Mixed Capillary Hemangioblastoma and Glioma
A Redefinition of the "Angioglioma"

JOSE M. BONNIN, M.D., CARLOS E. PENA, M.D., AND LUCIEN J. RUBINSTEIN, M.D.

Abstract. The histopathologic features of four cases of mixed capillary hemangioblastoma and glioma are described. In three cases, two of which arose in the cerebellum and one in the spinal cord, the hemangioblastic component may have originated from a neoplastic proliferation of the exuberant vascular stroma in a glial tumor. In a fourth case, a cerebellar hemangioblastoma was surrounded by a peripheral rim of atypical neoplastic-looking astrocytes ("reactive glioma"). The controversial concept of the "angioglioma" is reviewed, and it is proposed that the term be used to designate only true mixed tumors of glial and vascular tissue origin whose histologic features conform to the examples described in this report.

Key Words: Angioglioma, Hemangioblastoma, Mixed tumors, Reactive glioma.

INTRODUCTION

Current controversies on the nature of the stromal cells in capillary hemangioblastomas and recent reports that these tumors may include glial fibrillary acidic (GFA) protein-positive cells interpreted as astrocytes (1) or as stromal cells that have taken up GFA protein (2) have kindled new interest in the possible participation of astrocytes in primary vascular neoplasms of the central nervous system. Likewise, the existence of an ill-defined and poorly documented tumor entity sometimes designated as "angioglioma" has gained new attention.

The term "angioglioma" was formally proposed by Roussy and Oberling (3) to designate a highly vascular cerebellar tumor in which the intervascular spaces were packed with large eosinophilic cells that were, in their view, of glial origin. They distinguished the "angioglioma" from another highly vascular neoplasm, the "angioreticuloma," which they equated with the capillary hemangioblastoma of Cushing and Bailey (4). In fact, the "angioglioma" of Roussy and Oberling was identical to the rare variant of hemangioblastoma that was termed "cellular" by Cushing and Bailey and whose architectural pattern resembles that of a chemodectoma. The existence of transitional examples comprising both the "cellular" and "reticular" variants of capillary hemangioblastoma led to a general adoption of Cushing and Bailey's view of capillary hemangioblastoma as a single tumor entity and to the rejection of Roussy and Oberling's concept of "angioglioma." The validity of the term has from time to time been briefly analyzed in texts on tumors of the nervous system.

From the Division of Neuropathology, Department of Pathology, University of Virginia School of Medicine (JMB, LJR), Charlottesville, Virginia, and the Department of Pathology, Mercy Hospital and University of Pittsburgh School of Medicine (CEP), Pittsburgh, Pennsylvania.

Address reprint requests to Jose M. Bonnin, M.D., Division of Neuropathology, Department of Pathology, University of Virginia School of Medicine, Charlottesville, VA 22908, USA.

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system (5-7), usually with the conclusion that most examples with that designation represent either highly vascular gliomas or vascular malformations with a pronounced astrocytic reaction.

In this paper, we document the occurrence of central nervous system neoplasms that are composed partly of glial tumor cells but which include, or are contiguous with, areas whose morphologic appearances are those of a capillary hemangioblastoma. Whether these tumors are truly mixed neoplasms composed of independently proliferating glial and angiogenic tumor cells, or glial tumors in which the extraordinary angiogenic proliferation represents a phenomenon of mimicry by the vascular stroma, cannot be decided with assurance. However, these exceptional examples seem, in our view, to justify the designation of "angioglioma." Their importance lies in the diagnostic difficulty they may cause.

MATERIALS AND METHODS

Fifteen tumors referred for consultation to one of us (LJR) over a period of years with the tentative diagnosis of "angioglioma" were re-examined. The majority represented highly vascular astrocytomas, oligodendrogliomas, mixed gliomas, glioblastomas, capillary hemangioblastomas, or vascular malformations in which astrocytes were entrapped. However, four tumors demonstrated the microscopic features of both glioma and capillary hemangioblastoma and formed the basis of this report. In all cases, sections available for study were stained with hematoxylin and eosin (H&E), Weigert's iron hematoxylin-picrofuchsins of van Gieson, silver impregnation of reticulin fibers (Gordon-Swee's method), and Mallory's phosphotungstic acid hematoxylin (PTAH). In two cases, immunohistochemical studies for glial fibrillary acidic (GFA) protein were carried out by the peroxidase-antiperoxidase (PAP) method of Sternberger (8), utilizing as primary antiserum rabbit anti-bovine GFA protein serum (a gift from Dr. Lawrence F. Eng, Stanford, California) at a dilution of 1:1,000. Immunohistochemical examination for Factor VIII:von Willebrand-related antigen (kindly performed by Dr. R. D. McComb, Durham, North Carolina), and electron microscopy were performed in one case.

CASE REPORTS

Case 1 (PM 71/57)

A 52-year-old female had a five-month history of occipital headaches and vomiting, and presented with papilledema and minimal left-sided incoordination. Following a ventriculogram (performed in 1957), which demonstrated bilateral ventricular dilatation and a slight left-sided shift, a right-sided posterior fossa operation revealed tumor-like tissue arising from the region of the fourth ventricle. A biopsy was interpreted as a vascular hamartoma (arteriovenous angiomata) of the cerebellar leptomeninges. The patient died a few hours after operation, and autopsy disclosed a well-defined, granular pink and gray tumor with focal gelatinous cystic changes occupying the medial portion of the left cerebellar lobe, extending laterally, partially destroying the dentate nucleus, and reaching the surface of the hemisphere.

The histopathologic picture at the periphery of the tumor was different from that at the center. In the outer zones, the tumor had the features of a cystic and highly vascular anaplastic astrocytoma. Many of the tumor cells were gemistocytic (Fig. 1A), others more fibrillary (Fig. 1B). The tumor formed nodules that merged fairly sharply into normal cerebellum. Vascular endothelial proliferation was conspicuous throughout (Fig. 1C), and also involved the adjacent white matter. In the center, the picture was that of a mixture of the reticular and the cellular variants of capillary hemangioblastoma (Fig. 1D), as confirmed by the presence of an abundant reticulin fiber network that highlighted the vascular pattern (Fig. 1E). The immunoperoxidase stain for GFA protein was positive in the areas of astrocytoma (Fig. 1F)
Fig. 1. Case 1. A. Area of gemistocytic astrocytoma. PTAH, ×250. B. Area of fibrillated astrocytoma. PTAH, ×250. C. Vascular endothelial proliferation in cerebellar white matter adjacent to tumor. H&E. ×125. D. Central area of capillary hemangioblastoma. Note one entrapped reactive astrocyte in middle lower field. Immunoperoxidase reaction for GFAP, counterstained with hematoxylin. ×300. E. Reticulin fiber network in central area of capillary hemangioblastoma. Silver impregnation for reticulin. ×150. F. Area of astrocytoma with tumor cells positive for GFA protein. Immunoperoxidase stain for GFAP. ×315.
and negative in the cells forming the hemangioblastomatous component, with the exception of occasionally strongly staining cells that were interpreted as entrapped reactive astrocytes (Fig. 1D).

Comment

This case illustrates an anaplastic cerebellar astrocytoma with an exuberant degree of vascular endothelial proliferation, which appears to have given rise secondarily to a centrally situated capillary hemangioblastoma, therefore producing a mixed angiogenic and glial neoplasm. This tumor has previously been quoted by one of us (7, p. 190) in the context of a brief discussion on angiogliomas. Its true significance is now recognized in the light of the other examples described in this report and of our reanalysis of the histopathologic problems inherent in the concept of angioglioma.

Case 2 (C-4389)

A 65-year-old woman was admitted with a four-week history of progressive numbness over the abdomen, difficulty in walking and lower-limb spasticity. There was a left Babinski sign. Touch and deep sensation were decreased in the lower limbs. A myelogram and computerized axial tomography (CT scan) revealed widening of the spinal cord between the C4-5 and T2-3 intervertebral disc levels. A highly vascular intramedullary spinal tumor, measuring 2 × 1 × 1 cm, was excised.

Microscopic examination revealed two types of tumor that were contiguous to each other, but with some intermingling in the zones of juxtaposition. About half of the neoplasm consisted of a mixed glioma, partly ependymoma (Fig. 2A), partly astrocytoma, with the latter demonstrating abundant glial fibrils (Fig. 2B). This part of the tumor had an abundant intersecting vascular stroma, with only minimal local vascular endothelial proliferation. Adjacent to the zones of glioma, the microscopic features of the tumor were indistinguishable from those of the reticular variant of capillary hemangioblastoma (Fig. 2C), as confirmed by the presence of an abundant reticulin fiber network (Fig. 2D). In some fields, the vascular pattern of the hemangioblastoma was sharply demarcated from the gliomatous component (Fig. 2D).

The immunoperoxidase stain for GFA protein was positive in the areas of fibrillary astrocytoma and negative in the ependymomatous zones. In the hemangioblastomatous areas, the cells were negative for GFA protein, except for the presence of included reactive astrocytes (Fig. 2C).

Immunohistochemical staining for Factor VIII: von Willebrand-related antigen showed positivity only in the endothelial cells of both the hemangioblastic and glial areas. Electron micrographs revealed no unusual features in either the vascular or glial components.

Comment

This case illustrates an apparently composite spinal intramedullary tumor, composed partly of a mixed astrocytoma and ependymoma, and partly of a capillary hemangioblastoma. In this case, it is not possible to decide whether one type of tumor tissue stimulated the neoplastic proliferation of the other, or whether both types of neoplastic tissue arose independently and subsequently became intimately associated at their site of junction, resulting in a "collision tumor."

Case 3 (C-1898)

A 51-year-old woman presented with a six-week history of ataxia, headaches, and increased intracranial pressure. An apparently well-circumscribed cerebellar tumor was removed.

Histologically, the tumor consisted largely of a cellular mixed glioma, predominantly oligodendroglioma, but also demonstrating areas of astrocytoma and ependymoma. The oligo-
Fig. 2. Case 2. A. Area of ependymoma. H&E. ×110. B. Area of fibrillated astrocytoma. PTAH. ×250. C. Area of capillary hemangioblastoma. Note one entrapped reactive astrocyte in right middle field. Immunoperoxidase for GFAP, counterstained with hematoxylin. ×400. D. Area of capillary hemangioblastoma (lower half) adjacent to glioma (upper half). Silver impregnation for reticulin. ×200.
dendroglial areas showed the typical pattern of round or polyhedral cells with a clear cytoplasm intersected by an abundant thin-walled vascular stroma (Fig. 3A). Other areas included ependymal rosettes (Fig. 3B), in which apical blepharoplasts were demonstrable with the PTAH stain. In a few areas, the vascular pattern of the oligodendrogioma merged into areas that had the features of the reticular variant of capillary hemangioblastoma (Fig. 3C), as confirmed by the presence of a closely knit reticulin network (Fig. 3D). In the areas of juxtaposition of the two different tissue types, anastomosing extensions of hemangioblastoma segregated islands of glioma (Fig. 3D).

Comment

This case illustrates an example of mixed oligodendrogioma, astrocytoma and ependymoma, in which the areas of vascular proliferation in the oligodendrogioma merged with areas of capillary hemangioblastoma, suggesting that a hemangioblastoma developed from the vascular stroma of a mixed glioma.

Case 4 (C-790)

A 56-year-old woman presented with a poorly circumscribed mass in the posterior fossa. Angiography demonstrated a highly vascular tumor, interpreted as either glioblastoma or capillary hemangioblastoma.

Microscopically, the central portion of the tumor consisted of a capillary hemangioblastoma of the reticular variant (Figs. 4A and B), in which some of the included intravascular cells frequently displayed bizarre hyperchromatic and enlarged nuclei. The periphery of the resected neoplasm was composed of a rim of nodular glial areas (Fig. 4C), whose distinction from the central hemangioblastoma was emphasized in the silver impregnations for reticulin fibers (Fig. 4B). The glial areas comprised a number of astrocytic cells with atypical, bizarre, and hyperchromatic nuclei (Figs. 4C and D). No vascular endothelial proliferation, mitotic figures, or foci of necrosis were present in these atypical glial areas.

Although the patient has some residual cerebellar ataxia, she is alive twelve years after operation without evidence of recurrence.

Comment

This case illustrates an example of capillary hemangioblastoma with a peripheral rim suggestive of an astrocytoma. The presence of reactive as well as atypical neoplastic appearing glial elements in the islands incorporated within the invading front of the hemangioblastoma suggests that this tumor may represent an example of a "reactive" glioma induced by the hemangioblastoma.

DISCUSSION

The characteristics of our four examples of mixed capillary hemangioblastoma and glioma are summarized in Table 1. Three tumors were located in the cerebellum and one in the cervical-thoracic segment of the spinal cord. All cases occurred in females older than 50 years of age. The hemangioblastic component belonged to the reticular variant in three tumors, and consisted of a mixture of the reticular and the cellular variants in one. The glial elements were astrocytic in two cases. Two tumors had a mixture of astrocytes and ependymal cells, and one showed a predominantly oligodendroglial component in addition to both astrocytes and ependymal cells. The hemangioblastic and glial components were clearly distinguishable in many areas, but were also intimately associated with each other, without intervening connective tissue or non-neoplastic neural tissue. In Cases 1 and 3, the hemangioblastoma-like component represented only a small portion of the neoplasm. In Case 2, about half...
Fig. 4. Case 4. A. Central portion of capillary hemangioblastoma. Note occasional large hyperchromatic nuclei. H&E. ×250. B. Periphery of capillary hemangioblastoma (left half) adjacent to reticulin-free glial area. Silver impregnation for reticulin. ×100. C. Peripheral nodules of glial areas containing atypical cells (right half and lower middle of field), adjacent to periphery of hemangioblastoma (left half). H&E. ×150. D. Enlargement of peripheral nodular glial area containing atypical astrocytes. H&E. ×400.
of the tumor was represented by the hemangioblastic component. In Case 4, the tumor was largely hemangioblastic. In Cases 1 and 2, the immunoperoxidase stain for GFA protein confirmed the nature of the astrocytic cells entrapped within the hemangioblastoma, as described in previous studies (1, 2). In Case 2, bands of PTAH-positive fibers and fibrillary material staining positively for GFA protein were abundant in the periphery of the hemangioblastic component, and in places could be traced for some distance in the tumor, a feature previously noted by Deck et al (9). In Case 1, vascular endothelial proliferation was prominent both within and around the areas of malignant astrocytoma.

The first three tumors discussed in this report are, in our view, examples of highly vascular gliomas in which advancing tongues of intense vascular endothelial proliferation merged into zones in which the glial elements became indistinct or apparently absent, and which consequently became identical with capillary hemangioblastoma, usually of the reticular variant. Case 4 represents a hemangioblastoma surrounded by a rim of possibly “reactive” glioma, a secondary process that presumably remained localized, as indicated by the favorable outcome in this patient.

Our interpretation that the first three tumors represent true mixed capillary hemangioblastomas and gliomas rather than gliomas with an unusually exuberant vascular endothelial proliferation rests on purely morphologic grounds. However, even though the independent neoplastic potential of the hemangioblastoma-like component in the first three of these mixed neoplasms lacks biological verification, we suggest that all four tumors described in this report deserve the designation “angioglioma.”

Historically, Councilman (10) seems to have been the first author to designate as “angioglioma” a cerebellar tumor because of its unusual vascularity. The same neoplasm was subsequently reinterpreted as an ependymal glioma by Bailey (11) and as a hemangioma by Lindau (12). As mentioned in the introduction, the term “angioglioma” was subsequently used by Roussy and Oberling (3) to designate the cellular variant of capillary hemangioblastoma which, according to Cushing and Bailey (4), could be separated from the more common reticular variant because of the resemblance of its microscopic pattern to that of carotid body tumors. However,
both variants are not uncommonly bridged by transitional examples in which both patterns are readily demonstrable (2). Some support was given to Roussy and Oberling's views by Henschel (5), who likewise identified cerebellar angiogliomas with those cases that Bailey and Cushing compared with cataroid body tumors, and who interpreted such "cerebellar angiogliomas" as "tumors that are characterized by a simultaneous growth of angio blasts and glioblastic elements." On the whole, the view of Cushing and Bailey merging both variants within the single entity of capillary hemangioblastoma is the one generally accepted today.

The term "angioglioma" has, however, more frequently been used in an entirely different sense, i.e., to designate primarily glial neoplasms, either astrocytic or oligodendroglial, in which a considerable proliferation of the vascular stroma is present (5-7, 13). These examples, which in our experience are most often found in the cerebellum and, less frequently, in the parieto-occipital lobes in children, do not essentially differ from other forms of glioma, either benign or malignant, in which a marked vascular endothelial proliferation is present. The vascular component of these tumors seems to represent an exaggerated response of the vasculature to the neoplastic process. Thus, the two tumors identified by Fischer et al (13) as cerebral hemangiomas with glial neoplasia and for which the name "angioglioma" was indeed tentatively suggested simply represent, in our view, instances of gliomas in which the range of vascular stromatous reaction extends from a pattern of hyalinized telangiectases and cavernous vascular spaces to the development of venous fistulae.

On the other hand, some vascular anomalies, especially arteriovenous malformations and, to a lesser extent, cavernous and venous angiomas (5, 14-16), are often associated with a conspicuous reactive glial proliferation. In these lesions, the resulting morphologic picture often compounded with the added glial reaction due to repeated episodes of hemorrhage may at times suggest a true glioma. In our opinion, none of these examples represents a mixture or a combination of unquestionably neoplastic glial and vascular elements, and none, therefore, deserves the term "angioglioma." This, in our view, should be reserved for the combination of glioma and capillary hemangioblastoma occurring together, in intimate proximity to each other, and whose histologic features therefore conform to those of the examples described in this report.

Mixed intracranial neoplasms composed of glial and mesenchymal elements are well recognized (7). The most frequent type is the gliosarcoma, originally described by Stroebel (17), and further studied by Feigin and his colleagues (18-20). In this tumor, the exuberant vascular endothelial and fibroblastic proliferation occurring in the stroma of a malignant glioma develops into a sarcomatous component that is characteristically perivascular. This type of mixed glioma and sarcoma has been estimated to occur in approximately 8% of all glioblastomas (20).

In the second type of mixed sarcoma and glioma (sarcoglioma), the development of a mixed mesenchymal and glial tumor is interpreted as secondary to the hyperplastic gliosis occurring in the cerebral parenchyma invaded by a meningeal sarcoma or a malignant meningioma. A peripheral rim of glioma develops (21). In both variants of mixed cerebral neoplasms, the juxtaposition of tumor elements of different cell types is regarded, according to the concept of Foulds (22), as representing examples of dependent mixed neoplasia, i.e., one in which a secondary neoplastic change has taken place in the stroma or in the adjacent or included host tissue of a tumor. This concept postulates the horizontal transmission of malignancy to puta-
tively normal differentiated stromal host cells. Such a hypothesis is currently gaining support from experiments on the activation of transforming genes induced by the DNA of various human neoplasms and resulting in the in vitro or in vivo transfer of genetic information coding for malignant transformation in mouse fibroblasts (23, 24). The concept of dependent mixed neoplasms is in contrast to the two other types of mixed or combined tumors defined by Foulds (22): i.e., "collision tumors," which result from the development of independent primary tumors apposed to each other and intermingling only at their junction; and composite tumors, which result from the concurrent participation of both the parenchyma and the stroma in the neoplastic process.

The concept of "angioglioma" proposed here implies a true mixed neoplasm (i.e., composite or dependent), and not the result of the coincidental apposition (collision) of two independent lesions, as may happen when an arteriovenous malformation is associated with a distinctly separate astrocytoma (25). Three hypotheses can be advanced for the histogenesis of the angioglioma as we now define it: 1) Some capillary hemangioblastomas induce a prominent reactive glial proliferation that eventually progresses to neoplasia. 2) The vascular component of a glioma with intense endothelial proliferation undergoes secondary neoplastic change, developing into a focal hemangioblastoma. 3) Simultaneously or consecutively acting oncogenic factors determine the neoplastic transformation of both glial and angiogenic elements, resulting in a composite tumor.

The morphologic appearances of Case 4 support the first of the above hypotheses and suggest a focal neoplastic transformation of the reactive glial cells which are commonly found at the periphery of capillary hemangioblastomas (1, 2). We therefore align this tumor with those rare examples in which an intracranial sarcoma or a malignant meningioma is associated with a secondary peripheral glioma (sarco- glioma) (21).

The second hypothesis, tentatively applicable to the first three cases in this report, that the hemangioblastoma-like areas are the result of a neoplastic transformation of the proliferating vascular endothelial cells in a glioma, seems entirely possible by analogy with the gliosarcomas already mentioned above. It assumes that a tumor angiogenesis factor, which has been demonstrated to be mitogenic for endothelial cells and is produced by glioma cells as well as by other types of neoplastic cells (26–28), might in some instances result in the neoplastic transformation of the angiogenic elements. Unfortunately, the demonstration of relatively tissue- or cell-specific antigenic determinants by immunomorphologic techniques has not so far been successful in helping to answer the question of whether, in our cases, the angiogenic elements have become independently neoplastic. Positivity for GFA protein, which is demonstrable in both reactive and neoplastic glial cells, does not establish their neoplastic nature, which rests entirely on the demonstration of traditional microscopic features, such as cellular atypia, histologic pattern, and tissue invasion. The use of Factor VIII: von Willebrand-related antigen as a marker for the neoplastic stromal cells in capillary hemangioblastomas provided even less help. The positivity of stromal cells for this factor, reported by Jurco et al (29), has been denied by others (30), who found that the marker was demonstrable only in endothelial cells lining vascular spaces. Moreover, the same marker, while present in the lining endothelial cells of both glioblastomas and gliosarcomas, failed to stain the other neoplastic mesenchymal elements of gliosarcomas, perhaps because these
neoplastic cells had undergone antigenic loss following transformation (31). It is therefore unlikely that the use of Factor VIII: von Willebrand-related antigen would have established in our cases that the hemangioblastoma-like foci in the first three examples described in this report unquestionably represent a true neoplastic process. In any event, the diagnostic difficulties raised by these tumors are considerable.

The third hypothesis, i.e., that oncogenic factors act simultaneously on different cellular elements, has been invoked in explaining the development of tumors of mixed cell populations following the local transforming action of chemically implanted carcinogens or oncogenic viruses (32). In a naturally occurring tumor in man, this remains a possibility for which parallel examples exist in other organs (e.g., the fibroadenoma of the breast), but for which no other support can so far be adduced.

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