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Original Contributions

Frozen section discrepancy in the evaluation of nonneoplastic central nervous system samples

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Abstract Frozen section (FS) for intraoperative evaluation of central nervous system (CNS) lesions provides the neurosurgeon with a rapid preliminary pathologic diagnosis. Diagnosis of nonneoplastic lesions is particularly challenging in this venue. To highlight common diagnostic pitfalls, we sought to identify discrepancies between FS and final diagnoses among nonneoplastic CNS samples via a retrospective review of 303 FS cases encountered from 1997 to 2006. Thirty-nine (12.9%) discrepant diagnoses were identified, of which 27 were clinically suspected tumors. Final diagnoses in the discrepant group included the following: inflammatory lesions (n = 8, 20.5%), malformation of cortical development-cortical dysplasia (n = 5, 12.8%), gliosis (n = 5, 12.8%), vascular malformations (n = 5, 12.8%), demyelination/progressive multifocal leukoencephalopathy (n = 3, 7.7%), infarct (n = 3, 7.7%), hemorrhage/blood clot (n = 3, 7.7%), and no pathologic changes (n = 3, 7.7%). The remaining 4 (10.2%) discrepant cases involved one case each of amyloid angiopathy, nonspecific vasculopathy, vasculitis, and meningioangiomatosis. Nonneoplastic lesions are often more challenging than neoplastic lesions at FS, particularly because they are less commonly sampled for FS and, therefore, less familiar to pathologists.

Keywords: Frozen section; Nonneoplastic; Intraoperative consultation; Discrepant diagnosis; Central nervous system

1. Introduction

Central nervous system (CNS) frozen section (FS) consultation specimens usually target radiographically evident lesions; frequently, a neoplastic process is suspected. The diagnostic yield [1-3] and rate of concordance between FS and permanent diagnoses [1,4-7] have been reported to be consistently greater than 90%. In contrast, most series reporting on nonneoplastic CNS pathologic condition are much smaller with widely variable diagnostic yields that range from 20% to 84% [3,8-11]. The FS discrepancy rate of nonneoplastic lesions is even less established. Brainard et al [9] found 16 (34.8%) of 46 of nonneoplastic cases to be either nondiagnostic (n = 14) or misdiagnosed (n = 2) at the time of FS. One cytology-based study [12] showed a complete concordance rate between intraoperative consultation and final diagnosis of 37.5% and partial rate of 78% in their series of 112 nonneoplastic cases. These relatively small series suggest that the FS to final diagnosis concordance rate is much lower than similar tumor-based studies. Neither series, however, attempted to categorize or classify the discrepancies.

Herein, we present a large single-institution experience of nonneoplastic cases sent for FS consultation. Examination of discrepancies between the FS and final permanent diagnoses adds to the current understanding of the particular challenges that nonneoplastic CNS lesions can present at the time of FS.

2. Materials and methods

Upon receiving institutional review board approval, a search was performed to retrospectively identify all nonneoplastic CNS FS cases encountered during a 10-year period. The 303 cases identified were determined

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by the final diagnosis, and an FS neoplastic diagnosis did not preclude inclusion. The FS diagnoses were compared to the final diagnoses, and discrepancies were identified. Very few intraoperative cytologic preparations were performed during the study period, and the interpretations of these procedures were not included in the analysis. In effort to identify sampling differences between the discrepant and nondiscrepant groups, the number of specimens submitted for FS, total specimens submitted, FS slides examined, and total slides examined were tabulated. Statistical comparisons were performed using the Wilcoxon 2-sample test and χ^2 test, and a P value of .05 or less was considered statistically significant.

3. Results

Thirty-nine (12.9%) discrepant diagnoses were identified of 303 total nonneoplastic diagnoses; patients with these discrepant diagnoses constituted the study group. The mean age of the patients in the study group (22 females, 17 males) was 37.6 years (range, 2-73 years). The patients within the nondiscrepant group (126 females, 138 males) had a mean age of 46.3 years (range, 1-87 years). The discrepant group had a mean of 1.4 FS specimens, 1.5 FS slides, 2.5 total specimens, and 5.4 permanent slides evaluated, and the nondiscrepant group had a mean of 1.6 FS specimens, 1.8 FS slides, 2.3 total specimens, and 4.9 permanent slides evaluated. Although the nondiscrepant group tended to have more FS specimens and slides processed with fewer permanent specimens and slides, none of these differences were statistically significant. The proportion of stereotactic biopsies also did not differ significantly, with 25 (64.1%) of 39 of patients in the discrepant group and 180 (68.2%) of 264 undergoing stereotactic biopsy. All but 2 cases within the discrepant group were examined by a neuropathologist. In the nondiscrepant group, all but 4 cases were seen by a neuropathologist at FS with the final diagnosis rendered by a neuropathologist in all but 2 cases.

Final diagnoses in the discrepant case group included the following (Table 1): inflammatory lesions (n = 8; Figs. 1A, B), malformations of cortical development (n = 5; Figs. 1C, D), gliosis (n = 5; Figs. 2A-B), vascular malformations (n = 5; Figs. 2C-D), demyelination/progressive multifocal leukoencephalopathy (n = 3; Figs. 3A-D), infarct (n = 3; Figs. 4A-D), hemorrhage/blood clot (n = 3), and no pathologic changes (n = 3). The remaining 4 discrepant cases involved one case each of amyloid angiopathy, nonspecific vasculopathy, vasculitis, and meningioangiomatosis.

Discrepant FS diagnoses were grouped into 3 categories (Table 1): nonspecific findings (n = 23), tumor/suggestion of tumor (n = 11), and misclassified benign lesions (n = 5). Inflammatory lesions (n = 6), vascular malformations (n = 4), and malformations of cortical development (n = 3) were the most frequent final diagnoses in the nonspecific FS diagnosis category. Of the 11 cases diagnosed as or suggestive of a tumor, gliosis (n = 4) and malformation of cortical development (n = 2) were the most frequent final diagnoses. One of the 11 patients underwent biopsy 7 months later, and this was diagnostic of low-grade glioma. Seven of the remaining 10 patients were observed for 31 to 103 months and have not manifested a CNS neoplasm. Two of the remaining 10 patients were immediately lost to follow-up, and 1 died within days of admission from a myocardial infarct. The 5 misclassified benign lesions most commonly revealed no pathologic abnormality (n = 2).

Table 2 summarizes the preoperative clinical impressions for each discrepant category. Thirty-five (90%) cases targeted one or more radiographically evident lesions. Of these, 27 surgeries were performed for suspected tumors, and 8 surgeries were aimed at suspected nonneoplastic processes, mostly vascular malformations. The remaining 4 surgeries were performed to rule out either meningitis or vasculitis.

4. Discussion

Classifying the discrepant FS diagnoses into 3 broad categories emphasizes important factors that can contribute to FS discrepancy in neuropathologic cases—sampling, bias, and misinterpretation. Given the discrepancy rate of nearly 5 times that of neoplastic CNS lesions reported from our own institution (12.9% vs 2.7%) [13], these factors may present more of a pitfall when confronted with nonneoplastic lesions.

Many of the 23 cases marked by nonspecific findings at FS (56% of discrepant cases) illustrate the sampling problems inherent to FS. Diagnostic yields for nonneoplastic CNS pathologic condition are reported to range from 20% to 84% [3,8-11]. Although most FS (90%) were targeted at specific lesions, a subset represented diffuse or potentially multifocal processes, which often pose even greater diagnostic difficulty at FS. The surgeon also may be occasionally off target, resulting in nondiagnostic tissue. It is also well recognized that additional deeper sections generated from the same paraffin blocks may uncover pathologic condition not evident on the first tissue sections. In addition, not all available tissue sent for FS is subjected to FS processing, as it is advisable to reserve some unaltered tissue for paraffin embedding. This ensures good quality well-fixed specimens for evaluation and final diagnosis but does potentially contribute to sampling error. Similarly, not all sampled tissue is designated for FS by the surgeon.

Sampling error likely played a key role in the final diagnosis group of inflammatory lesions, which were all signed out with nonspecific FS diagnoses. Although not inconsistent with the final diagnoses, key features were not identified at the time of FS, such as chronic inflammation or granulomas.

The 11 cases diagnosed as tumors or suggestive of tumor (30.8% of discrepant cases) expose the possibilities of bias and misinterpretation in FS diagnosis. One of the tenets of surgical neuropathologic condition is to correlate the