Multiple supratentorial hemangioblastomas

Case study and ultrastructural characteristics

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Multiple hemangioblastomas were found above the tentorium in a 62-year-old woman who first had a discrete 2.5 cm tumor removed from the superior aspect of the tentorium adjacent to the falx, and 2 years later developed two more intracranial mass lesions, one in the right parietal area, the other attached to the dura of the right frontal fossa. Histological examination of all three tumors showed precisely the same well-differentiated morphology of hemangioblastoma. Foci of extramedullary hematopoiesis were present within them. Electron microscopic examination of the last two lesions disclosed secretory granules within the tumor cells, indicative of erythropoietin production, as described previously in a hemangioblastoma. Collagen and endothelial cells were not present in quantities consistent with an angioblastic meningioma. The genesis of hemangioblastomas is discussed.

KEY WORDS • hemangioblastoma, multiple, cerebral • erythropoietin • extramedullary hematopoiesis

HEMANGIOBLASTOMAS of the central nervous system are histologically benign vascular neoplasms considered to originate from the remnants of the mesoderm that is incorporated into the brain during the third fetal month. Predominantly, they occur in the cerebellum and only rarely have they been described in the pons, medulla, and spinal cord. Cushing and Bailey reported that this lesion does not occur in the cerebrum, but Russell and Rubinstein reported its rare occurrence in this location and the literature contains at least eight examples cited by Rivera, et al., in 1966. In each instance, the cerebral lesion has been solitary. The present case constitutes a unique example of multiple cerebral hemangioblastomas. These were studied by light and electron microscopy.

Case Report

A 62-year-old right-handed woman was initially admitted to Duke Hospital with a 1-year history of staggering gait, poor coordination of the right hand, and progressive right-sided weakness. She felt that her "thought processes were not normal" and expressed difficulty in the recall of words during speech. She manifested depression with lack of motivation. She had noted a gradual fading of her vision, more on the right than left. Headaches developed several months prior to admission.

Examination. The patient was well developed and obese; she was despondent, apprehensive, and afraid that she was going to die. The blood pressure was 140–90 and pulse, 78. The general physical examination was
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normal. Neurological examination showed the patient to be oriented as to person, place, and time. Speech was occasionally hesitant, and there were momentary periods of confusion. There was bilateral papilledema and a right homonymous field defect. The right arm showed a slight downward drift. There was no astereognosis, no extinction on double simultaneous stimulation, and minimal right-left disorientation without finger agnosia. The deep reflexes were equally hypoaactive on both sides. Plantar responses were flexor bilaterally. Hematocrit was 43, and all routine chemistries were normal. Skull and chest films were normal. A brain scan revealed a 6-cm area of activity in the deep portion of the left parietooccipital area. A left carotid arteriogram disclosed the space-occupying character of the lesion, showing neovascularity beginning late in the arterial phase and a prolonged blush in the venous phase (Fig. 1). No arteriovenous shunting was noted.

Operation. A left parietooccipital craniotomy revealed a large vascular tumor attached to the falx and tentorium. It was considered that the lesion was removed completely.

Pathological Examination. The well-encapsulated mass was ovoid and measured 2.5 cm in maximum diameter. It was formed of firm tissue that had a deep red hemorrhagic appearance on cut section. When viewed by light microscopy, it presented a highly vascular structure composed predominantly of delicate blood-filled channels, primarily capillary in type. The endothelial cells were plump and spindle-shaped. The interstitial cells contained central nuclei in abundant foamy cytoplasm (Fig. 2 left). Mitoses were not seen although rare nuclear gigantism and hyperchromasias were observed. Oil red O (fat) and periodic acid Schiff (PAS) stains did not demonstrate the presence of intracytoplasmic material. Reticulin stains showed a fine circle of argyrophilic fibers about individual endothelial cells and enclosing groups of cells in the vascular walls. The neoplasm most closely resembled a hemangioblastoma, but in view of the rarity of these lesions supratentorially and the gross description of attachment to the falx and tentorium, consideration was given to the possibility of an angioblastic meningioma. The slides were reviewed by Dr. Orville T. Bailey who commented that the histology was that of a hemangioblastoma with no unusual features except for its location.

Postoperative Course. Recovery was uneventful, and neurological examination at the time of discharge showed only a persistent right homonymous hemianopsia.

Over the next 2 years the patient was followed at periodic intervals with no change in neurological status. There was then a gradual deterioration; she developed headaches, and became progressively demented, confused, and listless. Her local physician referred her to Duke Hospital for a final examination prior to her placement in a nursing home.

Second Examination. The general physical examination was normal. However, the patient was confused and disoriented. When questioned concerning the date she was unsettled as to the year and was totally unaware of the month; she did not know the U.S. president or the governor of the state. There was a personal awareness of her impaired processes, and she expressed disgust. There was equivocal blurring of the right disc inferiorly, as well as the old right homonymous hemianopsia. There was a very subtle downward drift of the right arm, but no weakness on individual muscle testing. Sensory examination could not be satisfactorily performed. Plantar response was flexor on the left, equivocal on the right. Careful ophthalmoscopic examination revealed no evidence of angiomatous malformations. There was no family history of intracranial tumors.
nor were there any manifest familial diseases.

Hematocrit was 40, hemoglobin 13.3, white blood cell count 7900. The urinalysis and blood chemistries were normal. Chest x-ray showed no abnormalities. Electroencephalogram revealed rhythmic theta and delta activity in the left parietooccipital region when the patient was drowsy. Brain scan demonstrated a markedly positive activity in the right posterior parietal and right frontal regions. There was also some residual uptake from the previous left parietal postoperative region. The old scans were reviewed, and no evidence of the right-sided abnormality was noted. A right carotid arteriogram revealed a marked shift of the anterior cerebral artery to the left as opposed to the original shift from left to right 2 years earlier. There were two discrete cloud-like vascular lesions, one in the right parietal region, the other in anterior fossa (Fig. 3). Because of the multiple intracranial lesions, metastatic disease was suspected; histological review of the previous lesion raised the possibility of a clear-cell carcinoma of the kidney. Renal scan was normal. Intravenous pyelograms revealed that the left kidney was larger than the right, being 16 cm and the left 13 cm. Neither provided evidence of a neoplasm, and the metastatic bone series were negative. Barium enema was negative. A lumbar puncture revealed an opening pressure of 125 mm of water with clear, colorless fluid.

Fig. 3. Right carotid arteriogram, 2 years later, showing a large space-occupying lesion in the right parietal area and a separate similar lesion in the right frontal area.
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Second Operation. A right parietal craniotomy was carried out, and a discrete lesion was removed en masse. This tumor was not attached to the overlying dura grossly and was histologically identical to the tumor removed 2 years previously from the tentorial region (Fig. 2 center).

A right frontal craniotomy was then performed and a discrete extremely vascular lesion was removed from the right frontal region. This tumor was adherent to the dura over the roof of the right orbit. It was easily separated from the underlying frontal cortex with no vessels entering the tumor from the brain. The well-encapsulated mass measured $3.5 \times 3.0 \times 2.5$ cm and grossly and microscopically was identical to the previous two lesions (Fig. 2 right).

Second Postoperative Course. The patient did very well except for transient urinary retention. A repeat intravenous pyelogram performed prior to discharge once again revealed no abnormalities. Upon discharge, the patient was oriented as to place, month, and year. The gait was slightly unsteady but the patient could walk unassisted. The right homonymous hemianopsia persisted.

Further Pathological Examination. The three lesions were identical in appearance. They were firm, roughly ovoid with maximum diameters ranging from 2.5 to 3.5 cm, and had beefy red hemorrhagic cut surfaces. There was no evidence of cyst formation in any lesion, and all of them were well encapsulated. The lesions very closely resembled each other in their histological appearance. Each consisted of highly vascular tissue in which numerous blood-filled capillaries were lined by plump endothelial cells. Between the capillaries there were many large cells having central large nuclei in abundant foamy cytoplasm. There were no mitoses; however, slight nuclear hyperchromasia and gigantism were occasionally observed. There was no increase in this pleomorphism in the second and the third lesions as compared to the first. Fat and PAS stains did not demonstrate the presence of intracytoplasmic material. Reticulin stain showed a fine circle of argyrophilic fibers about individual endothelial cells and enclosing groups of cells in the vascular walls.

In all three lesions, but more abundantly in the second, there were scattered foci of extramedullary hematopoiesis. These contained numerous normoblasts (Fig. 4). The

Fig. 4. Photomicrograph characteristic of all three tumors. Left: Centrally located numerous normoblasts with large dark nuclei. H & E, x 400. Right: Higher magnification shows cells with the morphology of normoblasts containing large dense nuclei in polychromatophilic cytoplasm. H & E, x 1000.
foci were more frequent in or near the walls of large blood vessels. Normoblasts were also present within lumina of blood vessels.

Electron Microscopy. Immediately after surgical removal, fresh tissues from the second and third lesions were fixed in 5% glutaraldehyde, buffered to pH 7.3 with sodium cacodylate for a period of 16 hours at 5°C. These tissues were then rinsed in cacodylate sucrose buffer with several changes and were postfixed for 1 hour in 1% osmium oxide (Palade’s fixative). They were dehydrated and embedded in Epon. Sections were cut on an MTI, Porter-Blum ultramicrotome, and the sections were stained with uranyl acetate and lead citrate. For comparative purposes, tissue from a proven case of hypernephroma was studied in parallel fashion. Pictures were taken on an RCA, EMU 3G electron microscope. There was a general uniformity of the fine structure in all sections and between the two lesions. There were numerous blood-filled spaces lined by large spindle cells which bulged into the lumina. The interstitial cells had prominent and abundant smooth endoplasmic reticulum; this was dilated in correspondence with the vacuolated cytoplasm noted by light microscopy. These cells had in their cytoplasm numerous spherical, homogeneous, electron-dense bodies of diameters between 1200 to 2000 Å. These bodies were membrane-bound and resembled zymogen granules of the pancreatic acini (Figs. 5-7). The cytoplasm also contained fibrils in an irregular distribution.

By contrast, the cells of the hypernephroma from another case contained in their cytoplasm an abundant quantity of glycogen (Fig. 8). There were no membrane-bound dense bodies, as noted in the lesions under question.

Discussion

The occurrence of anatomically distinct tumors, with the morphology of hemangioblastomas, in the rare location above the tentorium, raises first the problem of identity. In these studies, three entities were given considered attention, namely, hemangioblastoma, angioblastic meningioma, and metastatic hypernephroma. With regard to the latter, the negative renal studies are strongly supported by the fine structure differences between a verified hypernephroma and the lesions under question. The presence of abundant quantity of glycogen in the former and its absence in the latter together with the presence of secretory granules in the latter are strong evidence.

Because of the rarity of hemangioblastomas supratentorially and the gross localization with attachment of the first and third lesions to the dura, the possibility of angioblastic meningiomas was entertained. The histological architecture was devoid of a whorled pattern and, when examined by electron microscopy, no collagen was detected. Collagen is a prominent feature of meningiomas. Dural attachment of hemangioblastomas has been noted by various authors.

It was then asked whether the present triad of lesions represents a recurrence, or a malignant process with intracranial dissemination, or multiple independent lesions. In this relation, it is noteworthy that the third lesion was distantly removed from the previous two; it is to be doubted that this lesion represented a recurrence. The first lesion was completely encapsulated and was removed en masse. Although recurrences of hemangioblastomas are quite common if the mural nodule is not completely removed, various authors point out that such lesions do not represent metastasis. Regularly, they are histologically well differentiated, although they might exhibit nuclear gigantism and hyperchromasia, and these features are quite common even in cases with long survival and without recurrence. In none of the lesions in the present case was there clear histological evidence of anaplasia. Thus, in conformity with all previously described hemangioblastomas, the present lesions were viewed as benign and separate multicentric lesions.

Stein, et al., have described multiple hemangioblastomas in the cerebellum, which they interpreted as separate growths rather than recurrence of an incompletely removed tumor. Similarly, Cramer and Kimsey, from experience with 53 cerebellar hemangioblastomas treated by repetitive operations, concluded that this entity is not infrequently multicentric in this region.

As has been stated, hemangioblastomas are extremely rare supratentorially. A search of the literature discloses a total of eight
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Fig. 5. Electron photomicrograph of the second tumor. To the left, a capillary lumen containing a portion of an erythrocyte. A large interstitial cell containing numerous electron-dense membrane-bound bodies. Uranyl acetate and lead citrate, × 7000.

cases. For the first time, in 1966, Rivera and Chason\textsuperscript{16} described a case in detail. This was an 11-year-old boy with a solid hemangioblastoma in the right parietal lobe. Postmortem studies performed 8 years later failed to disclose other lesions, either in the brain or elsewhere in the body. The remaining seven cases have been incompletely described, generally in studies carried out with other points of emphasis, such as the occurrence of polycythemia, the histogenesis of the lesion, cyst formation, etc.\textsuperscript{1,2,8,20} Relatively little emphasis was placed on their occurrence in the cerebrum.

Based upon Sabin’s work\textsuperscript{19} on the development of cerebral circulation, Lindau\textsuperscript{12} concluded that these vascular tumors arise from portions of vascular mesenchyma destined to form choroid plexus of the fourth ventricle which become isolated and incorporated into the cerebellum during the third fetal month of life. A certain number of these tumors form a portion of the von Hippel-Lindau syndrome, in which there are angiomas of the retina and other organs. In at least 20\% of these cases, there is a hereditary predilection with an autosomal dominant character, and either complete or incomplete penetration. It has been proposed that as the primitive vascular patterns are re-
placed by higher and more complex systems, blood channels that should normally disappear, persist and produce a great variety of congenital anomalies.\textsuperscript{9}

This neoplasm is not manifest at birth or in early life. In most series, the average age is 40 years. In the present case, the first lesion was clinically manifest at the age of 62 years; at this time the arteriogram showed but a single lesion. The occurrence of the second and third tumors 2 years later make it clear that the latter lesions developed over a short period. This favors their true nature as neoplasms rather than as hamartomas. Although much has been said, the nature of their histogenesis still remains highly speculative.\textsuperscript{13}

Finally, consideration was given to the secretory nature of hemangioblastomas. The association of erythrocytosis with neoplasia has been reported in at least 230 cases. The most frequent association is with renal carcinoma and the second most frequent is with cerebellar hemangioblastomas. In 1943, Carpenter, \textit{et al.},\textsuperscript{5} reported two patients with cerebellar hemangioblastomas with associated polycythemia. Since this report, 40 such cases have been recorded.

The concept of a humoral stimulating factor as the fundamental stimulus for red cell...
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Production was first proposed by Carnot and Deflandre\(^4\) in 1906. Later, erythropoietin was found in the fluid of renal cysts and in cerebellar hemangioblastomas.\(^{10,15,17,21}\) Assays have employed a number of techniques such as the polycythemic mouse, increase of reticulocytes, platelet counts in rabbits, and Fe\(^{59}\) incorporation in the induced polycythemic mouse.\(^{10}\) Although this did not constitute definite proof that the erythropoietin was synthesized by the tumor, regression of the polycythemia after removal of the tumor from patients provides strong and indirect support for the hypothesis.

Indirect evidence of the erythropoietic capacity of these lesions was also noticed by Dr. Margaret Murray\(^{14}\) in 1933, while studying an explant from a cerebellar hemangioblastoma (Cramer and Kimsey's case).\(^{9}\) She observed foci of erythropoiesis in the presence of numerous viable erythrocytes, naked nuclei possibly extruded from normoblasts, and a few large cells resembling erythroblasts.

In the second and third lesions of the present study, electron dense particles were observed in the cytoplasm of the tumor cells. These particles were membrane-bound and resembled the zymogen granules of the pancreas. Similar granules have been noted pri-
Fig. 8. Electron photomicrograph of a varified epidural metastatic hypernephroma from another patient showing glycogen granules and no secretory droplets. Uranyl acetate and lead citrate, × 16,000.

marily by Castaigne, et al.,⁶ in their study of cerebellar hemangioblastomas; they interpreted the finding as the granules of mast cells. They were not noted by Cancilla and Zimmerman.³ Scattered throughout the tissue of the second lesion, and in lesser concentrations in the first and third, were foci of hematopoietic tissue (Fig. 4). The cells were predominantly normoblasts. Occasionally, similar cells were present in the capillaries. It is interesting that this patient did not manifest frank polycythemia, though her hematocrit was in the high normal level of 43%. It can only be postulated that the electron dense granules represent erythropoietin or precursor material. If this is true, then perhaps these neoplasms exhibit intrinsic hematopoietic activity because of this local hormonal stimulus.

Summary

A 62-year-old woman developed three anatomically distinct histologically benign supratentorial neoplasms, each with the light and electron microscopic appearance of a hemangioblastoma. The presence of extra-medullary hematopoiesis in these lesions was of additional interest. The phenomenon of multiple supratentorial hemangiomas has been discussed.
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