Lack of histopathological correlation of malignant ependymomas with postoperative survival

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It is widely believed that an important determinant of clinical behavior and prognosis in patients harboring an ependymoma is the histological grade of malignancy of the tumor. Excluding from the present analysis examples of ependymoblastoma (a highly cellular, embryonal tumor occurring in children, with a notably poor prognosis and a tendency to subarachnoid spread), an attempt was made to correlate 15 cases of histologically malignant ependymoma with clinical recurrence and postoperative patient survival times. Ten patients (67%) were alive from 15 months to 14 years after surgery (median survival time 8.8 years); one patient had a histologically benign recurrence 11 years after surgical resection. Five patients (33%) died from a local recurrence of their tumor; their postoperative survival times ranged from 13 months to 6 years (median 2.5 years).

The prognosis of malignant ependymomas is therefore highly variable. No correlation was possible between the tumor’s histological features, site, or likelihood of recurrence. This lack of clinicohistopathological concordance contrasts with the known correlations that exist in astrocytomas.

KEY WORDS • malignant ependymoma • prognosis • ependymoma • postoperative survival • tumor • recurrence • brain neoplasm

IDENTIFICATION of morphological characteristics that are prognostically helpful in determining survival time is of primary importance in the assessment of many cerebral gliomas. Generally, an increase in histological anaplasia corresponds to greater clinical malignancy. Features of glial anaplasia include increased cellular density, cytological pleomorphism, loss of distinctive differentiating structures, high mitotic activity, spontaneous necrosis, and vascular endothelial proliferation. The prognostic utility of these histopathological features is well established in astrocytic gliomas but, save perhaps for necrosis, is much more controversial in the case of oligodendrogliomas. There is widespread belief that high-grade (histologically more malignant) ependymomas have a worse postoperative prognosis than low-grade ependymomas. However, many inconsistencies and exceptions are found in those reports, and there is a lack of consensus on the nomenclature applied to the less differentiated tumors. With one exception, no distinction has been made between the clinicopathological correlations applicable to the highly cellular, monomorphic embryonal tumor designated as ependymoblastoma and those concerning otherwise well-differentiated ependymomas which show histological evidence of anaplasia and to which the term “malignant ependymoma” is more appropriate.

In this study 15 cases of histologically malignant ependymoma have been correlated with their postoperative course. The findings indicate that, provided ependymoblastomas are excluded from the analysis, the histological features usually regarded as indicative of biological malignancy are of no predictive value in determining future recurrence or other subsequent clinical behavior.

Clinical Material and Methods

Table 1 summarizes our series of 15 malignant ependymomas. None of these patients has to our knowledge been included in previous studies. All but one patient (Case 7) were referred to one of us (L.J.R.) from other centers during the period 1967 to 1986, specifically because of the presence of malignant histological features. The diagnosis of tumor malignancy was based on the following criteria: high cellularity, increased mitotic activity, cellular or nuclear pleomorphism, loss of differentiating structures, focal necroses, and vascular endothelial proliferation. High cellularity alone was not
TABLE 1
Clinical features of 15 patients with histologically malignant ependymomas*

<table>
<thead>
<tr>
<th>Case No. (Accession No.)</th>
<th>Sex, Age at Presentation</th>
<th>Location of Tumor</th>
<th>Treatment for Original Tumor</th>
<th>Survival Time After First Op</th>
<th>Status; Last Follow-Up Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (C5737)</td>
<td>M, 8 yrs supratentorial</td>
<td></td>
<td>X</td>
<td>14 yrs</td>
<td>alive (1986: malignant meningioma)</td>
</tr>
<tr>
<td>2 (C1610)</td>
<td>M, 20 yrs infratentorial (4th ventricle)</td>
<td></td>
<td>X</td>
<td>12.5 yrs</td>
<td>alive &amp; well, no recurrence but blind</td>
</tr>
<tr>
<td>3 (C1946/5757)</td>
<td>M, 5 yrs infratentorial (4th ventricle)</td>
<td></td>
<td>X(i)</td>
<td>11 yrs</td>
<td>alive, but benign local recurrence after 11 yrs</td>
</tr>
<tr>
<td>4 (C579)</td>
<td>F, 19 yrs infratentorial (4th ventricle)</td>
<td></td>
<td>X</td>
<td>9 yrs</td>
<td>alive &amp; well, no recurrence</td>
</tr>
<tr>
<td>5 (C2697)</td>
<td>M, 1.5 yrs infratentorial (4th ventricle)</td>
<td></td>
<td>X</td>
<td>9 yrs</td>
<td>alive, no recurrence</td>
</tr>
<tr>
<td>6 (C2633)</td>
<td>F, 2 yrs supratentorial</td>
<td></td>
<td>X</td>
<td>8.5 yrs</td>
<td>alive &amp; well, no recurrence</td>
</tr>
<tr>
<td>7 (81-4489)</td>
<td>F, 23 yrs infratentorial</td>
<td></td>
<td>X(i)</td>
<td>6 yrs</td>
<td>alive, no recurrence</td>
</tr>
<tr>
<td>8 (C5074)</td>
<td>M, 27 yrs spinal (intradural &amp; extramedullary)</td>
<td></td>
<td>X(i)</td>
<td>2.3 yrs</td>
<td>alive, no recurrence</td>
</tr>
<tr>
<td>9 (C4938)</td>
<td>M, 11 yrs supratentorial extraventricular</td>
<td></td>
<td>X</td>
<td>2 yrs</td>
<td>alive, no recurrence</td>
</tr>
<tr>
<td>10 (C5073)</td>
<td>F, 2 yrs infratentorial (4th ventricle)</td>
<td></td>
<td>X</td>
<td>1.3 yrs</td>
<td>alive, no recurrence, then lost to follow-up</td>
</tr>
<tr>
<td>11 (C2096)</td>
<td>M, 1 yr infratentorial (4th ventricle)</td>
<td></td>
<td>X</td>
<td>6 yrs</td>
<td>dead with clinical recurrence, no autopsy</td>
</tr>
<tr>
<td>12 (C1310)</td>
<td>F, 13 yrs supratentorial extraventricular</td>
<td></td>
<td>X</td>
<td>5 yrs</td>
<td>dead, recurrence after 4½ yrs, no autopsy</td>
</tr>
<tr>
<td>13 (C1888)</td>
<td>F, 22 yrs infratentorial (lateral recess)</td>
<td></td>
<td>X</td>
<td>2.5 yrs</td>
<td>dead with recurrence on CT, no autopsy</td>
</tr>
<tr>
<td>14 (C3280)</td>
<td>F, 19 yrs infratentorial</td>
<td></td>
<td>X</td>
<td>1.2 yrs</td>
<td>dead with recurrence, no autopsy</td>
</tr>
<tr>
<td>15 (C1087)</td>
<td>M, 1.3 yrs infratentorial (4th ventricle)</td>
<td></td>
<td>X(i)</td>
<td>1.1 yrs</td>
<td>dead with recurrence, no autopsy</td>
</tr>
</tbody>
</table>

* Sy = surgery (i = subtotal resection); Rx = postoperative radiotherapy; Ch = postoperative chemotherapy; CT = computerized tomography.

used as an isolated criterion, since typical ependymomas often display this feature. Purposely excluded were the ependymoblastomas, of which the clinicopathological features of 12 examples have previously been recorded.18 All biopsies were reviewed without knowledge of the age of the patient, type of treatment, or length of survival.

**Results**

**Patients' Age and Sex**

The 15 patients ranged in age from 1 to 27 years (median 11 years, mean 11.7 years). There was no significant difference in age incidence between patients with a supratentorial tumor and those with an infratentorial tumor. Seven tumors presented in females, and eight in males.

**Tumor Site**

The posterior fossa was the site most frequently involved (10 cases). Four tumors were supratentorial; one was located in the spinal canal. Eight intracranial tumors were related to one of the ventricles, two (Cases 9 and 12) were extraventricular, and in four tumors the relationship to a ventricular cavity was uncertain or unstated. The one intraspinal tumor (Case 8) presented as an intradural extramedullary mass.

**Histological Features**

All of the tumors contained areas of typical ependymoma, including ependymal rosettes (Fig. 1) or tubules, heavily fibrillated perivascular pseudorosettes, or a more compact arrangement of cells forming a cobblestone pattern. The cellular nuclei in those areas had a spherical or ovoid contour and displayed a delicate punctate chromatin pattern typical of ependymal cells. Every tumor, however, presented fields with variable degrees of cellular atypia and nuclear pleomorphism. Where the pattern of typical ependymoma was lost, the tumor tended to grow in homogeneous, densely cellular sheets (Fig. 2). The cells in those areas were enlarged,
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FIG. 1. Case 1 (14 years postoperative survival). Photomicrograph showing ependymal rosette in malignant ependymoma. PTAH, × 900.

FIG. 2. Case 1. Photomicrograph of another field showing loss of architectural pattern, increase in cellularity, and mitotic figures (arrows). H & E, × 600.

the cytoplasmic processes lost, and the nucleocytoplasmic ratio increased. One or more conspicuous nucleoli were often seen.

All of the tumors, except that in Case 7, contained areas of necrosis which ranged from small punctate foci consisting of only a few cells to large infarct-like zones (Fig. 3). Numerous capillary blood vessels were present, many of which showed considerable hyperplasia of the endothelial cells. Vascular endothelial proliferation (Fig. 4) was present in all but one case (Case 2), and was most marked in Cases 3, 6, 12, and 14.

Mitotic figures (Figs. 2 and 4) were easily found in all of the tumors and were especially numerous in the more cellular areas. In the latter, the great majority of tumors revealed two to four mitotic figures per high-power field, with some areas showing a higher rate. Some of the mitotic figures were atypical.

Therapy

The therapeutic modalities are shown in Table 1. Surgical excision, either subtotal or complete, was performed in all 15 patients. Postoperative radiation therapy was given to 12 patients, and chemotherapy to five. The radiation ports, individual treatment doses, and total amounts administered varied, as did the chemotherapeutic agents.

Survival Times and Outcome

Ten patients (67%) were alive from 15 months to 14 years after the original operation (median survival times 8.8 years, mean 7.6 years). Most of them are well and clinically disease-free, but one patient (Case 2) is blind. Metastatic development is not known to have occurred in any of the patients in this series. Two patients are of interest in that one (Case 3) had a recurrence which took place 11 years after surgery and which was histologically benign, whereas the other (Case 1) developed a malignant meningioma, presumably radiation-induced, 14 years after surgical excision and radiotherapy for a malignant supratentorial ependymoma (Figs. 1 to 4).

Five patients (33%), all with known local clinical and radiological recurrence, died of their tumor; however, autopsies were not performed. The postoperative survival times of these patients ranged from 13 months to 6 years (median 2.5 years, mean 3.2 years).

Discussion

The aims of this study were to evaluate the postoperative course and incidence of recurrence of ependymomas which, on currently accepted histological criteria, would be regarded as malignant, and to determine whether a clinical correlation could be obtained with their histopathological features. As far as we are aware, this is the first study to address this issue.

In this analysis, we have made a clear distinction between the tumors evaluated herein and the highly cellular, embryonal form of ependymal tumor that occurs most often in infants and children under the age of 5 years and which has been defined as an ependymoblastoma. In patients with ependymoblastoma, there is general agreement that the clinical prognosis

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is very poor: the median postoperative survival time ranges from 12 months to 20 months, and there is a 100% mortality rate within 3 years of diagnosis.

The malignant ependymomas in this study have a different histological picture. In many fields they presented the typical characteristics of ependymoma, but in addition they displayed histological and cytological appearances suggestive of anaplasia. Ependymomas with these features may occur in patients at any age and, unlike ependymoblastomas, do not show a preference for the supratentorial compartment. The anaplastic changes are unaccompanied by the enhanced development of ependymal differentiation expressed by the formation of numerous rosettes, which is characteristic of the ependymoblastomas.

In the 15 cases of malignant ependymoma that we reviewed, two-thirds of the patients have survived from periods ranging for 15 months to 14 years, seven of them for 6 or more years. Only one of these patients had a recurrence after 11 years: in that case the histological features were those of a benign ependymoma, and the recurrence took place well outside the period of risk as defined by Collins' law. All five patients who died had local recurrence of their tumor. Four of the five recurrences took place within the period of risk, but one (Case 11), in which recurrent growth was demonstrated by computerized tomography more than 6 years after the excision of a fourth-ventricle ependymoma in a 12-month-old infant, was well outside it. We were unable to determine any histological criteria that would allow one to predict the biological behavior of these tumors, nor did the survival time or the histological picture correspond to the site of the growth or to the age of the patients. The different approaches in the selection of patients for the administration of postoperative radiation therapy and chemotherapy, and the different agents utilized make this type of retrospective study unreliable in demonstrating any differences of therapeutic benefits between individual patients. The only conclusions that could be drawn were that the prognosis of malignant ependymomas (as defined here) is highly variable, that it is favorable in about two-thirds of the patients, but that no correlation with any of the histopathological features or with the site of the tumor was possible.

Our analysis explains both some of the general conclusions and the inconsistencies that emerge from previous studies that have correlated the histological picture of ependymomas with length of postoperative survival. Although most of those surveys agree that high-grade ependymomas have a worse postoperative prognosis than low-grade ependymomas, the clinicopathological correlations derived do not, save for a single exception, take into account the distinction between ependymoblastoma and malignant ependymoma. In fact, the distinction is explicitly denied in two reports, in which the terms “malignant ependymoma” and “ependymoblastoma” are regarded as synonymous.

Reservations often qualify the general conclusion that histological grade is the most important determinant of tumor behavior and prognosis in ependymomas. Kricheff, et al., who graded 63 patients with intracranial ependymoma, noted that in many in-
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stances the grades correlated very poorly with the subsequent course of the disease and concluded that in most cases the histological appearance of the tumor is of less importance in estimating prognosis than are other factors. Fokes and Earle, who reviewed 133 ependymomas from the Armed Forces Institute of Pathology, found that no correlation between grading and survival time could be made and that an accurate prognosis based on a system of grading anaplasia was thwarted by the proximity of the tumor to vital structures of the central nervous system. The data of Barone and Elvidge, who divided their 45 followed-up cases of intracranial ependymoma into a benign or malignant category, show that the postoperative survival rate in the benign group (14 of 35 cases) is only 10% higher than in the malignant group (three of 10 cases). Dohrmann, et al., found that the overall 1-, 2-, and 5-year postoperative survival figures in patients with “ependymoblastomas” were only slightly less favorable than those in patients with “ependymomas.” Mørk and Lene16 concluded that the histological classification of ependymoma was only of limited prognostic value and that, during the first 4 postoperative years, patients with anaplastic tumors had the same survival rate as those with typical ependymomas; however, none of their seven patients with anaplastic ependymomas survived for more than 6 years, whereas all long-term survivors had typical ependymomas. Afra, et al., who divided their 80 cases of supratentorial ependymoma into three grades of malignancy, recorded that those in grade 2 had a similar 5-year survival rate as those in grade 3 (respectively, 28.5% and 27.2%) and noted that, among the recurrences in the most malignant group, two patients showed astonishingly long survival times. Finally, Ilgren, et al., in their study of 102 cases of ependymoblastoma found no correlation between postoperative survival times, mitotic activity, and tumor cell density.

Leibel and Sheline, who stated that tumor grade was the most important determinant of tumor behavior and prognosis for ependymomas, remarked, however, on the lack of consensus on the nomenclature of these tumors. This is most apparent in the correlations established by Salazar, et al., and by Pierre-Kahn, et al., both series included a surprisingly high proportion of malignant ependymomas. The latter were more frequent than benign ependymomas, and unusually high rates of recurrence and metastasis were recorded. It is possible that the tumors regarded as ependymomas in those three series included examples that might have been interpreted differently by other neuropathologists, perhaps as cerebral neuroblastomas in the case of supratentorial tumors, and as cerebellar medulloblastomas in the case of infratentorial tumors.

The data of Liu, et al., are most relevant to this discussion. These workers studied 34 ependymomas of childhood, grading them through a three-tier system of malignancy, but separating them from the ependymoblastomas. Their conclusions that most of the latter tumors were located supratentorially and that the patients’ average length of survival was 20 months were subsequently confirmed18 Liu, et al., also noted that the clinical course of ependymoblastomas differed somewhat from that of ependymomas with the highest grade (C) of malignancy. One of their patients in the latter category was alive and well 4 years after surgery. Liu, et al., concluded that an accurate prediction based solely on histological grading could not be made from their material because of too many variable factors, in particular the high rate of operative mortality, but that the prognosis for the less well-differentiated supratentorial tumors was unpredictable.

Our analysis, based on a larger number of malignant ependymomas, distinct from the ependymoblastomas, highlights these differences in postoperative behavior. The prognostic and therapeutic implications convey the need for exact histological identification. A diagnosis of ependymoblastoma makes it mandatory to treat the patient as for a medulloblastoma and therefore necessitates the administration of irradiation to the whole central neuraxis and possibly chemotherapy. In malignant ependymomas, the prognosis is unpredictable and often favorable, but fatal recurrence is to be anticipated in about one-third of the cases. Although most of the patients in this study were given postoperative radiotherapy, we were unable to determine its efficacy. A recent review13 states that the addition of postoperative radiation substantially improves the outcome of patients with intracranial ependymomas in general, and recommends radiotherapy to the craniospinal axis chiefly in patients with posterior fossa ependymomas who show evidence of cerebrospinal fluid seeding, as well as in those with high-grade or anaplastic ependymomas. That review estimates that 20% of these patients have anaplastic ependymomas, but, as with almost all other such correlative studies, no distinction was made between ependymoblastomas and malignant ependymomas.

In summary, whereas in cerebral astrocytic gliomas clear correlations have been established between the histopathological characteristics of cellular anaplasia and the subsequent postoperative evolution, no such correlation could be made in regard to those ependymomas that show histological features of malignancy, with the exception of the ependymoblastomas. Similar discrepancies have been recorded in regard to some of the histological features of oligodendrogliomas in a number of subependymal giant-cell astrocytomas associated with tuberous sclerosis, and in regard to the astroblastomas (Bonnin and Rubinstein, 1987, unpublished data).

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