Capillary hemangioma of the central nervous system

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Object. Capillary hemangiomas are benign tumors or tumorlike lesions that originate from blood vessels and have rarely been reported to develop in the brain or spinal cord. The authors summarize the clinical and histological features of capillary hemangiomas of the central nervous system (CNS).

Methods. The clinical features, imaging characteristics, and outcomes in 10 patients with CNS capillary hemangiomas were reviewed. Histological studies included immunostaining with CD31, α-smooth muscle actin, vascular endothelial growth factor, and Ki-67 antigen. Three patients with lesions in the brain presented with symptoms of increased intracranial pressure or seizures. Seven patients with lesions in the spinal cord presented with progressive sensorimotor disturbances of the lower limbs. Computerized tomography and magnetic resonance imaging demonstrated well-defined, enhancing lesions associated with marked perifocal edema. Angiography demonstrated hypervascular lesions, which have not recurred after resection. In two cases, multiple satellite lesions resolved after the systemic administration of steroid drugs or interferon-α. Histologically, all lesions were consistent with findings of capillary hemangioma of the skin or soft tissues. The CNS lesions differed significantly from other vascular neoplasms, such as hemangiendotheliomas, hemangiopericytomas, and hemangioblastomas.

Conclusions. Capillary hemangiomas of the CNS are benign lesions that can be surgically removed and cured without adjuvant therapy.

KEY WORDS • capillary hemangioma • vascular tumor • brain • spinal cord

Hemangiomas of the brain and spinal cord are generally considered to be malformations or hamartomas. Capillary hemangiomas are benign tumors or tumorlike lesions that are most often encountered in the skin and soft tissues. Histologically, these lesions are characterized by a lobular architecture, with each lobule fed by a large artery. Lesions consist of numerous capillaries that are lined by flattened endothelium. Capillary hemangiomas of infancy are the immature form of capillary hemangiomas. The lumina of the vasculature in these lesions are narrowed by plump endothelial cells, which results in a solid appearance.

Capillary hemangiomas of the central and peripheral nervous system are very rare. Most examples have been documented recently and have been shown to arise in spinal nerve roots or the cauda equina. In this report, we describe the clinical and histological features of capillary hemangiomas of the CNS. There has been only one report in the literature of a capillary hemangioma of the brain. Similar cases may have been reported using other terms such as cavernous hemangiomas, “benign hemangiendotheliomas,” and “Masson’s vegetant intravascular hemangiendotheliomas.” The histological differences among capillary hemangiomas, vascular malformations, and other vascular tumors are discussed.

Clinical Material and Methods

Patient Population

This study is a retrospective analysis of the records of 10 patients treated at six different medical centers, specifically: Hiroshima City, Asa Hospital, Hiroshima (five patients); and one patient each at Saga Medical School, Saga; Asahikawa Medical College, Asahikawa; Kagawa Medical School, Kagawa; Morioka Medical School, Kagawa; Morioka, Iwate; and Nagasaki Prefectural Shimabara Hospital, Nagasaki. Three patients had brain lesions and seven had spinal cord lesions. Six of 10 cases have been described previously. The clinical features, imaging characteristics, and outcomes were reviewed and summarized. Recent clinical follow-up data were obtained from the doctors who are treating the patients.

Histological Studies

Histological specimens were stained with H & E as well...
as with Watanabe reticulin. Multiple sequential sections were also cut and prepared for immunostaining with factor VIII–related antigen, CD31, α-SMA, VEGF, glial fibrillary acidic protein, and Ki-67 antigen. Mouse monoclonal antibodies against human von Willebrand factor (concentration 1:100; Novocastra Laboratories, Newcastle, UK), CD31 (1:50; Dako Corp., Glostrup, Denmark), α-SMA (1:150; Dako Corp.), glial fibrillary acidic protein (1:100; Novocastra Laboratories), Ki-67 antigen (1:50; Dako Corp.), and rabbit polyclonal antibody against VEGF (1:500; Santa Cruz Biotechnology, Santa Cruz, CA) were used. Endogenous peroxidase in the sections was inactivated with 0.3% H2O2 phosphate-buffered saline for 5 minutes. After rinsing in phosphate-buffered saline, the sections were submerged in 0.01 mol/L citrate buffer (pH 6) and were heated at 121°C for 5 minutes in an autoclave for antigen retrieval. After cooling to room temperature, the sections were incubated with primary antibodies for 2 hours, followed by horseradish peroxidase–conjugated goat antibody to mouse or rabbit immunoglobulin G (Dako Corp.). The labeled horseradish peroxidase was visualized as brown by the 3,3’-diaminobenzidine–hydrogen peroxide method. The sections were counterstained with hematoxylin. Negative control sections were treated with mouse or rabbit normal immunoglobulin G instead of the primary antibodies. Optimal antibody dilutions were selected after examination of sample slides at serial concentrations higher and lower than those recommended by the manufacturers. The percentage of positive cells on Ki-67 antigen immunostaining (MIB-1 index) was calculated by counting stained nuclei in tissue sections.

Results

Clinical Findings

Three patients with lesions in the brain (Cases 1–3, Table 1) included two males and one female 8 to 20 years of age (median age 16 years). Two patients presented with symptoms of ICP and one presented with seizures. Symptoms had lasted from 2 days to 2 months by the time the patients underwent surgery. Neurological examination on admission revealed papilledema with minimal abducens nerve paresis in one patient and no deficits in the other two.

Seven patients with lesions in the spinal cord (Cases 4–10) were all men between the ages of 43 and 80 years (median age 64 years). All patients presented with progressive sensorimotor disturbances of the lower limbs. Symptoms had lasted from 6 days to 4 months by the time the patients underwent surgery. Neurological examination on admission showed paraparesis in all patients. One patient (Case 4) had a history of lumbar injury due to a motor vehicle accident. No cutaneous or mucosal vascular lesions were noted in any of the 10 patients.

Imaging Findings

Plain CT scans revealed areas of slightly high attenuation surrounded by widespread areas of low attenuation, which was indicative of perifocal edema in all patients with brain lesions. A postcontrast CT scan revealed marked enhancement of the lesions (Fig. 1). Multiple lesions were found in two patients: in Case 1 these consisted of several small lesions and one that measured 15 mm in diameter. In Case 2 there were at least six lesions, ranging from those with small diameters to lesions that measured up to 30 mm in diameter. Cerebral angiography demonstrated hypervascular masses that were fed by pial arteries in all cases (Fig. 2). There was no evidence of meningeal arteries that could have supplied the lesions. The MR images demonstrated masses that were slightly hyperintense on T1- and hyperintense on T2-weighted images. Lesions were markedly enhanced following Gd administration (Fig. 3). Magnetic resonance imaging revealed intratumoral hemorrhage in one patient (Case 2).

On MR images of the spine, lesions that were iso- or
slightly hyperintense on T₁- and hyperintense on T₂-weighted images were demonstrated. Masses appeared to be homogeneous, with strong enhancement following Gd injection (Fig. 4). Lesions were located at the middle to lower thoracic spine levels (T₅–₁₁), and were intradurally located on the surface or inside of the spinal cord. Swelling of the spinal cord due to edema was demonstrated in all cases. Extensive swelling from the cervical cord to the conus medullaris was shown in one patient (Case 5). Spinal angiography was performed in two cases and demonstrated hypervascular mass lesions fed by radicular arteries (Cases 4 and 7).

Surgical Findings and Outcome

All patients underwent direct surgery after the preoperative potential diagnosis of metastatic brain tumors or vascular neoplasms. Craniotomy and microsurgical tumor resection were performed in patients with brain lesions. In the two patients with multiple lesions, only the largest one, located in the right frontal lobe (Case 1), and the superficial lesion in the parietal lobe (Case 2) were removed. Macroscopically, lesions were subcortical or cortical, red, vascular-rich masses that were well demarcated from edematous brain parenchyma (Fig. 5); red veins were seen in two cases. A hemorrhage was associated with the lesion in one patient (Case 2). The postoperative course was uneventful for both patients with multiple lesions. The remaining smaller lesions shrank after systemic administration of corticosteroid drugs. The smaller lesions had disappeared on contrast-enhanced CT scans obtained 5 months postsurgery in Case 1. Multiple lesions also regressed after systemic administration of corticosteroid drugs followed by IFNα, and had disappeared on contrast-enhanced MR images obtained 10 months postsurgery in Case 2.

Two-level laminectomy and microsurgical tumor removal were performed in patients with spinal cord lesions. On gross inspection, the lesions were soft, red, and often lobulated intra- and extramedullary masses (Fig. 6). The extramedullary portion often adhered to nerve roots, and the intramedullary portion was well demarcated from edematous spinal cord parenchyma. Surgical outcomes varied among patients: neurological deficits resolved in four, remained stable in two, and worsened in one. Postoperative MR images demonstrated disappearance of spinal cord swelling.

None of the 10 patients showed clinical recurrence during the follow-up period, which ranged from 1 to 15 years (median 6.5 years).

Histological Findings

Histological examination of the lesions revealed a lobular architecture with lobules that were separated by fibrous tissue septa and fed by thick-walled arteries. The lobules were composed of numerous, tightly packed, capillary-sized vessels that were lined by a single layer of cytologically benign endothelial cells (Fig. 7 upper left). Blood vessels varied widely in size from small lumina lined with plump endothelial cells to dilated vessels lined with flattened endothelium (Fig. 7 upper right). Stromal edema and
occasional mitoses of endothelial cells and stromal fibroblastic cells were observed. Scattered stromal lymphocytes were present (Fig. 7 center left), but there was no evidence of foamy stromal cells. The reticulin stain highlighted the delicate network of reticulin fibers that surrounded the vessels (Fig. 7 center right). Glial fibrillary acidic protein immunostaining showed no glial tissue present within the lesions. Factor VIII–related antigen was identified only in the flattened cells that lined the dilated blood vessels. The CD31 immunostaining showed positive results in plump endothelial cells that lined small lumina as well as in flattened cells that lined dilated blood vessels (Fig. 7 lower left). The α-SMA immunostaining showed positive cells in the subendothelial layer that were pericytes (Fig. 7 lower right). Immunostaining with VEGF showed positive cells in the solid or immature-appearing areas without vessel lumen formation, whereas positive cells were rarely found in areas with a well-developed lumen. Immunostaining with Ki-67 antigen showed positive cells among endothelial as well as stromal cells. The MIB-1 index (percentage of positive cells) varied widely among cases (2–12%, median 6.5%).

Discussion

Capillary hemangiomas comprise the largest single group of this tumor type. Histologically, almost all capillary hemangiomas are composed of nodules of small, capillary-sized vessels, each of which is fed by an artery. The lobular or grouped arrangement of vessels is a very helpful feature in distinguishing capillary hemangiomas from malignant vascular proliferations. This group of lesions includes capillary hemangiomas of infancy, epithelioid hemangiomas, lobular capillary hemangiomas (better known as “granulation tissue-type hemangiomas” or “pyogenic granulomas”), and variants of capillary hemangiomas.31

Capillary hemangiomas of infancy are an immature form of capillary hemangiomas. This lesion occurs during infancy at a rate of approximately one in every 200 live births. Approximately one fifth of cases involve multiple lesions. The tumor is most commonly located on the skin or in the mucosa of the head and neck. Although it may resemble a common birthmark in its early stages, with time it acquires an elevated, protruding appearance that has earned it the fanciful designation of “strawberry nevus.” It has been esti-
estimated that by the time a patient is 7 years old, 75 to 90% of these lesions will have involuted, leaving only a small pigmented scar. Histologically, the tumor varies with its age. Early lesions are characterized by plump endothelial cells that line vascular spaces with small inconspicuous lumina, resulting in a solid-appearing lesion. Systemic steroid drugs are currently used to retard or curtail tumor growth before surgery or to obviate surgery.

Fig. 7. Photomicrographs of the tumor specimen. Upper Left: Tumor section showing lobular arrangement of numerous, tightly packed, capillary-sized vessels lined by a single layer of endothelial cells. H & E, original magnification \( \times 200 \). Upper Right: High-power view of the tumor showing a combination of blood vessels with small lumina lined with plump endothelial cells and dilated vessels lined with flattened endothelium. H & E, original magnification \( \times 400 \). Center Left: Tumor section showing stromal edema widely separating vessels. Scattered stromal lymphocytes were observed. H & E, original magnification \( \times 200 \). Center Right: Tumor section showing reticulin stain highlighting fibrous tissue septum and the delicate network of reticulin fibers surrounding the vessels. Watanabe reticulin stain, original magnification \( \times 200 \). Lower Left: Tumor section with CD31 immunostaining showing positive staining of plump endothelial cells lining small lumina as well as flattened cells lining the dilated blood vessels. Original magnification \( \times 400 \). Lower Right: Tumor section with \( \alpha \)-SMA immunostaining showing positive cells in the subendothelial layer that are pericytes. Original magnification \( \times 400 \).
Epithelioid hemangiomas typically occur during early to middle adult life and affect women more often than men. Most epithelioid hemangiomas are superficially situated on the head and neck, particularly around the ear. As a result, they can be detected relatively early as small, dull, red pruritic plaques. In approximately half of all patients multiple lesions develop that generally occur in the same area. Considerable controversy exists about the basic nature of these lesions. A number of authors consider them to be reactive and others believe them to be neoplastic.

The lobular capillary hemangioma is a polypoid form of capillary hemangioma that appears on the skin, on mucosal surfaces, or in veins. Both sexes are affected approximately equally, and the disease is evenly distributed among all ages. Ordinarily, these tumors develop rapidly and achieve their maximum size of several millimeters to several centimeters within weeks or months. As a result, they may be detected relatively early as small, dull, red pruritic plaques. In approximately half of all patients multiple lesions develop that generally occur in the same area. Considerable controversy exists about the basic nature of these lesions. A number of authors consider them to be reactive and others believe them to be neoplastic.

Clinical Features

Patients with capillary hemangiomas of the brain present with symptoms of ICP or seizures; the median age of these patients was 16 years. The duration of symptoms was 2 days to 2 months by the time the patients underwent surgery. In one case, symptoms became evident after intratumoral hemorrhage. With the exception of Case 3, there have been no other reports in the literature of capillary hemangiomas of the brain. Nevertheless, similar lesions have been reported as cavernous angiomas with edema in the brain. One small nodule was removed and the histological diagnosis was cavernous angioma. The symptoms of ICP improved, but follow-up CT scans with addition of contrast agents demonstrated a remaining enhancing lesion accompanied by edema. A 36-year-old man had a highly vascular mass in the right parietal lobe. A biopsy procedure was performed, but the operation was terminated because of profuse hemorrhaging from the biopsy site. Histological studies revealed a benign hemangioendothelioma. The patient received radiation therapy and has done well, with a marked decrease in the size of the tumor, as shown on follow-up CT scans. A 16-year-old girl had multiple lesions with edema in the brain. Microscopic study of the resected lesion showed clusters of thin-walled vascular spaces that resembled sinuses of various sizes. The lesion was diagnosed as “Masson’s vegetant intravascular hemangioendothelioma.” Follow-up CT scans demonstrated no evidence of recurrence of the resected lesion or progression of other lesions.

These lesions may have been capillary hemangiomas because cavernous components can be observed in these tumors. Furthermore, the term “benign hemangioendothelioma of infancy” has been used for capillary hemangiomas of infancy. The name “Masson’s vegetant intravascular hemangioendothelioma” was used for intravascular endothelial hyperplasia with distinctive papillary structures. It may be useful to know that these benign vascular lesions...
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can manifest as multiple brain lesions in relatively young patients.
In our study, the seven patients with lesions in the spinal cord were all men whose median age was 64 years. All patients in this group presented with progressive sensorimotor disturbances of the lower limbs. Symptoms had lasted from 6 days to 4 months by the time the patients underwent surgery. Lesions were located at the middle to lower thoracic spine levels (T5–11).

Table 2 summarizes the clinical data on capillary hemangiomas of the neuraxis previously reported in the English literature. Twenty-four cases of spinal intradural capillary hemangioma have been reported previously in the literature and include those in the cauda equina and nerve roots. Nine of the 24 cases were not reported in great detail. Analysis of the other 15 cases in the literature plus our seven cases revealed 17 men and five women between the ages of 28 and 80 years (median age 55 years). It is noteworthy that spinal intradural capillary hemangiomas occurred more frequently in men and in elderly patients. Nonetheless, as the name implies, capillary hemangiomas of infancy occur during infancy.

Lobular capillary hemangiomas that appear elsewhere in the body affect both sexes almost equally and are evenly distributed among all ages. It is remarkable that most spinal lesions have been described in the lower thoracic spinal cord, conus medullaris, and cauda equina. The most frequent clinical symptom of capillary hemangioma of the cauda equina and spinal nerve roots is intermittent, progressive, and finally persistent low-back pain and lumbosacral pain, which are not as characteristic in patients with lesions in the spinal cord.

**Neuroimaging Findings**

Neuroimaging studies demonstrated hypervascular masses associated with perifocal edema in cases of brain lesions. The MR imaging findings in spinal capillary hemangiomas have been characterized as isointense relative to the spinal cord on T1-weighted images, hyperintense on T2-weighted images, and as strong homogeneous enhancement on contrast-enhanced T1-weighted images. Tumors arising from the spinal cord had both extra- and intramedullary components. In our patients, results of neuroimaging studies were indicative of highly vascular neoplasms that arose from the posterior surface of the spinal cord.

Two of our cases were remarkable for displaying multiple lesions with perifocal edema. These lesions were initially suspected to be metastatic brain tumors. A case of multiple capillary hemangiomas of the cauda equina nerve roots, conus medullaris, and lower spinal cord has been described. Multiplicity of lesions may be one of the features of capillary hemangiomas because multiple lesions often develop simultaneously in capillary hemangiomas of the skin and mucosa.

**Treatment and Outcome**

At surgery, capillary hemangiomas of the brain presented as well-demarcated vascular masses. Total removal of a small lesion in a noneloquent area is not difficult. Biopsy sampling or piecemeal resection should be avoided because it may cause profuse bleeding. Many of the residual lesions regressed after the systemic administration of steroid drugs or IFNα in our two cases. Angiogenesis is governed by a complex interaction of proangiogenic and antiangiogenic factors. Basic fibroblast growth factor and VEGF are proangiogenic molecules and are often produced by tumor cells. Removal of the main lesion leads to decreased proangiogenic factors and might induce regression of the residual lesions. Corticosteroid drugs and IFNα are classified as antiangiogenic molecules, as are angiotatin, endostatin, and thalidomide. Use of these drugs could be effective in treating capillary hemangiomas of the CNS, similarly to capillary hemangiomas of the skin and soft tissues. Spinal cord lesions presented at the cord surface, thus facilitating their exposure and dissection. On gross inspection, the lesions were soft red, often lobulated intra- and extramedullary masses. The extramedullary portion often adhered to nerve roots, whereas intramedullary portions were well demarcated from edematous spinal cord parenchyma. Surgical removal is the goal, although, as in resection of other intramedullary tumors, little neurological improvement or even worsening of symptoms is possible. The systemic administration of steroid drugs and IFNα before surgery could ameliorate and improve outcomes. Recurrence of capillary hemangiomas of the neuraxis has not yet been demonstrated. Nevertheless, because recurrence of capillary hemangiomas of the skin and soft tissues is not rare, follow-up imaging after resection is necessary.

**Histological Findings**

Histologically, lesions in our patients were consistent with capillary hemangiomas of the skin or soft tissues and differed from both cavernous hemangiomas and capillary telangiectasias. Unlike capillary hemangiomas, cavernous hemangiomas consist of dilated hyaline vessels and often exhibit thrombosis, perivascular hemosiderin deposition, and calcification. Capillary telangiectasias of the CNS have neural parenchyma between vessels and lack lobularity and demarcation. Capillary hemangiomas must be distinguished from highly vascular neoplasms of the neuraxis, which include hemangioendotheliomas, hemangiopericytomas, and hemangioblastomas. The term “hemangioendothelioma” has become a designation for vascular tumors in which the biological behavior is intermediate between a hemangioma and a conventional angiosarcoma. Tumors included in this group have the ability to recur locally and have some ability to metastasize. The epithelioid hemangioendothelioma is the most aggressive member of this family. Whereas the spindle cell hemangioendothelioma was previously considered to be in this group, it has been reclassified with the hemangiomas (that is, spindle cell hemangioma) because it has no metastatic potential. The term “benign hemangioendothelioma” is no longer used. Some of the reported cases of hemangioendotheliomas of the brain and the spinal cord could be reclassified with the hemangiomas. Histologically, some hemangioendotheliomas may possess nearly all of the features of capillary hemangiomas but display a greater degree of cellularity and mitotic activity. Other hemangioendotheliomas may contain well-formed vascular channels, but they are not arranged in lobules, as is the case in capillary hemangiomas. Hemangiopericytomas have stag-horn vasculature and pericellular deposition of reticulin fibers. Hemangioblastomas contain foamy stromal cells. Capillary hemangiomas must be distinguished from...
these vascular tumors that have aggressive potential so that overtreatment can be avoided.

In hemangioblastomas, VEGF is expressed by scattered stromal cells. Positive VEGF immunostaining was seen in capillary hemangiomas in areas of proliferating endothelial cells without vessel lumen formation. Nevertheless, staining for VEGF was not evident in vessels with a well-developed lumen. Production of VEGF appears to be limited to endothelial cell precursors or immature endothelial cells prior to the complete development of the vessels. This finding indicates the possibility that VEGF may act as an autocrine factor in circumstances of endothelial cell stimulation. Production of VEGF, which increases vascular permeability, may also be related to the edema fluid around the lesion.

Immunostaining with Ki-67 antigen showed a relatively high MIB-1 index (median 6.5%); the clinical significance of this is uncertain.2 Study of proliferative activity in lobular capillary hemangiomas of the skin and mucosa showed that the MIB-1 index varied from a few percentage points to greater than 15%. This variation may be attributable to the developmental stage of the lesions at the time of resection.22

Conclusions

In this study we report clinical and histological features of capillary hemangiomas of the CNS. Capillary hemangiomas presented as mass lesions either in the brain or in the spinal cord. Neuroimaging demonstrated well-defined vascular mass lesions associated with marked perifocal edema. Histologically, all lesions were consistent with capillary hemangiomas of the skin or soft tissues and differed from vascular malformations or other vascular neoplasms. Capillary hemangiomas of the CNS are benign lesions that must be distinguished from other neoplasms that have aggressive potential to avoid overtreatment.

Acknowledgment

We thank Prof. Hiroshi Iwashita of the Department of Pathology, Fukuoka University School of Medicine, for reviewing the pathological specimens.

References

13. Fukuoka University School of Medicine, for reviewing the pathological specimens.
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