Combined neurilemmoma and angioma

Tumor of ectomesenchyme and a source of bleeding

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Eight cases are described of intracranial and peripheral neoplasms composed of mixed neurilemmoma and hemangioma. It is proposed that ectomesenchyme can differentiate into neurilemmoma and angioma. The latter may be related to recently described angiogenetic factors, or to developmental factors as in rare cases of arterial angiomas. The angiomatous part may be common, but has often been overlooked. The presence of abnormal vessels, whether in kind or in number, helps explain various biological features of neurilemmoma. These vessels frequently bleed within the tumor, which results in the characteristic hemosiderin-laden macrophages. Bleeding may also occur into the cerebrospinal fluid (CSF) to create xanthochromia. The frequent increase in CSF protein in cases of neurilemmoma is attributed to transudation of serum from abnormal vessels. Less commonly, bleeding may be sufficient to cause subarachnoid hemorrhage. The dense collagen usually associated with these angiomas accounts for the relative infrequency of major hemorrhages.

KEY WORDS: combined tumor, neurilemmoma, angioma, hemorrhage

The term "combined" here means two types of neoplasm intermingled in the same mass, or contiguous, or both. Neurilemmomas combined with other tumors have been described: meningioma, lipoma, astrocytoma, rhabdomyosarcoma, and ganglioneuroma. Five cases of neurilemmoma mixed with vascular tumor have been reported. Eight additional cases are described here with consideration of the relations between neurilemmoma and angioma as derivatives of ectomesenchyme, and of the vascular abnormality as a source of bleeding.

Materials and Methods

A total of 103 patients seen in the Division of Neurosurgery from 1930 to 1977 had the diagnosis of acoustic neuroma, perineural fibroblastoma, schwannoma, or neurilemmoma. Of these, eight (7.8%) had a mixture of neurilemmoma and angioma in the same lesion. In five cases the neoplasm involved the posterior fossa; three were in the spinal cord or peripheral nerve (Table 1). All clinical records and two autopsy protocols of these eight patients were studied after review of the microscopic material. The tissues were fixed in 10% formalin and embedded in paraffin. Hematoxylin and eosin stain was used routinely, and occasionally phosphotungstic acid-hematoxylin.

Results

The clinical features and anatomic diagnoses in the eight cases are given in Table 1. The five tumors in the posterior fossa were all associated with unilateral deafness, ataxia, and roentgenographic evidence of cerebellopontine angle tumor. The single neoplasm of the spinal cord resulted in unilateral weakness and bilateral hyperreflexia. The two masses affecting peripheral nerve caused pain in a characteristic distribution.

Grossly, all tumors were well encapsulated, often with a nodular appearance. The color was yellow-gray or pink-white. The consistency was firm and rubbery, or friable. The smallest intracranial mass weighed about 10 gm, the largest weighed more than 33 gm. Only two tumors (Cases 2 and 3) were described as "vascular" on gross examination. The tumors in Cases 6 and 7 were gelatinous peripherally, and had a central hard white core.

Microscopically, all tumors contained cells in patterns of parallel rows and palisades. The loose
FIG. 1. Case 1. Palisades (below) and broad hyalinized collagenous vascular spaces (above). H & E, × 100.

TABLE 1
Clinical and pathological features

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age, (yrs)</th>
<th>Sex</th>
<th>Location</th>
<th>Duration of Symptoms (yrs)</th>
<th>Type of Hemangioma</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>47</td>
<td>M</td>
<td>rt, acoustic nerve</td>
<td>26</td>
<td>capillary &amp; cavernous; dense collagen</td>
</tr>
<tr>
<td>2</td>
<td>64</td>
<td>M</td>
<td>lt, acoustic nerve</td>
<td>7</td>
<td>cavernous</td>
</tr>
<tr>
<td>3</td>
<td>40</td>
<td>F</td>
<td>lt, acoustic nerve</td>
<td>5</td>
<td>cavernous</td>
</tr>
<tr>
<td>4</td>
<td>55</td>
<td>M</td>
<td>lt, acoustic nerve</td>
<td>3</td>
<td>cavernous</td>
</tr>
<tr>
<td>5</td>
<td>60</td>
<td>F</td>
<td>rt, acoustic nerve</td>
<td>0.5</td>
<td>arterial</td>
</tr>
<tr>
<td>6</td>
<td>66</td>
<td>F</td>
<td>spinal cord, C1-2</td>
<td>0.25</td>
<td>cavernous; dense collagen</td>
</tr>
<tr>
<td>7</td>
<td>58</td>
<td>F</td>
<td>rt, peroneal nerve</td>
<td>1</td>
<td>cavernous; dense collagen</td>
</tr>
<tr>
<td>8</td>
<td>60</td>
<td>M</td>
<td>lt, ulnar nerve</td>
<td>10</td>
<td>cavernous</td>
</tr>
</tbody>
</table>

reticular and less cellular zones were particularly prominent. The nuclei had rod or spindle shapes, and were arranged in wavy streams and loops. Hemosiderin was frequently seen in the loose and reticular areas as evidence of previous hemorrhage. Case 1 had striking areas of broad collagenous tissue associated with numerous small and large vascular spaces (Fig. 1); the vessels had walls with hyalin thickening. Telangiectases were also noted in the loose areas. In Cases 2, 3, and 4, many enormous and a few small vascular spaces were aggregated in loose reticular regions (Fig. 2). Most vessels were hyalinized. The cavernous spaces were separated by scant connective tissue, often containing hemosiderin-laden macrophages. Some vessels contained thrombi.

A large cluster of arterial vessels with normal walls was seen in the loose areas, as well as many malformed arteries in dense collagenous tissue in Case 5 (Fig. 3). The histological appearance in Cases 6 and 7 was similar. The peripheral gelatinous part contained extremely large vascular spaces in association with broad bands of dense collagen. The central core was related to the schwann cells (Fig. 4). An additional feature in Case 8 was the presence of large and small abnormal vessels closely related to the neurilemmoma rather than embedded in collagen (Fig. 5).

Discussion

Intracranial and spinal neurilemmomas usually become symptomatic in patients aged from 40 to 50 years. The median age in the 229 cases of Zülch43 was 41.5 years. Cavernous hemangiomas are found at all ages, but most often are clinically apparent in patients aged between 30 and 50 years.44 In the series of McCormick, et al.,38 the average age of 148 patients with posterior fossa angiomas was 43.6 years. The average age of 56 years in our series of combined lesions is slightly higher.

Neurilemmomas occur predominantly in women. Zülch43 reported 66% of cases in women, and Russell and Rubinstein18 gave a figure of 76%. Angiomas, however, are twice as common in men.45 In our series, the sex distribution was equal, probably because the two lesions were balanced, but the total number is small. The duration of symptoms of the intracranial lesions ranged from 0.5 to 26 years. The 4-month onset of the spinal cord lesion was less than in other locations because of cord compression. The two cases of peripheral nerve tumor had symptoms for 1 and 10 years. The autopsy in Case 2 showed a large amount of subarachnoid hemorrhage in the left cerebellopontine angle. None of the other four cases of acoustic tumor or at other sites was known to be complicated by external bleeding.

Cushing7 described the vascularity in neurilemmoma: "as a rule the tumors are sparsely vascularized
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but in some cases the vessels in certain areas are sufficiently numerous to give to the tumor an angiomatic appearance.” The angiograms of 32 patients with neurilemmomas of the head and neck were reviewed by Moscow and Newton. They found 22 (68%) had abnormal tumor vascularity, but did not consider that the blood vessels were those of angioma.

Anatomically, five cases of this combined tumor have been previously reported. A case of neurilemmoma and cavernous angioma in a tumor of the posterior mediastinum of a 17-year-old boy was briefly described by Willis. Inglis reported a case of “liponeurilemmoblastoma” of the kidney which retained an angiomatous component. A case of hemangiendothelioma of the sciatic nerve was associated with proliferation of schwann cells mimicking a schwannoma. This case was reviewed by Stout, who suggested that a large neurilemmoma was associated with a hemangiendothelioma, and that the latter invaded the capsule. A case of combined acoustic neurilemmoma with cavernous hemangioma was reported by Dykstra. Shuangshoti and Netsky described a case of neoplasm of mixed mesenchymal and neuroepithelial type (dedifferentiated meningioma, neurilemmoma, and poorly differentiated astrocytoma) in which numerous blood vessels clustered in some areas to form an angioma.

The question arises whether these angiomatous vessels are an acquired or a developmental abnormality. It is known that blood vessels in cerebral tumors undergo structural changes that may become more severe with increasing malignancy. Vascular proliferation can occur in some benign gliomas. When endothelium is affected, the phenomenon is regarded as the earliest evidence of dedifferentiation. Cox, et al., observed the fine structure of individual capillaries in and around ethylnitrosourea-induced gliomas and schwannomas in rats. These vessels in schwannoma had similar changes to those found in gliomas.
Several factors initiating the proliferation of vascular endothelial cells have been reported. Folkman, *et al.*,12 isolated a soluble factor in vivo, the tumor angiogenesis factor, from human and animal tumor cells, but not from normal tissue. It resembled a nondialyzable ribonucleoprotein of approximately 100,000 molecular weight.13 This factor stimulated endothelial cells, pericytes, and fibroblasts. This broad mitogenic response could result from an impure fraction. Suddith, *et al.*,39 observed another factor in vitro, an endothelial proliferative factor, elaborated by clonal cell lines of neural origin. It had some physical properties different from the tumor angiogenesis factor, and affected only endothelial cells. Gospodarowicz14 isolated a fibroblast growth factor, a polypeptide of 13,000 molecular weight, from bovine brain and pituitary gland. It had a mitogenic effect on many mesodermally derived cells, including endothelial cells and vascular smooth muscle.16 The nature of these factors, however, is not clearly understood. It is possible that they have common constituents. This factor or factors may be responsible for initiating tumor neovascularization.

The developmental origin of angiomas associated with neurilemmomas may be considered in relation to the neural crest. These cells of the crest have the ability to form various structures, including peripheral ganglia and subcutaneous connective tissue of the cranial region.21,40 They can differentiate into various cell types, such as schwann cell, branchial cartilage, arachnoidal, pial, and mesenchymal cells.18 Platt proposed the term “mesectoderm” for mesenchyme of ectodermal origin,21 and later this term has been frequently used for ectomesenchyme.20,21,25

The mesenchymal cells are pluripotential and may differentiate into types such as fibroblasts, lipoblasts,
and osteoblasts. The intra-embryonic blood vessels of the human embryo begin in the first visceral arch at the late presomite stage. The lateral plate becomes confined to a central core of visceral arches. The cells of the neural crest move into the arches and contribute to the formation of their walls. The angiogenetic cell clusters originating from the mesenchyme appear in the lateral plate mesoderm. The outermost cells of blood islands change to angioblasts. The innermost cells either form blood corpuscles or disintegrate to plasma. The blood islands then become plexiform and are transformed into small blood vessels. Johnston and Listgarten suggested that the blood vascular system is of mesodermal origin and extends out as capillary buds into the surrounding mesenchyme of the neural crest.

At the time that neural crest cells undergo proliferation in the arch, the lateral plate mesoderm is still loosely arranged. The mesenchymal cells of the crest thus may intermingle with comparable cells of lateral plate mesoderm. We therefore suggest that vascular elements can arise from mesenchyme of both neural crest and lateral plate mesoderm.

Based on these observations, the combination of neurilemmoma and angioma, or neurilemmoma and other mesenchymal tumors, such as lipoma, rhabdomyoma, or meningioma can be readily explained on the basis of their origin in ectomesenchyme. We therefore consider that the abnormal vessels in our series arise either as a fault of development, or as part of neoplastic growth, which may in turn relate to tumor angiogenetic factor or factors. Vessels arising on a developmental basis may retain normal structure, such as media muscularis or elastica. Those vessels arising secondary to neovascularization do not contain these normal structures. The combination of neurilemmoma and angioma may be common, but the angiomatous component largely has been ignored in the past. One reason may be that the vascular tumor is not recognized grossly, as in our series, where only Cases 2 and 3 were described as “vascular” at craniotomy.

The vascular changes in neurilemmomas have a wide range. Some tumors are sparsely vascularized, but most contain numerous scattered vessels, often with thin walls. These vessels may bleed within the tumor; the resulting hemosiderin in both macrophages and parenchyma is a characteristic but not specific feature of neurilemmoma. Occasionally these vessels cluster. If the cluster in the neurilemmoma is sufficiently large to warrant an independent diagnosis of angioma, we term the lesion a “combined” tumor. The walls of some angiomatous vessels were thin, others were thick and hyalin. In the single case of arterial angioma, most vascular walls had a normal architecture.

Various intracranial and intraspinal tumors have been associated with acute subarachnoid hemorrhage (SAH). These include gliomas, but the tendency of schwannomas to bleed is less well known. Recently, cases have been reported of acoustic neurilemmomas associated with SAH. McCoyd, et al., described a tumor consisting of neurilemmoma and numerous dilated vessels that we interpreted as an angiomatous part. The tumor was covered with blood, and hemorrhage extended into the subarachnoid space. Fine, et al., reported a case of spontaneous SAH complicating an acoustic neurilemmoma. There was frank hemorrhage in and around the tumor itself. Microscopically, the mass contained numerous hemosiderin-laden macrophages. The authors considered an enlarged internal auditory artery as a possible source of bleeding, but we suggest that hemorrhage in the tumor and subarachnoid space could have occurred from intrinsic vessels. Three cases of spinal neurilemmoma associated with SAH have been reported. One was a malignant tumor involving the conus and cauda equina; the remainder were histologically benign. The cerebrospinal fluid (CSF) in these cases ranged from xanithochromic to bloody.

Merritt reviewed the CSF changes in patients with various brain tumors. In his series of acoustic neurilemmoma, 14 of the 16 patients had a CSF protein content of more than 100 mg%, and seven had xanthochromia. Lups and Haan state that these tumors “nearly always cause xanthochromia.” The elevation of protein content in cases of acoustic neurilemmoma is well known but not clearly understood. Merritt suggested transudation of serum protein from vessels of the tumor. The presence of the neoplasm in close association with the CSF does not necessarily account for the rise in protein, because some meningiomas in the cerebellopontine angle do not cause this striking elevation. It should be noted that some small neurilemmomas may not be associated with elevated protein content. Increased permeability of thin-walled or otherwise abnormal blood vessels is probably the reason for the frequent elevation of protein. Xanthochromia could be the result of mild or moderate leakage of blood from these vessels, and SAH the consequence of major rupture of vessels. Liability of these blood vessels to bleed is increased when the multiple channels of an angioma are present.

Hemorrhage may arise from neoplasms not only as a result of rupture of thin-walled, poorly formed vessels in the tumor, but also from neoplastic erosion of vessels, or operative manipulation. Necrosis within tumor with loss of vascular support may be another factor. In our series of five cases of intracranial lesions, three were cavernous in type, one was mixed capillary and cavernous, and one was a thick-walled arterial type. The remainder in the spinal cord and peripheral nerves were cavernous. All the cavernous lesions in our series had previous hemorrhage as indicated by the presence of hemosiderin-laden macrophages. In our larger series of 103 cases of neurilemmoma and angioma, the combination of neurilemmoma and angioma was commonly observed.
moma, five had necropsy evidence of SAH, but only one of these had a demonstrable angioma. We consider that even small numbers of fragile vessels may result in major bleeding.

An important feature of the presence of abnormal vessels then is an increased liability to bleed. The occurrence of SAH with combined tumors, however, is not common. Several factors may be responsible for such an infrequent association. In our series, the angiomatous part was often associated with broad bands of dense collagenous connective tissue. These fibrous bands may either be part of the healing process after small hemorrhages into the tumor, or they may be produced by neoplastic cells. The dense bands can prevent further major hemorrhage. Surgical intervention before massive hemorrhage may be a preventive factor, and some hemorrhage may not be recognized because the CSF was not examined.

References
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