete, calcified, often cystic neoplasm that is seen most frequently in childhood. A noncalcified lesion with a slightly different histological pattern is usually seen in adults.[49,70]

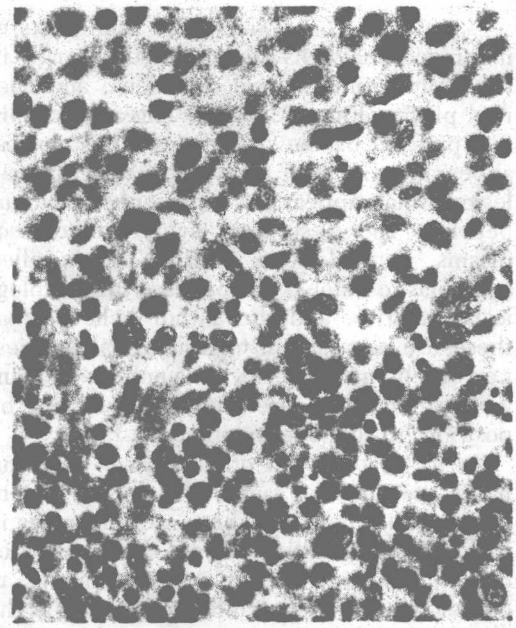

Figure 103–2. Histiocytosis X. The lesions of histiocytosis X are formed of large histiocytes with convoluted nuclei (Langerhans' cells) *(top)* and colonies of inflammatory cells consisting largely of eosinophils *(bottom)*.

The macroscopic appearance of the previously unoperated childhood lesion is one of an expansile mass that is generally discrete but is often bound to the tuber cinereum. Evidence of old hemorrhage and the subsequent tissue reaction are noted in fibrosis, calcification, and a brown "motor oil" fluid that sparkles with droplets of cholesterol. Microscopically, cells anastomose in ribbons to produce the "adamantinomatous" pattern (Fig. 103–4). Keratinized nodules, seen as white flecks with the naked eye or operating microscope, are also typical. During resection, pieces of the floor of the third ventricle can be avulsed, and microscopic study often reveals infiltration of the neoplastic cells. It is not surprising therefore that macroscopic total excision is difficult and that late recurrences can occur. The recurrent lesion is more widely adherent to local structures and is difficult, if not impossible, to remove.

The histological pattern of the craniopharyngioma seen most frequently in adults has been termed a "papillary craniopharyngioma" or "suprasellar squamous papillary epithelioma" (Fig. 103–5).[49,70] Although the claim to an entity distinct from the adamantinomatous lesion remains to be established, the histological identification of a papillary craniopharyngioma is nevertheless important, since its prognosis appears to be more favorable (perhaps because it is a more discrete lesion). Because a histological spectrum of anaplasia is not recognized for either adamantinomatous or papillary lesions, the craniopharyngiomas are not graded.

Figure 103–3. Histiocytosis X. In this electron micrograph of a Langerhans' cell, two of the diagnostic Birbeck granules are present in the center immediately below the nucleus (N).

Figure 103–4. Craniopharyngioma. Islands and anastomosing cords of epithelial cells form the classic adamantinomatous pattern of the craniopharyngioma.

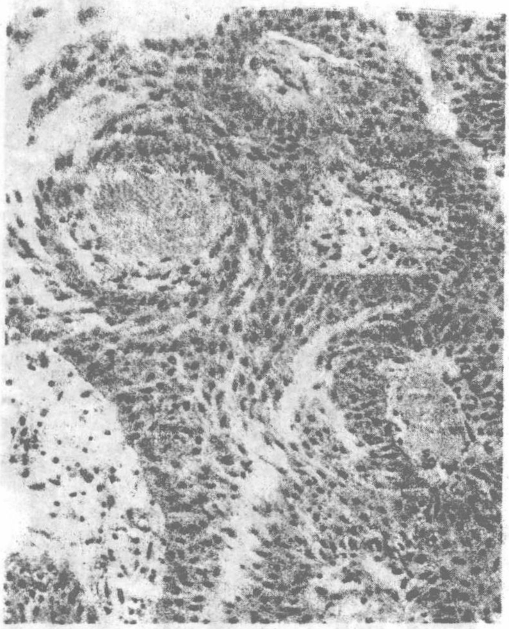

Figure 103–5. Craniopharyngioma. In adults, the craniopharyngioma is often noncalcified, is formed of a more squamous epithelium, and has been referred to as a papillary craniopharyngioma or papillary suprasellar squamous epithelioma.

The cell of origin for the craniopharyngiomas has not been determined, although a supposed displaced epithelium from Rathke's pouch is often cited. Small nests of squamous cells in the infundibulum are also candidates, although they become more prominent in adulthood and are seen only infrequently in the age groups in which the adamantinomatous craniopharyngiomas predominate. They could therefore be the progenitor of the papillary lesion.

MENINGIOMA

A neurosurgeon's education in regard to the biology and classification of meningiomas should begin with the classic work of Cushing and Eisenhardt in which this entity received its first comprehensive clinicopathological study.[35] A more recent volume provides an update and is a valuable additional resource.[74] The meningioma was defined by Cushing and Eisenhardt largely as any primary discrete mass in the meninges, although since that time there has been more emphasis on microscopic than on macroscopic appearance. A convincing argument can be made that most meningiomas arise from nests of meningothelial cells disseminated normally in the leptomeninges, tela choroidea, and choroid plexus (Fig. 103–6).[74,75] This relationship is supported by the similarities in histological appearances as well as by the frequent small lesions that appear to represent transitions between the nests and symptomatic neoplasms. Some lesions, such as the so-called angioblastic lesions, do not share this histological similarity, and the author believes that these are separate histopathological entities, i.e., the hemangiopericytoma and the hemangioblastoma, that are unrelated, except by position, to the true meningioma.[29]

As for virtually all other human brain tumors, the causative factor or factors of meningiomas are unknown. There are rare cases in which it is difficult to dismiss the appearance of a meningioma at the precise spot of an earlier trauma.[35] Even more convincing is the rare association of a meningioma with a prior history of local radiation therapy.[118] In the last decade it has also become apparent that many meningiomas have steroid receptors that are perhaps in some way related to the genesis of the neoplasms and also explain the higher incidence in women than in men.[66,87] Supratentorially this incidence occurs in a ratio of

Figure 103–6. Normal meningothelial cells. As in this section of the leptomeninges from a 79-year-old woman, nests of meningothelial cells are common findings and are the presumed site of origin for meningiomas.

approximately 3:2, whereas intraspinally it is even higher, 10:1.

Meningiomas arise throughout the central nervous system from the optic nerve sheath to the spinal cord, although they are rare below the thoracic region. Those around the optic nerve can arise within the sheath but also can appear in the orbital soft tissue without apparent relation to the nerve or sheath. A rare lesion appears to thicken the skull from within or to arise along the peripheral course of a cranial nerve. Displaced meningothelial cell rests are believed to cause lesions in these ectopic sites, as well as the rare lesions within the ventricular system. Some meningiomas are associated with considerable underlying cerebral edema. This is especially prominent about some of the larger lesions, although it may even be associated with a small neoplasm.[50] In the skull, hyperostosis is a common consequence of an invading or adjacent tumor (Fig. 103–7).

The histological appearance of meningiomas is exceedingly diverse, and categories and subcategories can be created at will. Cushing and Eisenhardt stopped at 9 categories and 20 subcategories, but there is now a trend to simpler systems. One that is widely used recognizes syncytial, transitional, fibroblastic, and meningothelial types.[34,114] Unfortunately, there are many other patterns and mixtures of patterns so that a concise histological subtyping is not, to the author, realistic or generally prognostically useful. The syncytial type has been linked suggestively to more aggressive behavior and to a more marked deviation of the karyotype from the normal diploid state, but this relationship between histological and karyotypic appearance and behavior needs to be confirmed.[126] Accordingly, the diagnosis of "meningioma" usually suffices, although it is admittedly tempting to append the descriptors "fibroblastic," "syncytial," or "microcystic" when these patterns occur in predominant or pure forms. The so-called papillary meningioma is an exception to this rule and should be specified in the diagnosis and recognized by the surgeon for its aggressive potential.[83] Another prognostically relevant distinction is that between the hemangiopericytic lesion and the true meningioma. As indicated earlier, the hemangiopericytoma is frequently classified as an "angioblastic meningioma," but the author considers it a distinct lesion unrelated to the meningioma because of its histological features, high rate of local recurrence, and late extracranial metastases.[29] The rare supratentorial meningeal hemangioblastoma also has distinctive features that, to the author, entitle it to an identity status independent of the meningioma.

Figure 103–7. Invasive meningioma. Overt invasion of the underlying cerebral cortex is a feature of many malignant meningiomas. As here, cytological atypia is also frequently seen.

The ultrastructural evaluation of the meningioma discloses many intracellular intermediate filaments and prominent desmosomal interconnections.[52] The intermediate filaments contain vimentin, the immunohistological identification of which may be a helpful diagnostic tool, although, like other intermediate filament proteins, it is by no means specific for one cell type.

The biological behavior of the meningioma is one of continued growth, although the markedly calcified and paucicellular appearance of some lesions suggests a state of growth arrest. The probability of total operative resection depends on the site, size, and involvement of adjacent structures such as the brain, cranial nerves, vessels, and skull. Following a macroscopically complete resection, the 5-, 10-, and 15-year recurrence-free rates were noted as 93 per cent, 80 per cent, and 68 per cent, respectively. For incompletely resected lesions, the progression-free rates at the same postoperative intervals were expectedly lower, at 63 per cent, 45 per cent, and 99 per cent.[92]