Malignant transformation in benign cerebellar astrocytoma

Case report

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The authors give follow-up information on Case 59 of Cushing’s 1931 series of cerebellar astrocytomas. The patient died with a malignant cerebellar astrocytoma 48 years after partial removal of a previously benign astrocytoma at the same site. Including the present one, there have been only five reported cases in which this has occurred. Ordinarily, juvenile pilocytic astrocytomas are of extremely benign character, and it is well established that even with incomplete resections patients have survived for years without progression of the tumor. Not all of the cases so reported can be wholly accepted as representing malignant transformation of the tumor, but may instead be instances of recurrence of an inherently benign glioma since the presence of features such as endothelial hyperplasia or nuclear atypicality in a juvenile pilocytic astrocytoma does not warrant its being classified as malignant. Features truly suggestive of malignancy are hypercellularity, frequent mitoses, necrosis, and, in some instances, a diffusely infiltrative growth pattern; all of these features were found in the present case.

KEY WORDS • Harvey Cushing • astrocytoma • cerebellum • recurrence • malignant transformation • long survival

This report presents a clinicopathological case study of Case 59 in Harvey Cushing’s 1931 series of 76 patients with cerebellar astrocytoma. In this case, the patient died recently with a recurrence of the tumor that Cushing had partially resected 48 years previously. Apart from its historical interest, the case is noteworthy in that it represents malignant transformation of a previously benign cerebellar astrocytoma, an extremely rare occurrence, of which there have only been a few previous reports.1,4,20

This paper presents our findings, and puts them into perspective with the other reported cases and with some of the general aspects of glioma growth.

Case Report

History. In 1928, a 5-year-old girl was examined at Children’s Hospital, Boston,
FIG. 1. Drawings of the operative field by Cushing himself. I: the initial incision of the bulging cerebellar vermis; II: the multicystic appearance of the tumor; III: the site of residual tumor (labeled "raw tumor base"); IV: Cushing's reconstruction of a sagittal section through the tumor and brain stem.

because of headache, vomiting, ataxia, and papilledema. Two years previously ataxia on the right side and diplopia had developed. She subsequently underwent surgical exploration, from which it was concluded that the tumor was a "pontine glioma" and hence inoperable. Radiation therapy, in an unknown amount, was given over the following 8 months; her symptoms persisted, however. Two months after completion of the course of radiation therapy, she was seen by Dr. Cushing at the Peter Bent Brigham Hospital. He re-explored the posterior fossa and encountered "a large cystic tumor, unmistakably a fibrillary astrocytoma of the roof of the fourth ventricle. There was a huge primary cyst, which capped the tumor and had many bladder-like, thin-walled cysts in it." Microscopically, the tumor consisted of "dense, wavy neuroglial fibrillae" with "foci of degeneration and small areas of cystic formations." No mitoses were seen. Dr. Louise Eisenhardt noted in her smear preparations a dense network of fibrillae and a few nuclei with finely stippled chromatin. Unfortunately, the original slides are not available for review.

After this second craniotomy, the patient received another course of radiotherapy. Neurological examination demonstrated that the right side of the face was numb and weak, and that she was deaf in the right ear. There was optic atrophy in the left eye, which was blind. She also showed mild weakness, ataxia, and diminished sensation on the right side of the body. In spite of these neurological handicaps she was able to graduate from high school with honors. She worked as a salesper-
son and labeling clerk during the ensuing years. She remained in good health except for recurrent keratitis of the right eye for which she had tarsorrhaphies.

At the age of 51 years, the patient fell and fractured her hip. On admission to the hospital, she was found to be demented, with urinary incontinence, and gait ataxia. She was transferred to the Massachusetts General Hospital (MGH) where moderate hydrocephalus was diagnosed and treated with a ventriculoperitoneal shunt. She improved enough to move back into her own apartment and to take care of herself.

Present Admission. A year later, the patient was again admitted to the MGH for a right-sided tremor, clumsiness of the upper limb, difficulty with speech, and increased gait ataxia. She was alert and able to give most of her history. Psychometric tests indicated a bright-normal verbal intelligence and superior verbal abstract reasoning. She was blind in the left eye, and had 20/70 acuity in the right. The right pupil was 4 mm and reactive, the left 5 mm and unreactive. The disc on the left was atrophic, in contrast to her normal right disc. There were right third and sixth nerve palsies, with bilateral left-beating nystagmus. Weakness of the right side of the face with atrophy of the frontalis, orbicularis oculi, and orbicularis oris muscles was also noted along with loss of facial sensation and the corneal reflex on the right. She was deaf in the right ear. The tongue was deviated to the right. When she walked, she leaned and stepped to the right, and could not walk in tandem. There was bilateral appendicular ataxia, worse on the right. Muscle power and tone were normal. Sensation was normal except on the face. A computerized tomography scan demonstrated an area of increased density in the right cerebellar hemisphere. She then underwent her third craniotomy, 48 years after Cushing's operation. On this occasion, she was found to have a mass that involved the right cerebellar hemisphere. The biopsy was interpreted as a low-grade astrocytoma. Profound hypotension induced by surgical manipulation prevented complete resection of the tumor. The immediate postoperative course was uneventful. However, 33 days later the patient was found unresponsive. A focal seizure began in the right foot and became generalized. Following the seizure, she was alert and able to answer questions. There were no new neurological findings. Two weeks later, the patient was found dead.

Gross Autopsy Findings. Noteworthy general findings included bilateral bronchopneumonia with necrosis of the upper lobe of the right lung, acute pyloric ulceration, acute renal tubular necrosis, and hemorrhagic cystitis.

Neuropathological Findings. A tumor, 3 cm in diameter, at the site where Cushing's drawing showed residual tumor (Fig. 1), filled the right cerebellopontine angle, foramen of Luschka, and fourth ventricle, severely compressing and displacing the pons and medulla to the left, but not infiltrating them (Figs. 2 and 3). The brachium pontis was splayed over the mass. The right abducens nerve was compressed by the tumor, and only a few caudal roots of the right hypoglossal nerve could be identified (Fig. 3). The fourth ventricle from the calamus scriptorius to the aqueduct was filled with tumor.

![Fig. 2. Transverse sections of the brain stem and cerebellum. The tumor mass fills the right cerebellopontine angle, foramen of Luschka, and fourth ventricle. The medulla and pons are displaced to the left but not infiltrated by tumor. The right brachium pontis is splayed over the mass, and tumor focally infiltrates the rostral pontine tegmentum (upper left). A dense band of collagen in the cerebellar vermis may represent scarring of Cushing's incision (lower left).]
On section the tumor was variably firm and tan, or gray and granular. There were two small cysts filled with gelatinous fluid. Only at its superior extent did the tumor focally infiltrate the tegmentum of the rostral pons (Fig. 2).

The histology varied from field to field (Fig. 4). In a few regions, particularly in the region of the fourth ventricle, the tumor was suggestive of cerebellar juvenile pilocytic astrocytoma with fascicles of coarsely fibrillated bipolar cells with scattered Rosenthal fibers. However, no microcysts were present (Fig. 4 left). These regions merged imperceptibly with more cellular fields made up of numerous stellate cells with larger hyperchromatic stippled nuclei. Some of these cells were giant forms with huge multilobulated nuclei, often containing massive eosinophilic inclusions (Fig. 5 right). In other
Malignant transformation of cerebellar astrocytoma

In the cerebellum, the majority of primary astrocytomas are, in contrast to astrocytomas elsewhere, circumscribed, slowly growing tumors, just as Dr. Cushing originally demonstrated with his series.\textsuperscript{7,17} Most of them are extensively cystic. In many cases the solid tumor is confined to a mural nodule in the wall of a large cyst, and only 20% are, in their gross appearance, mainly solid.\textsuperscript{7,18,19,22} Histologically these tumors have a characteristic pattern of dense fibrillary areas interspersed with microcysts. Rosenthal fibers, eosinophilic hyaline droplets, and granular bodies are commonly present, and foci of oligodendroglioma occasionally may be seen.\textsuperscript{18,21} Because of their distinctive features, these tumors constitute a distinct clinicopathological entity, which has been described under various names, but now is often known as "cerebellar juvenile pilocytic astrocytoma."

When anaplastic astrocytomas similar to those in the cerebral hemispheres occur in the posterior fossa, most of them arise in the brain stem, particularly the pons. Anaplastic astrocytomas originating primarily in the cerebellum are rare, and, in fact, some of the cases so reported may well represent spread of tumor into the cerebellum from the brain stem.\textsuperscript{8,10,12,17-19}

What relationship there may be between juvenile pilocytic astrocytomas and anaplastic astrocytoma is a question raised by the present case, together with the question as to whether, over the course of many years, an initially benign astrocytoma of the juvenile pilocytic type may become transformed into an anaplastic malignant neoplasm. In our case, Cushing's operative notes and drawing indicate that the original tumor was clearly identifiable as a cerebellar juvenile pilocytic astrocytoma. Moreover, fields of well differentiated fibrillary astrocytoma with scattered Rosenthal fibers still could be found in the tumor at autopsy. At the same time, there was gradual transition from this benign-appearing tumor tissue to areas of dense

\textbf{Discussion}

regions, especially adjacent to the medulla, fusiform or polar cells, often with a perivascular orientation (Fig. 4 right), were arranged in ribbons or palisades. These cells had large, elongated, hyperchromatic nuclei, frequent mitoses, and scant pale eosinophilic cytoplasm (Fig. 5 left). Focal necrosis and microcysts filled with homogeneous eosinophilic material were also seen in this region. The tumor was moderately vascular and there was endothelial hyperplasia in the more cellular regions of the tumor. Scattered perivascular infiltrates of lymphocytes, histiocytes, and occasional plasma cells were seen throughout the tumor. Rostrally, the tumor focally infiltrated the pontine tegmentum. A midline band of collagenous tissue was present in the cerebellum, presumably at the site of Cushing's incision of the vermis in 1928. The right cerebellar hemisphere was diffusely gliotic, with atrophy and gliosis of the contralateral inferior olivary nucleus.

TABLE 1

Summary of five cases reported as malignant transformation of a benign cerebellar astrocytoma

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Sex, Age* (yrs)</th>
<th>Initial Tumor Appearance</th>
<th>Gross; Extent of Resection</th>
<th>Microscopic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bernell, et al., 1972</td>
<td>F, 3</td>
<td>unknown; &quot;gross total removal&quot;</td>
<td></td>
<td>well differentiated stellate cells,</td>
</tr>
<tr>
<td></td>
<td>#1</td>
<td></td>
<td></td>
<td>loosely arranged with early microcyst</td>
</tr>
<tr>
<td></td>
<td>#2</td>
<td>large cyst with 2 mural nodules in rt cerebellar hemisphere; total resection</td>
<td></td>
<td>moderately cellular, well differentiated</td>
</tr>
<tr>
<td>Scott &amp; Ballantine, 1973</td>
<td>M, 9</td>
<td>large cyst in rt cerebellar hemisphere; biopsy of wall</td>
<td></td>
<td>stellate cells, numerous microcysts, &amp;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rosenthal fibers</td>
</tr>
<tr>
<td>Budka, 1975</td>
<td>F, 13</td>
<td>tumor with large central cyst in rt cerebellar hemisphere; subtotal resection</td>
<td></td>
<td>moderately cellular, well differentiated</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>stellate cells, prominent microcysts</td>
</tr>
<tr>
<td>Kleinman, et al., 1978</td>
<td>F, 5</td>
<td>multicystic glioma in roof of IVth ventricle; subtotal resection</td>
<td></td>
<td>well differentiated, densely fibrillar,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>with microcysts</td>
</tr>
</tbody>
</table>

*Age at diagnosis.

cellularity, nuclear atypia, bizarre tumor giant cells, frequent mitoses, and focal necrosis, typical of an anaplastic astrocytoma. At the time of the original operation, Cushing carefully illustrated the location of the unresectable portion of the tumor in the right lateral recess of the fourth ventricle. This is exactly where the anaplastic astrocytoma that we discovered at autopsy was located. All of these observations suggest that the original tumor, which was clearly identifiable as a benign cerebellar juvenile pilocytic astrocytoma, ultimately underwent transformation into a malignant glioma. The possibility that an independent glioma arose in the cerebellum or brain stem would have to be considered, but the fact that the recurrent tumor was located exactly at the site of known residual tumor makes this unlikely.

The outlook for survival with cerebellar juvenile pilocytic astrocytoma has in general been excellent.2,6,7,9,14,17 These tumors typically grow so slowly that simple evacuation of the cyst may be followed by years of relief.1 In the series of 50 cases of cerebellar astrocytoma reported by Geissinger and Bucy,11 22 patients were still living after periods of from 10 to 39 years after complete resection of the tumor. Even with only a partial resection, seven of 14 patients lived at least 12 to 39 years.11 Generally, these long-surviving patients remained free of progressive neurological symptoms.11,16 In several series, including Cushing’s, a few of the patients in whom the resection had been incomplete underwent recurrence of the tumor after an interval of from 1 to 10 years following the initial operation.2,7,14 When recurrence has taken place, this has tended to appear within the first few years after surgery.1,3

Although the cerebellar juvenile pilocytic astrocytoma accounts for 8% of all gliomas and 30% of all gliomas in children,16,19,22 the subsequent appearance of an anaplastic astrocytoma at the same site is rare, and only four cases have been previously reported.1,4,20 These and the present case are summarized in Table 1. Death from the anaplastic astrocytoma occurred 20 to 39 years after surgery in the previously reported cases, and 48 years afterward in our case, which constitutes one of the longest survival periods for any patient.
Malignant transformation of cerebellar astrocytoma

TABLE 1 (Continued)

<table>
<thead>
<tr>
<th>Radiotherapy</th>
<th>Age* (yrs)</th>
<th>Survival (yrs)</th>
<th>Recurrent Tumor Appearance</th>
<th>Gross</th>
<th>Microscopic</th>
</tr>
</thead>
<tbody>
<tr>
<td>no</td>
<td>23</td>
<td>20</td>
<td>solid gelatinous tumor in IVth ventricle, replacing lt cerebellar hemisphere, infiltrating lt dorsal medulla &amp; pons</td>
<td>moderately cellular stellate &amp; bipolar cells, moderate nuclear atypia, &amp; hyperchromasia, infrequent mitoses, endothelial proliferation</td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>33</td>
<td>23</td>
<td>soft solid poorly demarcated tumor, diffusely infiltrating cerebellum</td>
<td>hypercellular, frequent mitoses, nuclear atypia, &amp; hyperchromasia</td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>55</td>
<td>39</td>
<td>tumor occupying the rt cerebellar hemisphere, extending into aqueduct</td>
<td>moderately cellular stellate &amp; bipolar cells, Rosenthal fibers, microcysts, nuclear atypia &amp; hyperchromasia</td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>40</td>
<td>27</td>
<td>focally cystic tumor diffusely infiltrating rt cerebellar hemisphere, vermis, pons, &amp; medulla; infiltration of leptomeninges</td>
<td>densely cellular glioma with frequent mitoses, nuclear atypia &amp; tumor giant cells, endothelial proliferation</td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>53</td>
<td>48</td>
<td>focally cystic tumor in IVth ventricle, foramen of Luschka, &amp; cerebellopontine angle, with focal infiltration of rostral pontine tegmentum</td>
<td>dense cellularity, frequent mitoses, nuclear atypia, &amp; tumor giant cells; fields of bipolar astrocytes &amp; Rosenthal fibers</td>
<td></td>
</tr>
</tbody>
</table>

*Age at death.

with a glioma. All but one patient had received radiotherapy. In all of these cases the original tumor appeared to be identical to the cerebellar juvenile pilocytic astrocytoma. The cells were described as well differentiated bipolar or stellate astrocytes. Microcysts were observed in all but one case in which only a small biopsy of the wall of a cyst was obtained.

There was considerable variation in the late-occurring tumors. In two cases (Case 2 of Bernell, et al.,1 and Budka’s case4), the tumor contained fields of dense cellularity with nuclear atypia and frequent mitoses. In Case 2 of Bernell, et al., there was diffuse infiltration of the cerebellum by anaplastic astrocytoma; Budka’s case showed similar infiltration of the cerebellum and also of the pons. In both of these cases, the possibility that the later neoplasm arose from a separate, independent focus of tumor growth in the cerebellum or pons cannot be excluded. In the other two previously reported cases (Case 1 of Bernell, et al.,1 and the case reported by Scott and Ballantine20), the interpretation of the histological findings is open to doubt. In the former patient, the tumor which appeared after 20 years was similar to the original tumor, except for moderately increased cellularity, some nuclear atypia, occasional mitoses, and endothelial hyperplasia. In cerebellar juvenile pilocytic astrocytoma these features per se do not necessarily indicate anaplasia. Giant cells also do not necessarily indicate malignancy in cerebellar astrocytomas. The histological recognition of malignancy in this group of tumors requires more rigorous criteria, such as demonstration of dense cellularity, frequent mitoses, and necrosis.5,18 In the case reported by Scott and Ballantine20 we were able to review the histological material. In this instance, the recurrent tumor contained microcysts and dense fibrillated areas, suggesting that it was a recurrent benign cerebellar juvenile pilocytic astrocytoma rather than a neoplasm that had truly undergone malignant transformation.

In our case, for the reasons given, the evidence indicates that in addition to its late recurrence, the tumor had indeed undergone malignant transformation.
References


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