The use of tissue culture in differentiation between angioblastic meningioma and hemangiopericytoma

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A solid, extrinsic hemangiopericytoma of the cerebellopontine angle was studied histologically and by means of tissue culture. The explanted tumor cells formed classic meningiomatous whorls indicative of the meningeal derivation of this neoplasm. Whorls were entirely absent in the histological preparations, however. The cases reported under the diagnosis of intracranial hemangiopericytoma and angioblastic meningioma have been reviewed; no valid histological distinction between these two types could be made.

Key Words • hemangiopericytoma • angioblastic meningioma • tissue culture

In 1954 Begg and Garret described a well-encapsulated left centroparietal dural tumor diagnosed as hemangiopericytoma. Stout and Murray, who described this entity in 1942, concurred with this diagnosis. The authors could find no previous case but considered that the three cases reported in 1928 by Bailey, et al., as angioblastic meningioma should be redesignated as hemangiopericytoma.

We are reporting a comparable case in which tissue culture clarified the histological characteristics.

Case Report

Clinical History

In 1959 a posterior fossa exploration was performed on a 51-year-old physician who had developed papilledema, cerebellar ataxia, and left-sided involvement of the fifth through tenth cranial nerves. A solid tumor was removed from the left cerebellopontine angle where it was attached to the undersurface of the tentorium. Histological diagnosis of hemangiopericytoma was made. A clinical recurrence of the tumor 5 years later led to reexploration in 1965. Extensive solid tumor was encountered from which only biopsies could be obtained; firm adherence to the brain stem and surrounding structures prevented complete removal. Following surgery, hydrocephalus was treated by a ventriculo-atrial shunt plus postoperative radiation of 5000 R delivered over 8 weeks. The patient remained functional for another 2 years but then developed progressive bulbar symptoms and died of aspiration pneumonia in 1968, 9 years after the onset of symptoms.

Autopsy Findings

Significant pathology was limited to the brain stem and cerebellum. A large, almost spherical, 6 cm firm mass was found in the left cerebellopontine angle compressing the pons, brachia, and the remnant of the cerebellar hemisphere on that side (Fig. 1). The
tumor was well demarcated, and had not infiltrated into the substance of the pons, mesencephalon, or cerebellum, although many adhesions were present. The tumor itself had a rather gritty consistency, and on cross section was quite variegated with soft, gelatinous, pale areas alternating with darker areas, some large blood vessels, and even frank hemorrhage.

Histological Findings

The histological features of the tumor in 1959, 1965, and 1968 were quite similar. The later specimens showed somewhat more scarring and a few areas of necrosis. There was a well-collagenized fibrous capsule. The tumor itself was rather variable with quite solid avascular areas (Fig. 2 left) alternating with other areas with much larger vascular spaces or even sinusoidal lakes. The tumor cells were closely packed, rounded, or elongated, and contained a relatively clear cytoplasm. The nuclei did not vary much and were round to ovoid with a delicate chromatin network, a heavy nuclear membrane, and small nucleoli. Mitoses were rare. More elongated or even spindle-shaped cells occurred. The capillary walls were usually thin and quite delicate; endothelium was either flattened or absent. Even in relatively large vessels this thin, sinusoidal-type wall could be established; well-differentiated veins and arteries were hard to find. In most areas there was no definite pattern of the intervascular cells. Despite thorough search in all tissues obtained, no meningioma whorls or

Fig. 1. Gross appearance of tumor at time of autopsy.

Fig. 2. Left: Photomicrograph of solid area of tumor. H & E, × 200. Right: Photomicrograph of larger vascular spaces as well as many small vascular channels. Reticulin stain, × 100.
Hemangiopericytoma

Fig. 3. Left: Clusters of tumor cells in tissue culture. Phase contrast, \( \times 360 \). Right: Clear-cut whorling and imbrication in clusters of migrating elements in tissue culture. Phase contrast, \( \times 800 \).

similar structures could be found.

Connective tissue stains demonstrated a few delicate strands of collagen around the vessels. Most striking were the reticulum silver impregnations (Fig. 2 right) in which numerous reticulin fibers could be seen coursing between the vessels and breaking up the sheets of intervascular cells into small clumps or even individual elements. A definite, delicate perivascular reticulum sheath closely surrounded the flattened vascular endothelium. Thus the tumor cells were perivascular. The scarring in the later specimens was fairly extensive.

_Tissue Culture_

From the surgical specimen obtained in 1965, approximately 250 explants of tumor tissue were placed on glass coverslips and incubated in Leighton tubes. The medium was TC-199. Growth was quite apparent within 24 hours. All the explants showed vigorous outgrowth of cells. Within 4 days of inoculation, the cells started to form little heaps and clusters, often at the intersections of long strands. Elongated cells soon formed in these clusters with the axis of the cell tangentially oriented. Under phase contrast, the cytoplasm of the cells could be seen to follow the same tangential course. Quite obvious whorls were formed in this culture (Fig. 3). These whorls were seen in the living cultures as well as in those fixed and stained after 15 days of growth. It should be emphasized that wherever little clusters of cells accumulated, this imbricated pattern with whorling around the geometric center of the cluster eventually supervened.

_Discussion_

The histological appearance of this tumor is such that tissue could be classified into three different categories: 1) angioblastic meningioma; 2) angioblastoma, hemangioblastoma, or hemangioendothelioma; and 3) hemangiopericytoma.

_Angioblastic Meningioma_

This particular variety of meningioma was delineated by Bailey, et al., in 1928, and their description cannot be improved:
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The term "angioblastic meningioma" coined by Cushing\(^2\) was used to designate the small vascular tumors often found as mural nodules in cerebellar cysts, first collected by Lindau.\(^3\) In spite of a number of regressive changes,\(^2,5,5,5\) the histology is sufficiently characteristic to permit recognition. Differentiation from angioblastic meningioma is not by histology but purely by location (intra- versus extracerebellar, attached to dura) and by the fact that the intracerebellar lesion tends to be cystic as well as occasionally associated with lesions of other organs.\(^5,5,5,6\) Cases of this tumor occurring above the tentorium are summarized in Table 2. In none of these tumors have transitions to meningioma tissue (whorls, psammoma bodies, and the like) been observed.

**Hemangiopericytoma**

Hemangiopericytoma, as defined by Stout and Murray,\(^6,6\) is a vascular tumor, composed of numerous capillaries often collapsed with a flat endothelial lining (proliferation of the endothelium puts it into the hemangioendothelioma group) and a well-developed reticulin sheath. The bulk of the tumor is formed by intervascular cells, which are thought to be derived from the pericytes of Zimmerman.\(^6,6\) Although most of these tumors are widely distributed throughout the

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**TABLE 1**

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of Cases</th>
<th>Remarks*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bailey, et al. (1928)</td>
<td>3</td>
<td>pure</td>
</tr>
<tr>
<td>Cleuet (1928)</td>
<td>1</td>
<td>whorls</td>
</tr>
<tr>
<td>Bailey (1929)</td>
<td>1</td>
<td>whorls</td>
</tr>
<tr>
<td>Bailey and Bucy (1931)</td>
<td>1</td>
<td>pure</td>
</tr>
<tr>
<td>Bergstrand and Olivecrona (1935)</td>
<td>5</td>
<td>cannot be separated from psammoma body and whorls</td>
</tr>
<tr>
<td>Wolf and Cowen (1936)</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Globus (1937)</td>
<td>?</td>
<td>all transitions</td>
</tr>
<tr>
<td>Cushing and Eisenhardt (1938)</td>
<td>?</td>
<td>all transitions</td>
</tr>
<tr>
<td>Bland and Russell (1938)</td>
<td>2</td>
<td>pure</td>
</tr>
<tr>
<td>Häussler and Döring (1939)</td>
<td>1</td>
<td>pure; cystic</td>
</tr>
<tr>
<td>Courville and Abbott (1940)</td>
<td>13</td>
<td>all transitions</td>
</tr>
<tr>
<td>Courville and Abbott (1941)</td>
<td>10</td>
<td>equivalent to angioblastic meningioma</td>
</tr>
<tr>
<td>Zeitlin (1942)</td>
<td>1</td>
<td>pure</td>
</tr>
<tr>
<td>Bailey and Ford (1942)</td>
<td>2</td>
<td>pure</td>
</tr>
<tr>
<td>Corradini and Browder (1948)</td>
<td>4</td>
<td>pure</td>
</tr>
<tr>
<td>Lapreusle, et al. (1952)</td>
<td>1</td>
<td>whorls</td>
</tr>
<tr>
<td>Marsh, et al. (1957)</td>
<td>1</td>
<td>pure</td>
</tr>
</tbody>
</table>

* Pure = the histology was purely angioblastic, without an admixture of meningiomatous whorls.

"By the term angioblastic meningioma we do not mean meningiomas that merely happen to be highly vascular in the sense that angioma is sometimes used for a highly vascular glioma. What we do mean is that a meningial tumor which possesses the unmistakable naked-eye appearance of the usual and familiar type of one of these lesions may prove histologically to have the same architectural features and reticular network that is possessed by the hemangioblastomas which originate within the brain itself, more frequently, if not exclusively, in the cerebellum."
TABLE 2
Supratentorial hemangiblastomas reported

<table>
<thead>
<tr>
<th>Author</th>
<th>Location, Type</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rochat (1931)</td>
<td>solid, deep</td>
<td>also cystic cerebellar lesion; family history</td>
</tr>
<tr>
<td>Barnard and Walshe (1931)</td>
<td>cystic, surface, dural attachment</td>
<td></td>
</tr>
<tr>
<td>Abbott and Love (1943)</td>
<td>solid, surface, eroding through skull, metastasizing</td>
<td></td>
</tr>
<tr>
<td>Bennett (1946)</td>
<td>solid</td>
<td></td>
</tr>
<tr>
<td>Bennett (1946)</td>
<td>solid</td>
<td></td>
</tr>
<tr>
<td>Bennett (1946)</td>
<td>solid</td>
<td></td>
</tr>
<tr>
<td>Löwenthal (1950)</td>
<td>solid, surface, attached to dura &quot;molluscum pendulum&quot;, osteoid present</td>
<td>also solid cerebellar lesion</td>
</tr>
<tr>
<td>Kautzky and Vierdt (1953)</td>
<td>solid, deep, reaches surface, no dural attachment</td>
<td>also cystic cerebellar lesion, two solid medul lary lesions</td>
</tr>
<tr>
<td>Courville (1957)</td>
<td>solid, surface, parasagittal</td>
<td>also cystic cerebellar lesion, family history</td>
</tr>
<tr>
<td>Stein, et al. (1960)</td>
<td>cystic, deep</td>
<td></td>
</tr>
<tr>
<td>Stein, et al. (1960)</td>
<td>solid, deep</td>
<td>also cystic cerebellar lesion; two solid medul lary lesions</td>
</tr>
<tr>
<td>Brasseur (1961)</td>
<td>solid, deep</td>
<td>no other lesions; tissue culture showed fibro blasts, epithelioid cells</td>
</tr>
<tr>
<td>Lentze (1965)</td>
<td>no details available</td>
<td></td>
</tr>
<tr>
<td>Rivera and Chason (1966)</td>
<td>solid, surface, dural attachment</td>
<td></td>
</tr>
<tr>
<td>Hoff and Ray (1968)</td>
<td>surface, cystic</td>
<td>two cystic cerebellar lesions, family history</td>
</tr>
</tbody>
</table>

* Cases of Gross (1939) and Keller (1933) omitted because equivocal.

TABLE 3
Cerebral hemangio pericytomas reported

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of Cases</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stout (1949)</td>
<td>1</td>
<td>probably not primary intracranial</td>
</tr>
<tr>
<td>Begg and Garret (1954)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peace (1954)</td>
<td>1</td>
<td>newbon: similar case by Corten (1921)</td>
</tr>
<tr>
<td>Stout (1956)</td>
<td>4</td>
<td>mentioned casually in review, no data</td>
</tr>
<tr>
<td>Fisher, et al. (1958)</td>
<td>1</td>
<td>same case as Peace</td>
</tr>
<tr>
<td>Kaufman and Stout (1960)</td>
<td>1</td>
<td>choroid plexus</td>
</tr>
<tr>
<td>McDonald and Terry (1961)</td>
<td>1</td>
<td>one with bone, cartilage; metastasis in one; also one spinal case</td>
</tr>
<tr>
<td>Begg (1961)</td>
<td>1</td>
<td>not published; see McDonald and Terry (1961)</td>
</tr>
<tr>
<td>Kruse (1961)</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Kernohan and Uihlein (1962)</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Stefanko and Glowacki (1964)</td>
<td>1</td>
<td>not detailed</td>
</tr>
</tbody>
</table>

At recess, Bailey, et al., and others, suggested that the intracerebellar lesions are deep-seated and cystic, whereas those on the surface, whether cerebellar or cerebral, are solid and attached to the dura. However, classical cerebellar lesions may be solid (Lindau, two out of 16 cases; Cushing and Bailey, four of 11 cases; Bergstrand, et al., one of 20 cases; Stein, et al., two of 16 cases). Also, cerebellar tumors of this type are often not as deep as they seem, and indeed some authors believe that they are all superficial, as was the celebrated case by Bergstrand, et al., in a newborn infant. Of the 15 incontrovertible supratentorial lesions (Table 2), three were cystic rather than solid. The same overlap between cystic and solid differences are not sufficient to serve as guidelines for differentiation. If these three tumors indeed are different, considerations other than purely histological must be employed.

Clinical Differentiation

As remarked, Bailey, et al., and others, suggested that the intracerebellar lesions are deep-seated and cystic, whereas those on the surface, whether cerebellar or cerebral, are solid and attached to the dura. However, classical cerebellar lesions may be solid (Lindau, two out of 16 cases; Cushing and Bailey, four of 11 cases; Bergstrand, et al., one of 20 cases; Stein, et al., two of 16 cases). Also, cerebellar tumors of this type are often not as deep as they seem, and indeed some authors believe that they are all superficial, as was the celebrated case by Bergstrand, et al., in a newborn infant. Of the 15 incontrovertible supratentorial lesions (Table 2), three were cystic rather than solid. The same overlap between cystic and solid

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versus deep to superficial forms occurs in the spinal cord.\textsuperscript{35} It could be argued that the cerebral lesions are not really related to the cerebellar ones, but cases in which the cerebral tumor was associated with a classical cerebellar lesion,\textsuperscript{18,31,32,44,51} cystic in all but one,\textsuperscript{44} or in which other members of the family were involved,\textsuperscript{19,31,51} clearly exclude this argument. Therefore, neither location nor solid versus cystic appearance, nor the familial incidence or associated lesions of the full-blown von Hippel Lindau complex, serve to fully differentiate angioblastic meningiomas from angioblastomas.

The supratentorial hemangioblastomas listed in Table 2 are those published as such; many of the angioblastic meningiomas reported would fit in this listing without difficulty, or the hemangiopericytomas for that matter. The only difference is the identification of meningioma whorls in some of the angioblastic meningiomas; whorls are lacking in the other neoplasms.

**Tissue Culture Studies**

Meningiomas have been grown in tissue cultures since Kredel (1928)\textsuperscript{39} but no useful growth patterns were obtained until Costero, \textit{et al.}, working in Pomerat's laboratory (1955)\textsuperscript{16,17} demonstrated the development of typical meningioma whorls formed by cells migrating from meningioma explants. The one angioblastic meningioma cultured\textsuperscript{11} preceded this epochal discovery. Even full-fledged meningiomas do not always give rise to these specific whorls,\textsuperscript{37,38,45} the occurrence of whorls, however, is characteristic and has not been recorded from other tumors, whether intra- or extracerebral. Cerebellar angioblastomas have been cultured\textsuperscript{12,24,37} but the results have not been helpful. No cerebral hemangiopericytoma has been cultured as yet.

**Electron Microscopy**

Differentiation of these three tumor types by electron microscopy is as yet in its infancy, although some attempts have been made.\textsuperscript{49}

**Conclusions**

The literature survey as well as the tissue culture observations clearly indicate that angioblastic meningiomas, as originally proposed, indeed arise from the leptomeninges and that no pressing need exists to reclassify the tumor as hemangiopericytoma. Inclusion of cerebellar angioblastomas in this broad classification of vascular tumors, although tempting, will have to await further study.

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