Utility of Intra-operative Consultations for the Diagnosis of Central Nervous System Lesions

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Abstract. The inherent soft nature of the central nervous system (CNS) renders poor-quality frozen sections. Cytology has been shown to be of great value in intra-operative consultations of CNS pathology. The current study was undertaken to examine the utility of intra-operative consultations regarding CNS lesions, comparing the usefulness and limitations of frozen section and cytology techniques. A retrospective study of 103 cases of CNS intra-operative consultations was performed. Concordance between the intra-operative diagnosis and the final diagnosis was seen in 94% of cases. Most discrepancies were due to failure to recognize atypia in meningiomas. The cytology technique was more useful for astrocytomas, small round cell tumors, and certain metastases. The frozen section technique was better for the diagnosis of meningiomas, reactive lesions, ependymomas, and most metastatic lesions. Using a combination of the two techniques is most beneficial. (received 22 December 2000; accepted 6 February 2001)

Keywords. CNS pathology, frozen section, cytology, brain tumors, consultations during neurosurgery

Introduction

Brain tissue is predisposed to show ice-crystal artifacts, making frozen sections difficult to interpret. The soft texture, however, aids in smear preparation, often revealing exquisite cytological details. Several authors [1-3] have stressed the value of intra-operative (Iop) smears. The issue is particularly important with the increasing incidence of stereotactically guided biopsies and the prospect that fine needle aspiration (FNA) may become a common diagnostic tool in CNS lesions. With these aspects in mind, we decided to study Iop consultations for diagnosis of CNS lesions.

The aims of the present study were: (a) to study the accuracy of Iop consultations for CNS lesions; (b) to compare the utility of intra-operative cytology (IopC) and frozen sections (FS); (c) to identify entities where one technique is more helpful than the other for diagnosis; and (d) to delineate the limitations of each technique.

Materials and Methods

From January 1997-June 1999, 103 consecutive Iop consultations for CNS lesions were performed. In this retrospective study, after a review of each patient's history, the cytology smear (IopC) was examined, followed by the FS slide. All of the slides were examined by a qualified neuropathologist and a senior pathology resident.

The cytology smears were prepared at the time of intra-operative consult by the “squash method,” ie, placing a small piece of tissue between two slides, gently squashing it, and pulling the slides away from each other. Usually, these squash smears were immediately fixed in 95% alcohol and stained with hematoxylin-eosin. Sometimes, one of the smears was also air-dried and a “Diff-quik” (Romanovsky) stain was performed. Frozen section slides were cut on a cryostat apparatus, fixed in 95% alcohol, and stained with hematoxylin-eosin.

An Iop diagnosis was made after examination of the IopC and FS slides. Sections from subsequent paraffin-embedded tissue were then examined. The study was conducted without knowledge of the
Fig. 1. Cytology smears of astrocytoma Grade III (anaplastic astrocytoma). The copper-wire fibrillary architecture (straight arrow) is well appreciated. Nuclear atypia is also evident (curved arrow). (H & E, x 400).

Table 1. Comparisons of the utility of intra-operative cytology smear (IopC) and frozen section (FS) for the diagnosis of various lesions of the central nervous system (CNS).*

<table>
<thead>
<tr>
<th>Category</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IopC more useful</td>
<td>FS more useful</td>
<td>IopC &amp; FS equally</td>
<td>IopC &amp; FS non-contributory</td>
<td></td>
</tr>
<tr>
<td></td>
<td>than FS</td>
<td>than IopC</td>
<td>useful</td>
<td>equally useful</td>
<td></td>
</tr>
<tr>
<td>Astrocytic tumors</td>
<td>22</td>
<td>8</td>
<td>11</td>
<td>1</td>
<td>42</td>
</tr>
<tr>
<td>Metastatic tumors</td>
<td>4</td>
<td>6</td>
<td>1</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>Meningioma</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Primitive neuroectodermal tumor</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Oligodendroglioma</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Ependymoma</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Germinoma</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Vascular lesion</td>
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<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Reactive lesions</td>
<td>0</td>
<td>7</td>
<td>0</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>Total</td>
<td>32</td>
<td>27</td>
<td>14</td>
<td>9</td>
<td>82</td>
</tr>
</tbody>
</table>

*The FS was of “good” quality in 13 of 15 cases in which IopC was not performed.
diagnoses that had previously been reported at the time of Iop consultation or at “sign-out” of the cases. The relative utility of IopC and FS was determined and categorized as follows:

“A” IopC more useful than FS;
“B” FS more useful than IopC;
“C” IopC and FS equally useful; or
“D” Both techniques non-contributory.

In cases in which IopC was not available, the FS was classified as either “good” or “poor” in quality.

Results

Of the 103 cases, 60 were males and 43 were females. Seventeen were children <20 yr of age. In 18 cases, the biopsies were stereotactic; in 52, open biopsies were performed; in the remaining 33, the type of biopsy was unspecified. Most tissue specimens had been labeled “brain tumor,” whether or not the lesion was neoplastic. In 35 cases, the lesion site was specified. Intraoperative imprint smears were made in 85 cases. There was concordance between the Iop consultation diagnosis and the final diagnosis in 97 cases (94%).

The 82 cases in which IopC and FS were both performed were categorized as "A" to "D," depending on whether the cytology smear or frozen section was more useful for diagnosis. Table 1 summarizes their relative usefulness for particular diagnoses during Iop consultation. Discrepancies between the Iop diagnosis and the final diagnosis were observed in 6 cases, as summarized in Table 2.

Discussion

Surgical techniques in brain lesions have evolved over the past few decades. Advances such as microscopic

Fig. 2. Cytology smears from a lymphoma (left) and a medulloblastoma (right). These small round blue cell tumors were difficult to differentiate on frozen sections, but cytology shows a clear difference. Lymphoma cells have coarse chromatin. Numerous lymphoglandular bodies (arrow, left panel) are identified in the lymphoma. The primitive neuroectodermal tumor (PNET) category of neoplasms exhibits nuclear molding (arrow, right panel) and contains fine chromatin.
surgery, improved imaging techniques, stereotactic biopsies, endoscopic surgery, and fine needle aspiration biopsies have posed challenges for diagnostic pathologists. Intra-operative (Iop) consultations about the pathology of brain lesions are requested for a number of reasons:

1. To confirm that a lesion has been identified;
2. To differentiate neoplastic from reactive lesions;
3. To differentiate metastatic from primary neoplasms;
4. To estimate the degree of malignancy;
5. To determine tumor margins (eg, dural margin in meningiomas);
6. To obtain tissue for culture or other special procedures; and
7. To ensure safe handling and processing of tissue (eg, Creutzfeldt-Jakob disease).

Brain tissue is inherently soft, especially when edematous, and this renders frozen sections prone to

Table 2. Cases in which there were discrepancies between the intra-operative diagnosis and the final diagnosis.

<table>
<thead>
<tr>
<th>Diagnosis based on intra-operative consultation</th>
<th>Final diagnosis</th>
<th>Number of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meningioma</td>
<td>Atypical meningioma</td>
<td>2</td>
</tr>
<tr>
<td>Epithelial neoplasm with atypia and necrosis</td>
<td>Atypical meningioma</td>
<td>1</td>
</tr>
<tr>
<td>Meningioma</td>
<td>Malignant meningioma</td>
<td>1</td>
</tr>
<tr>
<td>Metastatic tumor</td>
<td>Glioblastoma multiforme</td>
<td>1</td>
</tr>
<tr>
<td>Small round blue cell tumor; pineoblastoma versus pineocytoma</td>
<td>Anaplastic small cell astrocytoma</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>6</td>
</tr>
</tbody>
</table>

Fig. 3. Cytology smear of meningioma showing wispy cytoplasmic processes (arrow) that resemble the fibrils of astrocytoma.
ice-crystal artifacts. Despite modifications described in the literature [4], it is difficult in some cases to obtain good quality frozen sections (FS). Cytological material in the form of imprints is of considerable value as it provides exquisite cellular details without any freezing artifact. FS, however, is still deemed the gold standard in Iop consultations. A comparison of these techniques is therefore important, especially in view of the limited quantity of material provided by stereotactic biopsies and fine needle aspirations. In cases of AIDS, the smear technique is of great help, since it can avoid the need for FS, which poses a risk of contaminating the cryostat. We therefore studied the utility and accuracy of Iop consultations in brain lesions, comparing the usefulness of the techniques (FS versus IopC) and the limitations and pitfalls of each.

In 32 cases, IopC was more useful than FS (ie, Category “A”). Most of these cases were astrocytic neoplasms (22/32). Astrocytomas are the commonest primary neoplasms of the brain. Except rare cases where mesenchymal elements are a significant component of the tumor, these lesions are soft in consistency and tend to show freezing artifact. IopC showed characteristic “copper-wire” fibrillary architecture in H & E stained smears (Fig. 1), a feature that was not apparent in FS. Nuclear details were also better appreciated in IopC. FS, however, was more valuable for the diagnosis of glioblastoma multiforme exhibiting palisading necrosis. This characteristic necrosis also differentiated glioblastoma multiforme from metastatic tumors.

Small round blue cell tumors include a wide variety of neoplasms. In the present study, lymphoma and medulloblastoma exhibited similar appearances on FS. The smears, however, distinguished these lesions (Fig. 2). Lymphoma cells were discohesive and contained nuclei with clumped chromatin, at times with nucleoli. A background of lymphoglandular bodies was characteristic. These are fragments of lymphoid cytoplasm which, being fragile, break off during the smearing process. These are differentiated from other debris by the fact that they are identical in appearance to the intact cytoplasm of adjacent cells. Medulloblastoma cells, on the other hand, were loosely cohesive, contained nuclei with fine “salt and pepper” chromatin, and showed focal molding.

Meningiomas are firm neoplasms and do not yield good smears. The “wispy” cytoplasm (Fig. 3) could mislead the pathologist to consider such tumors as astrocytic neoplasms on IopC, an observation also made by others [5]. On FS a diagnostic whorling pattern was seen. Most meningiomas therefore fell into category “B.”

Metastatic tumors showed a variety of results. Many (6/11) were better recognized on FS due to preservation of the architecture. In some (4/11) cases, IopC was more useful, especially in melanomas or breast tumors. In one case of metastatic colon cancer, IopC and FS were equally diagnostic.

Non-specific reactive astrocytosis was difficult to differentiate from low-grade astrocytic neoplasms since both showed increased cellularity and mild cytologic atypia. These lesions were responsible for the majority of non-contributory IopC and FS. Specific non-neoplastic conditions (eg, infarct or abscess) were better recognized on FS.

In ependymomas, especially of high-grade, the appearance on IopC mimicked small round blue cell tumor, an observation also made by other authors [6]. FS, however, showed the presence of perivascular rosettes, a helpful diagnostic feature. Oligodendroglialoma was better diagnosed on IopC. The oligodendrogial component in a mixed glial tumor was difficult to recognize, these being diagnosed as astrocytic neoplasms. Some pathologists view this feature as important [7], but others do not [8].

Vascular lesions did not yield good results on IopC or FS; both techniques were non-contributory in this lesion. These lesions are paucicellular and delicate, rendering unsatisfactory cytology and frozen sections respectively.

Three of the 6 discrepancies between intraoperative and final diagnoses were related to diagnosing meningiomas and assigning histologic grades to them. The authors were unable to detect frequent mitoses in what appeared to be “typical” meningiomas. In the case of malignant meningioma, brain invasion was not evident in the FS slide. This criterion, however, has been debated as an indication of malignancy [9]. In one case in which there was cytological atypia and necrosis, the authors were unable to ascertain the histogenesis as a meningioma; the lesion was called a malignant tumor and was not recognized to be of meningeal origin. To complicate matters, four of these patients were atypical in age and sex (ie, 32 yr male,
79 yr female, 66 yr male, 77 yr female), in contrast to the common occurrence in middle aged women.

One glioblastoma multiforme was diagnosed as a metastatic tumor. This case showed marked necrosis and a few bizarre cells both in FS and IopC, which were interpreted as those of metastatic malignancy. The permanent sections revealed features of glioblastoma multiforme with foci of marked cytological atypia.

A pineal tumor in a young adult had features of a small round blue cell tumor, and a differential diagnosis of pineoblastoma or pineocytoma was rendered. On permanent sections a small cell variant of astrocytoma, proven by immunohistochemistry, was diagnosed.

One potential pitfall could be misinterpretation of normal or neoplastic choroid plexus for metastatic papillary carcinoma. A case in this study contained normal choroid plexus tissue that the authors were able to identify correctly, correlating with the site. A detailed clinical history and discussions with the clinician are of utmost help in such cases, a privilege not available in retrospective studies.

The aim of this study was to determine the accuracy of diagnosis of Iop CNS consultations and to study the utility of IopC and FS techniques. The authors recognize that the numbers in certain categories of lesions are insufficient to draw significant conclusions. Overall, the Iop consultations for brain lesions provided accurate diagnoses in a high percentage of cases (94%). Several studies have documented the accuracy as between 86% to 95.3% [10]. The entities that are most subject to misinterpretation are atypical versus malignant meningiomas, small cell tumors in unusual sites, and metastatic tumors versus high-grade gliomas.

While the utility of IopC and FS techniques may not be so different in other organs, IopC was superior to FS in most primary CNS neoplasms, due to the better cytological details and the absence of freezing artifacts, as also noted by other authors [3,5,11-13]. Generally, IopC was superior to FS in gliomas, some metastatic lesions, and small round blue cell tumors including lymphomas. FS was the better technique for diagnosis of meningiomas, some metastatic tumors, and glioblastoma multiforme, and also for reactive processes. Vascular lesions were difficult to diagnose by either technique. Pitfalls of IopC were the absence of architecture and the difficulty of differentiating astrocytic cells from meningeal cells. Pitfalls of FS were the poor cytological details and the absence of fibrillary background in astrocytic neoplasms. Based on these observations, the present authors concur with other authors that it is helpful to use both techniques [14,15].

Acknowledgement

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