Prognostic Implications of Atypical Histologic Features in Choroid Plexus Papilloma

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Abstract
The prognostic significance of atypical histologic features in choroid plexus tumors remains uncertain. Therefore, a series of 164 choroid plexus tumors was evaluated for the presence of atypical histologic features, including mitotic activity, increased cellularity, nuclear pleomorphism, blurring of papillary growth pattern, and necrosis. The impact of histopathologic and clinical features on the probability of recurrence and survival was investigated. Twenty-four tumors displaying frank signs of malignancy were diagnosed as choroid plexus carcinoma according to World Health Organization criteria. Of 124 choroid plexus papillomas that had not received adjuvant treatment, 46 tumors (37%) displayed at least one atypical feature, including increased cellularity (n = 25 [20%]), mitotic activity (≥2 mitoses per 10 high-power fields; n = 19 [15%]), nuclear pleomorphism (n = 16 [13%]), solid growth (n = 15 [12%]), and necrosis (n = 5 [4%]). Only one tumor-related death, but 10 recurrences, were observed on a mean observation time of 58 months. On univariate analysis, incomplete surgical resection (p = 0.03) and mitotic activity (p < 0.001) were the only clinicopathologic factors associated with recurrence. Using a multivariate model, an independent effect of mitotic activity on the probability of recurrence could be confirmed (p = 0.001). Because mitotic activity is the sole atypical histologic feature independently associated with recurrence, we propose to define atypical choroid plexus papilloma by mitotic activity (≥2 mitoses per 10 high-power fields) corresponding to World Health Organization grade II, thus adjoining other intermediate tumor entities associated with increased mitotic activity such as atypical meningioma. Close follow up of patients harboring atypical choroid plexus papillomas may be warranted.

Key Words: Atypical choroid plexus papilloma, Choroid plexus carcinoma, Diagnosis, Gross total resection, Mitotic activity, Prognosis.

INTRODUCTION
Choroid plexus tumors are rare intraventricular papillary neoplasms derived from choroid plexus epithelium, which account for only between 0.4% and 0.6% of all intracranial neoplasms, but represent 13% of pediatric brain tumors that occur within the first year of life (1). In contrast to benign choroid plexus papillomas (World Health Organization [WHO] grade I), choroid plexus carcinomas (WHO grade III) are characterized by frank signs of malignancy, that is, frequent mitoses, nuclear pleomorphism, increased cellular density, blurring of the papillary growth pattern, and necrosis (1, 2). Histologic grading is recognized as an important prognostic factor in choroid plexus tumors (1, 3–8) and also affects the decision toward adjuvant radiotherapy and chemotherapy (9–12). The distinction between choroid plexus papilloma and choroid plexus carcinoma, however, is not always clear because some tumors show only one or a few atypical histologic features but are not unequivocally malignant (1, 3, 4, 9, 13–19). These tumors have been designated atypical choroid plexus papilloma, but clear diagnostic criteria have not been established and data on prognosis remain scarce (4, 9, 20). Reflecting these uncertainties, atypical choroid plexus papilloma did not receive a clear definition and grading in the current WHO classification of nervous system tumors (2). We thus aimed to examine frequency and prognostic relevance of atypical histologic features in a large series of choroid plexus tumors. We demonstrate that mitotic activity is the sole independent factor influencing the probability of recurrence in choroid plexus papillomas.

MATERIALS AND METHODS

Patients
Specimens from cases with a file diagnosis of choroid plexus tumor were retrieved from the archives of the
Institutes of Neuropathology Munster, Essen, Tübingen, and Bielefeld, Germany. Twenty-two of the cases were examined as part of the Société Internationale d’ Oncologie Pédiatrique choroid plexus tumor (CPT-SIOP 2000) study. Only primary tumors (no recurrences) were included. Some of the cases had been included in previous studies on histology and genetics of choroid plexus tumors (4, 21, 22). To delineate choroid plexus tumors from other entities, immunohistochemistry was performed using a panel of conventional diagnostic markers as well as antibodies directed against potassium channel Kir7.1 (highly and specifically expressed in choroid plexus tumors [22]) and hSNF5/INI-1 (BAF47, not expressed in most atypical specifically expressed in choroid plexus tumors [22]) and directed against potassium channel Kir7.1 (highly and specifically expressed in choroid plexus tumors [22, 23]) using the avidin–biotin method on an automated staining system (TechMate; DAKO, Glostrup, Denmark). Of 197 cases with a file diagnosis of choroid plexus tumor that were reviewed, 175 cases were confirmed to be choroid plexus tumors; other diagnoses included atypical teratoid/rhabdoid tumor (young children, median age: 3 years [range, 1–17 years], n = 5), papillary tumor of the pineal region (adolescents, median age: 25 years [range, 10–29 years], n = 7) (24), cerebral metastasis of carcinoma (adults, median age: 51 years [range, 44–71 years], n = 6) as well as cases of glioblastoma, medulloblastoma, endolymphatic sac tumor, and xanthogranuloma of the choroid plexus. Data on tumor location, extent of surgical resection, adjuvant treatment, and postoperative course were compiled by reviewing patient records. Moreover, general practitioners, pediatricians, and neurosurgeons were contacted to provide follow-up information on recurrence and survival. Sufficient clinical information could be retrieved for 94% of the cases (n = 164).

### Histopathology

Neuropathologic reevaluation of choroid plexus tumors involved assessment of histologic features proposed as atypical by the current WHO classification (2). The presence or absence of high cellularity, solid growth, necrosis, and nuclear pleomorphism was assessed by 3 raters (AJ, MH, and WP). Mitotic activity was assessed by counting mitoses in 10 randomly selected high-power fields (HPF, area of view 0.23 mm²). In line with previous studies (4), increased mitotic activity was defined as the presence of more than one mitosis/10 HPF. In case of discrepancies, cases were jointly reviewed and a unanimous decision was reached in all cases. Supplementary data on histologic rating, including various grading examples, is available at the author’s web site (http://neuropathologie.klinikum.uni-muenster.de/plexustumors/). Choroid plexus tumors displaying frank signs of malignancy, defined here as the presence of at least 4 of the previously mentioned atypical histologic features, were classified as choroid plexus carcinoma. The prognostic value of atypical histologic features in the remaining choroid plexus papillomas was further evaluated.

### Statistics

Comparison of patient characteristics was done by the Fisher exact test or Mann-Whitney U test. Before survival analysis, CART analyses (25) were performed to determine an optimal age categorization. Partitioning the ages of patients into groups ≤8 years recurrence versus >8 years was found to yield most differing groups. Univariate survival analysis of clinical (age, location, and extent of resection) and histopathologic (cellularity, mitotic activity, nuclear pleomorphism, solid growth, and necrosis) cofactors was performed using Kaplan-Meier estimation of survival curves and the log-rank test on significant differences. To adjust for confounders among cofactors, a multivariate Cox proportional hazards model was fit. Forward stepwise model selection was performed by the Wald approach, the saturated model including as cofactors all of the previously mentioned clinical and histologic cofactors as well as the interaction terms “age*mitosis” and “age*cellularity.” Statistical analyses were performed using software packages S-PLUS version 7.0 (Insightful Corp., Seattle, WA) and SPSS version 13.0 (SPSS Inc., Chicago, IL).

### RESULTS

As shown in Table 1, the 24 cases of choroid plexus carcinoma as well as the 140 cases of choroid plexus papilloma differed substantially with regard to patient characteristics, treatment, and outcome. As compared with choroid plexus papillomas, patients harboring choroid plexus carcinoma were significantly younger and more frequently had supratentorial tumors. Gross total resection could only be achieved in 50% of choroids plexus carcinomas (n = 12). Despite adjuvant treatment, the majority of choroid plexus carcinoma patients (14 of 24) experienced recurrences on a median follow up of 9 months (range, 1–49 months). Tumor-related death ensued in 10 of 24 cases with a median follow up of 16 months (range, 1–36 months).

In contrast, gross total resection could be achieved in more than 90% of choroid plexus papillomas. Patients harboring infratentorial choroid plexus papillomas were significantly older as compared with supratentorial tumors.

| TABLE 1. Characteristics of Patients With Choroid Plexus Papilloma and Patients With Choroid Plexus Carcinoma |
|---------------------------------|--------------------|------------------|
| Patients With Choroid Plexus Papilloma (n = 140) | Patients With Choroid Plexus Carcinoma (n = 24) |     |
| Age (median, interquartile range) | 15 (1–42) years | 2 (1–4) years | p < 0.01 |
| Sex (male:female) | 1.3: 1 | 1.4: 1 |     |
| Location | | |     |
| Lateral ventricles | 62 (44.3%) | 23 (95.8%) | p < 0.001 |
| Third ventricle | 9 (6.4%) | 1 (4.2%) |     |
| Fourth ventricle | 68 (48.6%) | 1 (4.2%) |     |
| Ectopic (spinal) | 1 (0.7%) | 1 (4.2%) |     |
| Treatment | | |     |
| Gross total resection | 128 (91.4%) | 12 (50%) | p < 0.001 |
| Radiotherapy | 9 (6.4%) | 4 (16.7%) |     |
| Chemotherapy | 9 (6.4%) | 11 (45.8%) | p < 0.001 |

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Sixteen patients with choroid plexus papilloma (11%) had received heterogeneous adjuvant treatments; these patients were excluded from further analysis. Forty-six (37%) of the remaining 124 choroid plexus papillomas displayed at least one atypical histologic feature (Table 2). Eighteen choroid plexus papillomas displayed one, 22 displayed 2, and 6 displayed 3 atypical features. Most frequently encountered features were increased cellularity as well as mitotic activity (≥2 mitoses/10 HPF; for details, see Table 2). Median mitotic activity in choroid plexus papillomas was 0 (interquartile range: 0–1). Increased mitotic activity (≥2 mitoses/10 HPF) was encountered in 19 cases (15%). In contrast to increased cellularity, increased mitotic activity was only rarely encountered as an isolated atypical feature (7 cases vs 1 case).

Irrespective of the presence or absence of atypical histologic features, overall survival in patients with choroid plexus papilloma was favorable: only 1 tumor-related death was observed with a mean observation time of 58 months; recurrent tumor growth necessitating neurosurgical intervention occurred in 10 patients. The presence of any atypical histologic feature, however, tended to be associated with increased probability of recurrence (p = 0.06, log-rank test) (Fig. 1B; Table 2). We thus aimed to determine if individual histologic factors might especially contribute toward an increased risk of recurrence in choroid plexus papillomas. Indeed, on univariate analysis, mitotic activity (≥2 mitoses/10 HPF) was significantly associated with increased probability of recurrence (p = 0.001, Fig. 2), whereas incomplete tumor resection was the only clinical factor significantly linked to recurrence (p = 0.03). On multivariate analysis taking into account all of these clinical and histologic cofactors, mitotic activity remained the only independent factor influencing the probability of recurrence (p = 0.001). Based on Kaplan-Meier estimates, the presence of mitotic activity was associated with a 4.9-fold higher probability of recurrence after 5 years of follow up. Malignant progression was not observed in any of the 4 recurrent choroid plexus papillomas that could be examined.

Univariate analysis (log-rank [Mantel-Cox]). Follow-up data on surgical resection in 124 patients with choroid plexus papilloma not receiving adjuvant treatment were analyzed.

**TABLE 2. Effect of Clinical and Histologic Features on the Probability of Recurrence in Choroid Plexus Papillomas**

<table>
<thead>
<tr>
<th>Frequency</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young age (&lt;8 years)</td>
<td>47 (38%)</td>
</tr>
<tr>
<td>Young age (&gt;8 years)</td>
<td>77 (62%)</td>
</tr>
<tr>
<td>Supratentorial location</td>
<td>60 (48%)</td>
</tr>
<tr>
<td>Gross total resection</td>
<td>118 (95%)</td>
</tr>
<tr>
<td>Any atypical histologic feature</td>
<td>46 (37%)</td>
</tr>
<tr>
<td>Increased cellularity</td>
<td>25 (20%)</td>
</tr>
<tr>
<td>Mitotic activity (≥2 mitoses/10 high-power field)</td>
<td>19 (15%)</td>
</tr>
<tr>
<td>Nuclear pleomorphism</td>
<td>16 (13%)</td>
</tr>
<tr>
<td>Solid growth</td>
<td>15 (12%)</td>
</tr>
<tr>
<td>Necrosis</td>
<td>5 (4%)</td>
</tr>
</tbody>
</table>

![FIGURE 1](http://jnen.oxfordjournals.org/). Recurrence-free survival in choroid plexus papilloma. Kaplan-Meier analysis of (A) overall survival and (B) recurrence in choroid plexus papilloma without any atypical histologic feature as compared with choroid plexus papilloma with 1, 2, or 3 atypical features. Log-rank test, p < 0.05.

![FIGURE 2](http://jnen.oxfordjournals.org/). Effect of mitotic activity on recurrence in choroid plexus papilloma. Kaplan-Meier analysis of recurrence in choroid plexus papilloma according to mitotic activity (≥2/10 high-power field). Log-rank test, p < 0.001.
DISCUSSION

The question if histologic features in choroid plexus papillomas influence prognosis has remained unsettled because most series were too small to allow for statistical analysis. Moreover, because uniform diagnostic criteria for atypical choroid plexus papilloma have been lacking (2), this problem has been virtually impossible to address by review of previously published cases.

The present study represents the largest series of choroid plexus tumors reported to date. Patient characteristics correspond closely to a meta-analysis of previously published cases with regard to male:female ratio and age at diagnosis, but also confirm that choroid plexus tumors are more frequently located supratentorially in younger patients (3). Importantly, our data also confirm the overall benign course of choroid plexus papilloma with regard to survival in contrast to the dismal prognosis in choroid plexus carcinoma (2–4, 6, 12) as well as the impact of gross total surgical resection on recurrence (3, 6).

Among clinical and histologic factors examined in the present series, mitotic activity (≥2 mitoses/10 HPF), present in 19 of 124 cases (15%), was the only atypical histologic feature significantly associated with recurrence in choroid plexus papillomas, the probability of recurrence being 4.9-fold higher after 5 years of follow up. We therefore propose to define atypical choroid plexus papilloma by mitotic activity (≥2 mitoses/10 HPF) corresponding to WHO grade II, thus adjoining other intermediate tumor entities associated with increased mitotic activity such as atypical meningioma (26).

The findings of the present study confirm earlier observations linking mitotic activity with poor prognosis and malignant progression in choroid plexus tumors (4, 18, 27). The failure of 2 other series to detect an influence of mitotic activity on recurrence (7, 9) might well be related to sample size (7) as well as patient heterogeneity, including a high percentage of incompletely resected tumors (9). Several authors have demonstrated lower Ki-67 proliferation indices in choroid plexus papilloma as compared with choroid plexus carcinoma (28, 29) and high MIB-1-labeling indices have also been associated with less favorable postoperative outcome in choroid plexus carcinomas and in one case of choroid plexus papilloma with atypical histology (15). We would thus have been highly interested to study the impact of Ki-67 labeling on recurrence and survival in choroid plexus papilloma. Because sufficient homogenously processed paraffin-embedded material was not available for many of the cases of this retrospective study, however, this task will need to be accomplished within ongoing prospective trials.

Besides mitotic activity, a plethora of other histologic features has been used to define atypical choroid plexus papilloma (1, 3, 4, 9, 13–17); histologic features deemed atypical have been reported in as many as 15 of 26 (58%) choroid plexus papillomas (9). Notably, however, none of these studies had used multivariate survival analysis to address the impact of histologic features on recurrence or survival.

In the present series, the frequency of atypical features was somewhat lower (37%). Moreover, our data clearly demonstrate that besides mitotic activity, neither increased cellularity nor other histologic features such as nuclear pleomorphism, solid growth, and necrosis are significantly associated with recurrence in choroid plexus papillomas. Because no significant effect or interaction of age on recurrence could be detected, our results do also not support anecdotal evidence that high cellularity and mitotic activity in young children might have a better prognostic value than in adults. The prognostic value of brain invasion in choroid plexus papilloma is controversial (2, 4, 7, 30). Because most choroid plexus papilloma samples of our series did not contain brain tissue, this item, which is prone to sampling bias, was not included in analysis.

Immunohistochemistry might possibly also contribute to identify tumors at risk of recurrence; it has been previously reported that S-100 expression status and absent transthyretin immunoreactivity both are associated with a more aggressive clinical course (4). Expression of polysialylated isoforms of neural cell adhesion molecule (16) as well as CD44 (14) have been described in atypical choroid plexus papilloma and choroid plexus carcinoma, but their influence on recurrence will need to be validated.

To conclude, mitotic activity is the sole atypical histologic feature independently associated with recurrence in choroid plexus papillomas. We propose to define atypical choroid plexus papilloma by mitotic activity (≥2 mitoses per 10 HPF) corresponding to WHO grade II. The results of this retrospective study might help to establish clear diagnostic criteria for choroid plexus tumors in therapeutic trials such as the ongoing CPT-SIOP 2000 study. Close follow up of patients harboring mitotically active atypical choroid plexus papilloma may be warranted.

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