

Intraoperative consultations in neuropathology

Nöropatolojide intraoperatif tanı

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Summary

This is a practical review of intraoperative consultations in neuropathology. The idea of intraoperative consultation, its philosophy, use, and expectations of the surgeon and the pathologist alike, are discussed, as well as the techniques used to perform this function. Later, the practical cytologic and histologic/frozen section features of major neuropathological entities, which are commonly encountered by the practicing neuropathologist, are reviewed. A reference is made to the specific diagnostic pitfalls and the differential diagnosis of the lesions that can potentially mimic each other.

Key words: Intraoperative consultation, frozen section, neuropathology.

Introduction

Pathology is a consultation service and as such, provides direct input to the management of patients by examining (the tissue of) the patient, by requesting additional work-up on that (tissue of the) patient and by rendering an opinion which may be in the form of a diagnosis, a recommendation and/or a suggestion, thereby contributing to the diagnosis, treatment and management of the patient. This consultation can be carried out in several different ways, one of which is the intra-operative. Since, in contemporary pathology, not only freezing, cutting and looking at the tissue with a microscope, but many different techniques are used, the traditional *frozen section* (FS) (1) is replaced here when possible by *intra-operative consultation* (IOC).

Needless to say, any of the following entities requires and is usually easily diagnosed in the presence of relevant clinical, radiological and intra-operative impressions. However, the discussion in this text is intentionally limited to the morphologic discussion because of the

Özet

Burada nöropatolojide intraoperatif tanının uygulamadaki yeri gözden geçirilmektedir. Intraoperatif tanının kullanımı, felsefesi, cerrahin ve patoloğun beklentileri yanısıra, konunun teknik yönleri tartışılmaktadır. Daha sonra ise, nöropatolog tarafından sıkça görülen belli başlı entitelerin uygulamadaki sitolojik ve histolojik özellikleri, dondurma kesitlerde görüldüğü gibi gözden geçirilmektedir. Tanısal özellikler ve birbirini taklit edebilecek lezyonların ayırıcı tanısal özelliklerine değinilmektedir.

Anahtar sözcükler: Intraoperatif tanı, dondurma kesit, nöropatoloji.

nature of this course and also because of the fact that in many instances, pathologists find themselves alone with the tissue and the microscope, and nothing else, to rely on. Where relevant for the sake of better understanding, certain clinical and radiological features will be mentioned only briefly.

Purpose of IOC

IOC from a central nervous system (CNS) lesion is usually requested in an attempt to classify the lesion. Most of the time there is a distinct, focal or multi-focal (but usually not diffuse), space occupying lesion that has been previously worked-up by other means and a surgical approach decided. These are most likely neoplasms of various histological types, primary or metastatic. Some lesions, such as infarcts and demyelinating pseudotumors, however, can produce a mass effect and masquerade as neoplasms, while some neoplasms, such as lymphomas, may not produce a distinct mass. Therefore, deciding whether the tissue is abnormal or not, and classification of the lesion in general terms into

neoplastic (and then primary or metastatic), inflammatory, reactive, demyelinating, vascular, or infectious is the first step in the decision making process. A more specific diagnosis can usually be made.

This is the time to request more tissue if the amount of the tissue is not enough for possible ancillary studies, for a subsequent definitive diagnosis, or the amount and/or quality of the tissue is not enough to classify the lesion. The latter situation should preferably be accompanied by a comment to guide the surgeon. For example, if the tissue is completely necrotic, it may be coming from the center of a glioblastoma, and therefore, retargeting will be needed to obtain viable tissue from the periphery of the lesion. Likewise, if the tissue shows mildly increased cellularity, it may represent the infiltrative periphery of a glial neoplasm.

Especially in stereotactic needle biopsies, one should remember that when the procedure is over, that will be the only tissue available to make a subsequent definitive diagnosis. This is essentially the idea behind IOC during stereotactic needle biopsies: To make sure the tissue is representative and will be useful later for diagnosis and work-up and to make sure that the needle is placed in a diagnostic area so that further tissue can be obtained from that region of the lesion.

Again, depending on the initial impression, fresh tissue can be submitted for cultures, cytogenetics, flow cytometry, research, kept frozen for submitting to other institutions, and submitted for electron microscopy. Amount of tissue for ancillary studies that can be performed on formalin-fixed, paraffin-embedded tissue should also be considered. These are usually a panel of immunohistochemical and histochemical stains, but *in situ* hybridization and other molecular studies may be needed as well. Cytogenetics is becoming increasingly important with diagnostic, grading, prognostic and treatment implications. This strategy applies to all types of neurosurgical specimens, stereotactic biopsy, open biopsy and resections, and may be useful even in the autopsy setting.

Due to the infiltrative nature of glial neoplasms, status of margins is not an issue in neuropathology. It is virtually impossible to find and remove every individual infiltrating malignant cell in an attempt to achieve a complete resection (2); therefore, neurosurgeons talk about "gross total resection". However, in some institutions, as part of treatment protocols or an aggressive surgical approach,

or to finish surgery with an idea of how much tumor is left and where for further treatment options, after gross total resection, selected "margins" can be sampled and evaluated. The idea here is not to be able to tell whether a rare atypical cell is really neoplastic or not, but to give the neurosurgeon an idea about the extent and amount of residual tumor with a descriptive statement such as "rare atypical cells present", "prominent neoplastic population present" or "reactive astrocytes present, no definitive tumor seen", and so on. Based on the above discussion, "negative for malignancy" will not be accurate, while "positive for malignancy" will not serve the purpose.

In a College of American Pathologists/ Centers for Disease Control and Prevention Outcomes Working Group study pertaining to the indications and immediate patient outcomes of pathology IOCs (3), although the data not specified as to the surgical subspecialties, while the purposes mentioned above formed the majority, expediting obtaining diagnosis to inform patient and family, for surgeon's knowledge, to facilitate patient management, other professional communication or discharge planning prior to permanent section availability, academic protocol were also mentioned.

The information that the pathologist provides during IOC has implications for the neurosurgeon and for the patient. In general, gross total resection as much as possible depending on the location, is carried out in a number of low grade, well circumscribed lesions such as pilocytic astrocytoma, pleomorphic xanthoastrocytoma, subependymoma, myxopapillary ependymoma, central neurocytoma, ganglioglioma, dysembryoplastic neuroepithelial tumor, hemangioblastoma and subependymal giant cell astrocytoma and is not followed by radiation therapy or chemotherapy. In high grade gliomas, less aggressive or minimal surgical resection followed by radiation therapy and chemotherapy is performed. Cystic lesions such as Rathke cleft cyst and colloid cyst are removed as much as possible. Gross total resection, with subsequent chemotherapy and radiation therapy, is the treatment of choice for medulloblastoma. In metastatic carcinoma, usually the resection is carried out to alleviate mass effect, but minimal surgical intervention with subsequent gamma knife therapy can be elected. Certainly, the recognition of a non-neoplastic process will keep the surgical trauma to a minimum. Sometimes, a mass lesion with surrounding edema leads to an emergency surgery to obtain a tissue diagnosis and

alleviate the mass effect by various treatment modalities to avoid herniation and death or cord compression and disability.

Prerequisites

All of what will be said here applies to an ideal setting. Due to the wide variation in the practices and ideology of the participants of the system however, this may not apply to some institutions, which makes the IOC more challenging for the pathologist.

In many cases, a miniscule amount of tissue is all the neurosurgeon may be able to provide or the pathologist will be able to get. This is not unexpected given the delicate organ, the brain, with numerous functional/vital centers and essentially no regenerative activity, which precludes obtaining generous material due to quality of life concerns, at least initially. Additionally, it is difficult, if not impossible, in some situations to appreciate any expected architecture and a particular orientation in the CNS tissue. This is in contrast to tissues of comparable sizes from other organs with a mucosal lining or with an organization of tissues in certain ways.

To compensate for these limitations, one has to call into play all the available resources, i.e., one has to be equipped at the time of IOC with all the information, clinical and radiological, about the patient, be aware of any specific purposes for the procedure, and should have discussed, ideally in advance or at the time of IOC the case with the radiologist and surgeon, and be able to interpret the pathologic findings in the presence of all the above for a more productive IOC.

The other extreme is the situation where the pathologist is left with a piece of tissue and the clinical history of "brain tumor", a term pertaining to anything that has to do with the "head" and in some cases with the spinal cord and spine. Nonetheless, some neurosurgeons are knowledgeable enough to give an advance warning and information, at least in some "critical" cases.

The critical information good to have is the precise location, including intra or extra-axial, relation to certain structures such as a cranial nerve or dura, clinical diagnosis, radiological features and impression, prior history of disease and treatment, other systemic conditions, and surgeon's specific questions.

On the other hand, pathologist's responsibility is to ask for information, to be familiar with the brain lesions and their terminology, including World Health Organization

Classification of Tumors of the Nervous System (4), with their characteristic clinical and radiological features and to be familiar with the normal appearances of various regions of the CNS.

Tissue Preparation

The quality of FS is greatly affected by technical artifacts. CNS tissue is especially prone to such artifacts and rapid freezing is of utmost importance, which is also difficult due to the high lipid content of the tissue. As expected, additional problems arise in the edematous tissue and in loosely textured tissues where cellularity is low and the background is rich in glucoseaminoglycans, or in lesions with extensive cystic/microcystic change. Rapid freezing in liquid nitrogen/ isopentane or in the cryostat with the use of cryospray is preferred. In most cases, evaluation of cellularity is crucial and FS procedure can be misleading due to shrinkage or expansion of the tissue. For these reasons, cytological evaluation is an indispensable part of IOC in neuropathology. Imprints do not generally produce satisfactory preparations due to the numerous cytoplasmic processes in the CNS tissue and its lesions, with the exception of pituitary adenoma (5) where the reticulin network is essentially nonexistent, and possibly metastatic poorly differentiated carcinomas where cohesion is lost. Therefore, smear technique with crushing an approximately 1 mm³. piece of tissue is the widely used method (6, 7, 8), although an occasional study claimed the usefulness of imprint preparations for neurosurgical specimens (9). Evaluation of cellularity in these cytological preparations may become a problem since it is variable depending on the amount of tissue smeared, the quality/nature of the tissue, how much pressure is applied, and so on. This can be overcome in time with experience and by adhering to a standard tissue amount and technique, performed by the same person every time. In general, if the tissue is heterogeneous grossly, areas with different appearances should be sampled. CNS tissue should never be placed on gauze, cloth or paper towel. Keeping it on a glass slide or plastic surface is the best way to prevent tissue loss, and artifacts while cutting.

Cytological features of the CNS lesions are specific enough that some institutions completely rely on them in IOC, taking the opportunity to save more tissue for permanent sections. Already high specificity and sensitivity slightly increase when combined with FS (10).

Intra-operative fine needle aspiration biopsy has been performed for IOC purposes with good diagnostic results

(11, 12), but did not become popular most likely due to the advent of stereotactic procedures (13), which provide more planned and controlled needle movement and which also provide tissue for histological evaluation through essentially a similar surgical procedure.

Fixation and subsequent staining are a matter of individual/institutional preference with options ranging from toluidine blue, Papanicolaou and Diff-Quik, to hematoxylin and eosin (H&E), with appropriate fixation depending on the staining planned. It is also possible to find in the literature the application of rapid histochemical or immunologic techniques. In most institutions, H&E-stained smears and FS, together with the appropriate interaction with the surgeon, are the standard procedure.

Morphological Features

Since brain has a few types of cells, the features to be evaluated in a given setting, especially if one is equipped with the clinical/radiological information, are few, quite specific for their respective entities and allow easy differential diagnosis using an algorithmic approach. Familiarity with the normal morphological variations is very important and a few major situations will be mentioned here.

“Normal” (14)

Although brain is referred to as a single organ for practical purposes, and is composed of only a few cell types, the morphological appearances of these cell types and their organization and mixture in different functional/anatomic centers are quite variable. For instance, neurons can be seen as the large Betz cells of the motor cortex with polygonal cytoplasm or, at the other extreme, small lymphocyte-like cells of the granule layer of the cerebellum with no discernable cytoplasm by light microscopy. These may be misinterpreted as inflammation or as one of the small blue cell tumors, such as medulloblastoma. Small neurons of the olfactory bulb have a similar appearance and may cause problems in IOCs for the identification of olfactory neuroblastoma invasion through the cribriform plate. In general, neurons are limited to the gray matter, but it is possible to find neurons in the white matter of the temporal lobe, creating an appearance reminiscent of ganglioglioma in mildly cellular specimens. In addition, such neurons may normally be associated with satelliting glial cells and may be mistaken for a glial neoplasm infiltrating the gray matter. Ependymal lining of especially the occipital horns of lateral ventricles usually show ependymal “pinching” with

prominent rosette-like structures entrapped in white matter and may be mistaken for an ependymoma. Immature neurons of the periventricular germinal matrix and the cerebellar fetal layer of Obersteiner may be interpreted as a primitive neuroectodermal tumor (PNET). Normal pineal gland may resemble germinoma, a tumor commonly encountered in the pineal region.

A simple way to become familiar with such structures and variations of normal is to submit a few extra sections of these areas from autopsies to educate our eyes. Following will be a review of the microscopic features in general that one can encounter during the IOC.

Microscopic Features

Gross features are of little or no help, mostly due to the small amount of tissue, but may sometimes provide a helpful initial impression as to the nature of the tissue. Usually, firm tissue suggests a meningioma or schwannoma, rubbery tissue suggests a diffusely infiltrating process, necrosis can be apparent and suggest a high grade neoplasm or radiation effect, gelatinous or mucinous tissue suggests a low grade glial neoplasm. Even the impression that one gets while smearing the tissue may give a clue as to the type of the lesion. Usually, normal brain tissue will smear with almost no pressure and will yield a smear with a homogenous, thin gross appearance. Tissues with increased cellularity will show some resistance and create a granular smear pattern. Lesions with tightly packed cells, such as fibrous meningioma and schwannoma, may not even smear at all and may remain as a whole fragment of tissue on the slide.

Microscopic features can be evaluated in FS and cytological preparations (15), some better in one than the other and are not so much different than the general microscopic concepts that apply to other tissues. It should also be kept in mind that no matter how specific, these features must be put into proper context for optimal interpretation. Scanning at low power provides an impression about cellularity and background. “Normal” brain shows low cellularity with a homogenous background with no prominence in fibrillarity. In smears, this looks as a homogenous finely granular, eosinophilic material. An occasional delicate capillary can be seen, along with scattered cellular elements. It is when there is an increased fibrillarity in the background, usually together with an increase in cellularity, that an abnormal proliferation of cells is suspected. In primary brain

lesions, the increased cell population is glial, explaining the fibrillarity in the background due to glial processes. The cells are entangled and form a meshwork, but it is possible to identify the individual cell borders, especially in smears. Astrocyte cytoplasm is plump in reactive conditions and in the so-called gemistocytic astrocytoma. In reactive conditions, there may be evidence of inflammation, necrosis, infection or adjacent neoplasm, or it may be impossible to tell a reactive gliosis from a low grade glial neoplasm. Oligodendroglial cells are not as rich in cytoplasmic processes as astrocytes are, and their processes are very delicate. A background devoid of processes is seen mainly in meningiomas, metastatic tumors and pituitary adenomas. Necrotic background is a feature of high grade glial neoplasms, metastatic tumors and infarcts, and can be seen in lymphomas as well.

Intermediate and high power examination is helpful for the evaluation of cell clusters and cytological features. In contrast to the clusters of entangled cells seen in glial neoplasms, metastatic carcinoma has cohesive cell clusters with distinct cytoplasmic borders, whereas lymphomas consist of individually distributed cells, with a perivascular predilection. Cell clusters of meningiomas show a syncytial arrangement with no distinct cytoplasmic borders in most areas.

Nuclear features are also important and are best appreciated in the cytological preparations. Astrocytic neoplasms have a characteristic angular nucleus with more nuclear membrane irregularities and hyperchromasia with increasing grade. Oligodendroglial cells tend to retain the overall roundness and uniformity of their nuclei even in high grade (anaplastic) tumors. Same is true for ependymomas. Metastatic carcinomas usually have open chromatin patterns and prominent nucleoli. They are also associated with a more prominent mitotic activity, even more so than glioblastoma. Brain lymphomas are usually of large B-cell type and therefore, have the characteristic nuclear features.

There are also certain structures formed by certain types of tumors. Meningiomas tend to form characteristic whorls, although it should be kept in mind that they are one of the most histologically versatile neoplasms, including, but not limited to, fibroblastic, myxoid, papillary, chordoid, clear cell, rhabdoid types, to name a few. In general, in any given tumor, careful search usually provides some clues that can be used in conjunction

with other information. Intranuclear cytoplasmic invagination in meningioma is another characteristic feature, without the obviously malignant features of melanomas. Ependymomas form perivascular pseudorosettes, and less commonly, true rosettes (or ependymal canals). The glial background and bland cytological features rule out the possibility of gland formation in carcinomas. Metastatic neoplasms form a distinct border with the adjacent brain tissue, in contrast to the infiltrative border of glial neoplasms. The perivascular pseudorosette-like structures are also seen in central neurocytoma; however, in contrast to the pseudorosettes of ependymoma, they don't have the punched-out appearance but display irregularities at the border of nuclear-anuclear zones. In addition, background fibrillarity is more delicate in central neurocytoma.

Pituitary adenoma shows a very monotonous population of cells, with uniform, round nuclei and lack the fibrillary background of glial tumors, an especially useful feature in its distinction from oligodendroglioma. They may lose their fragile cytoplasm in smears, which creates a finely granular eosinophilic background. Nonetheless, epithelial clustering and small amount of polygonal cytoplasm with eccentric nucleus should be evident in some areas. These features contrast with the polymorphous cell population and distinct nesting pattern in non-neoplastic pituitary, a question that may arise occasionally, especially in the case of microadenoma.

Since the characteristic clear cytoplasm of oligodendroglioma is an artifact of delayed fixation, it is not seen in FS or smears. Therefore, a constellation of uniformity and roundness of nuclei, a delicate chicken-wire vasculature and the presence of the mini- (micro-) gemistocytes is helpful. In the face of the difficulties encountered in the diagnoses of low grade oligodendroglioma, oligoastrocytoma and astrocytoma in more than a few cases even on permanent sections, the conservative phrase "low grade glial neoplasm" appears very attractive.

Pilocytic astrocytoma can have various histological presentations. The classical appearance is that of an increased cellularity in a fibrillary, loosely textured background, uniform, elongated nuclei with bland cytological features, and long processes that run across and beyond the microscope field. These can be associated with typical Rosenthal fibers and eosinophilic granular bodies.

PNET is composed of small round to oval cells with inconspicuous cytoplasm and nucleoli, coarse chromatin pattern, high turn-over rate with brisk mitotic activity and apoptotic debris, reminiscent of a poorly differentiated neuroendocrine carcinoma. Not much of a diagnostic problem in the typical clinical setting, it may be impossible to differentiate from a metastatic small cell carcinoma in the adult.

In the pineal region, in addition to PNET, germ cell tumors present various tissue components and may cause misinterpretations. Individual malignant cells of germinoma may resemble metastatic carcinoma, but the overall architecture is that of a typical seminoma/dysgerminoma, including lymphocytes, fibrous septa and granulomata.

In addition to all of these main categories, there are reports of virtually every type of tumor arising in or metastasizing to CNS and its coverings. Following section will concentrate on some pitfalls that should be kept in mind as general rules during IOC.

Difficult Differential Diagnoses and Pitfalls (16, 17, 18)

Normal choroid plexus vs. choroid plexus adenoma

A single layer of cells covering papillary structures are seen in both. Replacement of hobnail arrangement of the epithelium by a flat surface, together with the knowledge that the specimen is from an intraventricular/choroid plexus mass, favors papilloma.

Dysembryoplastic Neuroepithelial Tumor (DNET) vs. Oligodendroglioma

Floating neurons in a myxoid background, a mixture of cell types, i.e., astrocytes, oligodendroglial cells and neurons, well-defined nodules, lack of satellitosis in a cortical, usually multi-nodular lesion favors DNET.

Infarct vs. Glial Neoplasm

Especially in subacute infarcts with numerous macrophages and vascular prominence, disruption of macrophage cytoplasm and collapse of tissue can create a high grade glial appearance. Lack of high grade nuclear features, presence of macrophages in smears, and sharp demarcation of the lesion should alert one to the possibility of infarct.

Demyelinating Lesion vs. Glial Neoplasm

Similar to "infarct vs. glial neoplasm".

Hemangioblastoma vs. Glial Neoplasm

Collapse of the tissue and disruption of the cytoplasm of the vacuolated cells of hemangioblastoma, together with its vascular background may create a glioma-like appearance. Lack of fibrillary background especially in smears favors hemangioblastoma, and knowledge of clinical and radiological information is helpful.

Progressive Multifocal Leukoencephalopathy (PML) vs. Glial Neoplasm

Extremely atypical astrocytes and, depending on the stage of lesion and what part of the lesion the tissue is obtained from, the presence of macrophages and large oligodendroglial cells may mimic a glioma. Smears are helpful in identifying the macrophages and in appreciating the presence of intranuclear inclusions in oligodendroglial cells in an immunocompromised patient, favoring PML.

Reactive Gliosis vs. Low Grade Glial Neoplasm

Usually difficult, at times impossible distinction to make; hence the term "atypical glial proliferation". Both have mildly increased cellularity. A uniform, regular distribution of cells, lack of satelliting around neurons and capillaries and presence of gemistocytic cytoplasm with prominent fibrillary processes favor a reactive process.

Pilocytic Astrocytoma vs. Reactive Gliosis

A mild increase in cellularity rich in Rosenthal fibers is sometimes encountered around tumors, cysts, malformations and other long-standing processes and may lead to a diagnosis of pilocytic astrocytoma. The presence of a cyst and a mural nodule, and absence of other reactive features mentioned above favor pilocytic astrocytoma.

Pilocytic Astrocytoma vs. High Grade Glial Neoplasm

There is prominence and proliferation of vessels in both tumors, feature of high grade glial tumors outside the setting of pilocytic astrocytoma. The uniform distribution of cells in a loosely textured background, bland nuclear features, presence of microcysts, Rosenthal fibers and eosinophilic granular bodies support the diagnosis of pilocytic astrocytoma.

Radiation Change vs. Glial Neoplasm

It is important to give the surgeon an idea, as in the case of "margins", about the extent of the tumor and radiation

change with the descriptive statements. It is always possible to find a few neoplastic cells, since these neoplasms are not cured. A fibrinoid quality to the necrosis, fibrinoid necrosis of the vessel walls, telangiectatic changes, bizarre cells with smudgy chromatin and proportional enlargement of cytoplasm and nucleus favor predominantly radiation change. The knowledge of the histological type of the previous tumor is also helpful.

Pleomorphic xanthoastrocytoma (PXA) vs. glioblastoma

Due to its pleomorphism, PXA can be mistaken for glioblastoma. A paucity of mitoses and absence of necrosis relative to the degree of cytological atypia, presence of eosinophilic granular bodies in a cortical tumor from a young adult favor PXA.

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Pitfalls

Consider metastatic carcinoma in the differential diagnosis (ddx.) of glioblastoma if there is brisk mitotic activity and more than occasional prominent nucleoli. Consider non-neoplastic lesion in the ddx. of malignancy if there are more than occasional macrophages.

Warn the surgeon about the likely presence of higher grade areas and request more tissue when faced with a low grade glial neoplasm in the elderly.

Some clinicians and pathologists use the term "glioma", "low grade glioma" (a term that also encompasses pilocytic astrocytoma) and "well differentiated glioma" interchangeably, while "malignant glioma" is used to indicate any high grade, i.e., WHO grade 3 and 4, glial neoplasm. Therefore, any communication should be as clear and specific as possible.

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