Cavernous hemangioma of the orbit

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The clinical and pathological data of 66 patients with orbital cavernous hemangioma are presented. This tumor occurs in females more frequently than in males, and has its peak incidence in early middle age. Visual disability results from a high degree of relative hyperopia or from optic-nerve compression. Postural or temporal variation in proptosis is not characteristic. Multiple cavernous hemangiomas are rare, but may occur simultaneously or separated by long intervals. In this series, incompletely excised lesions did not cause recurrent proptosis. Relative hyperopia may persist, in spite of complete removal of the tumor. Improved preoperative localization with modern techniques appears to be reducing the morbidity associated with surgical excision of the lesion. A local hemodynamic disturbance may initiate proliferation of vascular channels that undergo progressive ectasia. Growth of the lesion may occur intrinsically by the budding-off of capillary channels from cavernous spaces into the interstitium. Clinical and pathological findings fail to demonstrate any relationship between this lesion and capillary hemangioma of childhood.

KEY WORDS • orbital tumor • hemangioma • proptosis • pathogenesis • cavernous hemangioma

Materials and Methods

All histopathological slides coded as orbital vascular tumors or malformations in the Algernon B. Reese Laboratory of Ophthalmic Pathology at the E. S. Harkness Eye Institute were reviewed. The clinical records of those cases meeting the histopathological criteria for cavernous hemangioma were carefully studied and pertinent information was abstracted. Follow-up data were obtained from the office records of the surgeons involved, from records of referring physicians, and from contact with the patients themselves. A total of 66 cases of orbital cavernous hemangioma was obtained, spanning an interval from 1937 to 1976. All specimens were derived from surgical procedures performed at one institution with little variation among surgeons regarding techniques of orbital surgery.

The histological criteria for inclusion in this study were as follows: a well circumscribed and, to our knowledge, an extensive study devoted exclusively to many of these cases has not been reported. The present study, consisting of 66 cases of orbital cavernous hemangioma, was undertaken to answer a number of important clinical and histological questions that have persisted with respect to this tumor: 1) what is its clinicopathological relationship, if any, to capillary hemangioma of childhood; 2) which clinical features are distinctive to this tumor and which may be shared with other vascular tumors (for instance, intermittency or fluctuation of proptosis, postural variations of proptosis, pulsation or bruit, phlebolith formation, and hemorrhagic cyst formation); 3) what are the appropriate indications for surgery since the advent of computerized tomography (CT) and ultrasonography, which generally can accurately identify and locate the lesion preoperatively; 4) what are the expected gains and complications of surgery; and 5) what does a close scrutiny of the histological features of these lesions tell us about its classification, histogenesis, and relationship to other vascular tumors?

Cavernous hemangioma is frequently cited as the most common primary orbital tumor; yet, to our knowledge, an extensive study devoted exclusively to many of these cases has not been reported. The present study, consisting of 66 cases of orbital cavernous hemangioma, was undertaken to answer a number of important clinical and histological questions that have persisted with respect to this tumor: 1) what is its clinicopathological relationship, if any, to capillary hemangioma of childhood; 2) which clinical features are distinctive to this tumor and which may be shared with other vascular tumors (for instance, intermittency or fluctuation of proptosis, postural variations of proptosis, pulsation or bruit, phlebolith formation, and hemorrhagic cyst formation); 3) what are the appropriate indications for surgery since the advent of computerized tomography (CT) and ultrasonography, which generally can accurately identify and locate the lesion preoperatively; 4) what are the expected gains and complications of surgery; and 5) what does a close scrutiny of the histological features of these lesions tell us about its classification, histogenesis, and relationship to other vascular tumors?
lobular but unencapsulated pattern were diagnosed as capillary hemangiomas. Some of these tumors showed ectasia or enlargement of luminal spaces, but, in general, more hypertrophic areas were present that established this as being a secondary transitional stage of a capillary hemangioma. These latter cases were not included in this study.

Summary of Cases

**Signs and Symptoms**

Of the 66 patients in this series, 70% were female and 30% male. Although every patient was Caucasian, this may merely reflect the local and referral population served by the Eye Institute in the period covered by this study. All cases were unilateral and there was no predilection for involvement of either the right or left side. The average age of symptom onset was 42 years, with a range of 18 to 67 years. There was definite clustering in early middle age, with over two-thirds of the patients aged between 30 and 49 years. The duration of symptoms averaged approximately 4 years, but ranged from 3 weeks to 24 years.

Most patients (72%) complained of proptosis. None of the patients reported intermittency of proptosis or increased proptosis with dependency or with any other cause of increased venous pressure. Indeed, only one patient had intermittency of any symptom; he experienced three episodes of spontaneous ecchymosis of the upper lid during a 3-month interval. The rate of progression of proptosis was quite variable. One patient demonstrated 10 mm of relative proptosis after what was alleged to have been only 4 months; another had only 3 mm of proptosis after a symptomatic interval of 8 years. When the degree of relative proptosis was plotted against the duration of proptosis as a symptom, the average rate of increase was found to be approximately 2 mm annually.

Almost half of the patients in the series complained of blurred vision. Most had a partially, if not totally, correctable hyperopia which resulted from indentation of the posterior globe and will be considered below. Only three patients complained of diplopia, in spite of a much greater number with obvious displacement in the frontal plane.

On physical examination, the average degree of relative proptosis just before surgery was 5.5 mm, with a range of 0 to 12 mm. Even in the most extreme cases there was no evidence of corneal compromise. Most patients had axial proptosis, but many eyes were displaced in the frontal plane and the most common eccentric position was downward.

The average patient's vision was correctable preoperatively to 20/40, but the median acuity was 20/25+. The range was from 20/15 to finger-counting vision. About one-half of the patients had visual acuity correctable to that of the fellow eye. However, achievement of this preoperative acuity required correction of an average of 2.00 diopters of relative, acquired hyperopia of the affected eye (range -1.50 to +9.50 diopters). Most patients were reported to have limited ductions, most commonly in elevation. However, it is possible that marked displacement may
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have given a false impression of limited motility. A minority of patients were heterotropic in primary gaze.

Some abnormality of the visual field was detected in more than half of the cases in which this examination was performed. The most common finding was a field cut that corresponded to the orbital location of the cavernous hemangioma and implied direct compression of the optic nerve or its blood supply. One 49-year-old patient had visual loss in the temporal field which suggested a nasal location of the tumor (Fig. 1 left). The CT scan, however, demonstrated that the lesion was temporal to the optic nerve, compressing it against the medial orbital wall, and producing visual loss on a contrecoup basis (Fig. 1 right). Some patients had central or centrocecal scotomata, whereas others merely had enlargement of the blind spot and generalized depression of the visual field consistent with their disc edema.

Most patients had choroidal folds ("retinal striae"). When the location of these folds (determined ophthalmoscopically) was compared with the orbital location of the tumor determined at surgery, no correlation was found. Patients with choroidal folds had a greater average degree of relative acquired hyperopia (3.00 diopters) than those without folds (1.50 diopters), implying that there was a more marked indentation of the posterior pole. However, there were several patients in the series with relative hyperopia of up to 4.50 diopters who had no choroidal folds.

Most patients (70%) had signs of mild disc edema with slight elevation, blurred margins, and dilatation of veins. In no case was there marked elevation of the optic nerve head or hemorrhage on the disc. A minority of patients demonstrated frank optic atrophy.

In the series, neither a bruit nor a pulsation was reported in any of the cases. Intraocular tensions were usually symmetrical, although both higher and lower values were found on the affected side.

Plain film radiographs in approximately one-half of the cases were reported to show an increase in orbital size. Disparities in orbital volume were minimal when compared to those seen with the onset of orbital tumor growth in childhood (such as capillary hemangioma). Phleboliths were not found.

All of the ultrasonograms in this series were performed in the laboratory of D. Jackson Coleman, M.D. The acoustic characteristics of orbital cavernous hemangioma were found to be rounded or ovoid contour, some internal echoes, and fair to good sound transmission. The differential diagnosis by this modality included lymphangioma when the regular contour of the lesion could not be discerned, meningioma when the tumor could not be distinguished from the optic nerve, and Graves' disease when the lesion could not be distinguished from the extraocular muscles, implying enlargement of the muscles.

The CT scan characteristics included rounded or ovoid contour, internal heterogeneity, and enhancement with contrast infusion. In many cases, the lesion appeared distinct from the optic nerve and frequently displaced it (Fig. 1). The differential diagnosis by this technique included any well encapsulated lesion, such as a hemangiopericytoma or neurilemoma. When only a few cuts were made through the orbits, the lesion was not always separable from the optic nerve, suggesting a neurogenic tumor such as an optic glioma or intrasheath meningioma.

Operation

All of the lesions in this series were managed surgically by an anterior or lateral orbital approach. In all but one case, a single tumor was found at surgery. A 36-year-old woman was distinguished by the presence of five discrete cavernous hemangiomas which were removed during a single orbitotomy. She has been followed for 12 years without recurrence.

The majority of tumors were found within the muscle cone, although several were described as extraconal. The most common orbital location was temporal, but a significant number of lesions were considered to be nasal. In most cases, the cavernous hemangioma was easily dissected from the surrounding tissues. In other cases, the lesion was adherent to the optic-nerve sheath, to extraocular muscles, or to the periosteum; this made delivery more difficult and frequently mitigated the final visual result.

Postoperative Course

Fifty percent of the patients in this series were followed for at least 6 years, and 83% for 1 year or longer. The average follow-up period was 10 years, and the longest 40 years. In two cases the surgeon felt that excision had been incomplete; there were several other cases in which review of the pathological material suggested the same conclusion. There has been no evidence of recurrence from incompletely excised lesions. One patient developed a second separate cavernous hemangioma several years after complete removal of a first. He was seen in 1977, 40 years after his first surgery and 25 years after his second, without further recurrence.

Overall, 76% of the patients in the series had postoperative visual acuity equal to or better than that before surgery; 24% were worse after surgery. Of those patients who were preoperatively correctable to 20/20 or to the level of acuity of their fellow eye, 70% remained the same, 15% lost one line, 7% lost two lines, and 7% lost all light perception. Of those patients with noncorrectable visual loss before surgery, 46% improved, 37% remained at the same level, and 17% had further loss of vision.

The most dramatic example of improvement was provided by a 49-year-old patient who presented with
finger-counting vision in the affected eye. A cavernous hemangioma, lodged in the orbital apex and compressing the optic nerve, was completely excised, and vision improved to 20/25.

Although most patients had some reduction in relative acquired hyperopia as a result of surgery, on the average, approximately three-fourths of the preoperative amount was retained, in spite of complete removal of the tumor. Reduction of hyperopia ranged from 0 to 9 diopters.

In several cases, choroidal folds ("retinal striae") were found on examination to be persistent many years after complete removal of the tumor. In other cases, resolution of these folds was observed.

A minority of patients were left with the complications of orbital tumor surgery in general: 20% had limited ductions, although usually only in extreme abduction; 17% had mild ptosis; 9% had dry eyes; and 2% had corneal anesthesia.

Fig. 2. Gross appearance of cavernous hemangioma. The lesions are usually discrete, but rarely are tightly adherent to muscle capsules, optic nerve sheath, or periorbita.

Fig. 3. Photomicrograph showing two of five separate small encapsulated tumors (arrows) that were removed at the same surgical procedure. H & E, × 8.

Fig. 4. Photomicrograph showing enlarged venous channels (arrows) immediately outside the capsule (C) of a cavernous hemangioma. The lowest channel communicates with the tumor. H & E, × 60.
Pathological Findings

The tumor, as measured upon delivery to the laboratory, averaged approximately 8000 cu mm or the equivalent of 20 × 20 × 20 mm, although it was more frequently ovoid than spherical (Fig. 2). The range was from 9.5 to 30 mm in each dimension. Most of the tumors in this study were very well encapsulated, and usually occurred as a single mass in the orbit. Anteriorly located orbital tumors were likely to be partially encapsulated. At surgery, one patient was found to have five separate well encapsulated small cavernous hemangiomas (Fig. 3). Another patient had two separate hemangiomas in different orbital locations removed at different times; these lesions were quite similar and had classical histopathological characteristics of cavernous hemangioma. A few tumors displayed lobulation, in that the fibrous capsule would encroach into the substance of the tumor and divide its cavernous spaces into irregular subunits.

The capsule was usually formed by moderately thick fibrous tissue, and in some areas it might be perforated by medium-sized vessels of venous character derived from the surrounding orbital tissues (Fig. 4).

The main mass of the tumor was composed of large ectatic or “cavernous” spaces lined by flattened but not particularly attenuated endothelial cells. Immediately outside these endothelial cells of the luminal lining, one commonly observed a variable mantle of closely apposed spindle cells (Fig. 5). The trichrome stain revealed that these mural cells frequently contained longitudinal cytoplasmic filaments. In some instances, these apparently smooth muscle-type cells flowed into the interstitium to form short interrupted bundles.

The interstitium itself was generally composed of fibrous tissue of different degrees of cellularity and hyalinization. Some tumors had areas virtually devoid of an interstitium, with endothelial cells in a back-to-back arrangement, defining much larger than normal cavernous spaces which were blood-filled but frequently gave the impression of lymphangiomatous structures. Other trabeculae were composed of looser myxomatous connective tissue, showing in areas a mucinous or stringy degeneration of the stroma. In a few cases, scattered clusters of fat cells were present in the stroma (Fig. 5 left). Also present in a few cases were short strands of smooth-muscle cells with intense...
cytoplasmic fuchsinophilia on the trichrome stain, or weaker cytoplasmic staining indicative of myofibroblasts (Fig. 6 right).

Sometimes these bundles were related to the mural cells. Uncommonly, the intercavernous trabeculae were thick and heavily hyalinized, and were likely to contain scattered inflammatory cells such as lymphocytes, plasma cells, and hemosiderin-laden macrophages. In general, the inflammatory component within the lesions was quite mild, and follicular hyperplasia was exceedingly rare.

Hemosiderin-laden macrophages were occasionally seen in the lumens of the cavernous spaces as well as in the interstitium. Stasis of the blood within the lumens was also signified by layering of serum and red blood cells, presenting almost a hematocrit within the cavernous spaces. One tumor was remarkable in that the vascular spaces in its center were filled only with serum; progressing toward the periphery, the layering effect previously mentioned was discovered, and, finally, in the subscapular region, the channels were completely filled with blood. Stasis was also evidenced by a pseudosarcomatous proliferation of endothelial cells around small clots or fibrin papillae (Fig. 6 left). This endothelial proliferation could progress to partial obliteration of the space and, in other instances, channels so affected underwent complete fibrous replacement and incorporation into the interstitium. An intraluminal phlebolith was not observed in any of the tumors, nor was dystrophic calcification identified in any of the trabeculae. One curious finding was the budding-off from some of the larger cavernous spaces of small capillary endothelial channels. In some specimens, these spaces appeared to have become progressively ectatic, and tended to bud-off into zones with looser interstitia (Figs. 6 right and 7).

Electron microscopic studies performed on four specimens revealed endothelial cells with cytoplasmic filaments, intercellular junctions, and a basement membrane. Immediately outside these endothelial cells were two or three layers of well differentiated smooth-muscle cells with cytoplasmic filaments containing fusiform densities, hemidesmosomes,
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FIG. 7. Left: Photomicrograph showing spectrum of lumen sizes ranging from capillary spaces (arrows) to large cavernous spaces. H & E, X 40. Right: Outbudding of capillaries into the interstitium (arrows) from a cavernous lumen (L). H & E, X 160.

pinocytotic vesicles, and well defined basement membranes. No elastic fibers were found. These findings will be described in greater detail in a separate paper.

Discussion

In this series of 66 cases of cavernous hemangioma, the average age at which patients noticed symptom onset was 42 years, ranging from 18 to 67 years of age. In contrast, among 39 cases of capillary hemangioma reviewed in the course of selecting material for this study, the oldest patient was 3 years old. This indicates a fairly distinct separation between the two groups on the basis of age, and challenges the concept that with time and growth a capillary hemangioma can evolve into a cavernous hemangioma. It should be mentioned that, in other smaller series, younger patients have been reported as having had cavernous hemangiomas. Although most of these cases are fairly well documented, it is possible that some represent lymphangiomas or capillary hemangiomas in which the vascular spaces are more ectatic than usual.

In the latter instances, one would expect to find lobular proliferations of endothelial cells which characterize capillary hemangiomas and which are lacking in true cavernous hemangiomas.

The lack of postural change in proptosis is consistent with a vascular lesion which, although generically venous, has such a limited connection with the systemic circulation that orbital venography fails to opacify it. Other authors, however, have reported positional changes in proptosis in this disease.

It has been suggested that there may be a waxing and waning of the degree of proptosis over a period of time; however, this was not supported by our study. In no case was there any indication of spontaneous reduction in proptosis, either by history or by serial measurements. It is conceivable that permanent reduction of proptosis does occur in cases that never require surgery, and therefore were not included in this surgical series. Perhaps the cases of episodic proptosis observed by others were caused by lymphangiomas, which are known to vary in size with...
upper respiratory infections and with blood-cyst formation, or perhaps were similar to the patient described by Rowbotham and Little, in whom an orbital hemangioma situated near the superior orbital fissure produced intermittent interference with orbital venous drainage.

We had little evidence for spurts of growth as compared to gradual steady enlargement. However, some cases characterized by accelerated growth that was attributed to hormonal influence have been reported.

Neither bruit nor pulsation was noted in any of the cases. We find this to be consistent with a lesion of such limited connection with the arterial system that arteriography fails to opacify it. Other investigators, however, have commented on the pulsatile nature of these lesions.

Among the 80% of the cases in this series with reported x-ray findings, there were no examples of phlebolith formation. Other authors have noted the occasional finding of phleboliths in x-ray examination of patients with orbital cavernous hemangioma. Although our histological material occasionally demonstrated thrombus formation or hyalinization in single cavernous spaces, no frank calcification was observed. This should be contrasted with orbital varices, in which phleboliths are common.

One of our cases demonstrated that multiple separate lesions may coexist. We can presume from another patient that independent tumors can become manifest in the same orbit several years apart. One of the six patients studied by Kopelow, et al., had two noncommunicating lesions. Pertuiset and Aron-Rosa reported multiple lesions in 30% of their 48 patients with cavernous hemangiomas. However, the fact that 65% of their cases had “intra-angiomatous hematomas” which were opened as a “definite aid to removal,” and which were “always present in patients who suffered a rapidly progressing proptosis” suggests that many of their lesions were in fact lymphangiomas.

Overall, approximately three-fourths of the patients in this series either retained their preoperative visual acuity or improved following surgery, and about one-fourth of the patients suffered a reduction in visual acuity as a result of surgery. We reviewed the findings for the group of 12 patients who were visually worse after surgery and compared them to the average findings for the entire series, hoping to find some factors of prognostic value. In general, only those factors that reflected potential difficulty in surgical removal were of significance; that is, a higher percentage of the group with postoperative decreased vision, in comparison with the entire series, had impalpable lesions situated deep in the orbit that caused striae, disc swelling, enopthalmos, or adhesion to the optic nerve, or periorbital or muscles. On the average, this group also had larger lesions than the overall series. Among the group of patients with noncorrectable visual loss before surgery who improved postoperatively (11 patients), the only significant difference from the overall series was a smaller average lesion size.

To our knowledge, the last case of lost light perception reported after surgery occurred in 1960, although more than 50% of the operations were performed since that time. Moreover, of the 12 orbitotomies that resulted in any decrease in vision, only three were performed after 1960. It is assumed that more sophisticated diagnostic and localization methods, as well as improved surgical techniques, are responsible for better results. It is interesting that none of the seven patients who underwent preoperative CT scanning suffered a postoperative reduction in vision.

The discovery of unequivocal smooth-muscle cells surrounding the endothelial cells in two or three layers suggests to us that, at the time of their discovery, cavernous hemangiomas are more than capillary spaces and probably are venous in character. Our recognition of small capillaries budding-off from the main cavernous spaces into the interstitium is a refinement of a similar observation made by Kopelow, et al., who ascribed the small-bore spaces to a tendency for histological variations in the tumors. We feel that these capillary proliferations offer an explanation for the progressive growth of the tumors and appear to be a more reasonable basis for their intrinsic enlargement in comparison with the suggestion that dilated vascular spaces outside the capsule become slowly incorporated into its outermost portion. We do not believe that cavernous hemangiomas can be inferred to represent transformed capillary hemangiomas because of the presence of these smaller spaces. The occurrence of pseudosarcomatous endothelial proliferation in cavernous hemangiomas should not be interpreted as a malignant transformation, which has never been reported in this tumor. This phenomenon reflects stagnation within the tumor and a secondary proliferation of what occasionally may be alarming-looking endothelial cells around microthrombi.

Cavernous hemangioma appears to be an acquired lesion that probably begins as a capillary-type proliferation, as exemplified by the interstitial capillarization mentioned previously. Over an extended period of slow growth these channels may undergo progressive ectasia and acquire a coat of well differentiated smooth-muscle cells. The neoplastic properties of cavernous hemangiomas are apparently quite slight, as witnessed by their slow growth (at times over 10- to 15-year periods), and by the absence of recurrence following incomplete excision. Given their low order of neoplastic potential, a hemorrhagic cause for their formation is attractive, a mechanism that has been explored by Witschel and Font for the development of the not altogether dissimilar cavernous hemangioma of the choroid. Besides being compatible with the slow evolution of the tumors, this theory can also account for the presence of multiple separate lesions in two of our patients. We
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propose that some local hemodynamic disturbance produces an endothelial cell proliferation that enlarges in quasi-neoplastic fashion over a protracted period of time. In support of this contention is our observation, in several arteriovenous malformations (AVM's) of the orbit, of a secondary capillary proliferation, probably reflecting the altered hemodynamics created by the AVM.

In cavernous hemangioma, according to our proposal, the acquisition of smooth muscle would be a secondary event. In careful electron microscopic studies of capillary hemangioma and lymphangioma, we have discovered the constant association of primitive pericytic cells with basement membrane formation. These cells are capable of smooth-muscle differentiation. Alternatively, mesenchymal cells in the stroma, under the influence of the endothelial cells, might be induced to undergo pericytic or smooth-muscle differentiation. In a few of our cases, bundles of either smooth-muscle cells or myofibroblasts with incomplete smooth-muscle differentiation were seen in the interstitium. Despite the presence of smooth muscle in the walls of cavernous hemangiomas, we are, nonetheless, of the opinion that these tumors are separate from venous hemangiomas or varices. Phlebolith formation is very common in these latter unencapsulated tumors, but was totally absent from the material in this study.

Conclusions

We have posited that cavernous hemangioma is composed of endothelial cells of a different character from those of capillary hemangioma. Because we were stringent in our histopathological review of the lesions included in this study, we believe that we have segregated a group of homogeneous tumors that are different from capillary hemangiomas, varices, venous angiomas, AVM's, and lymphangiomas. We attribute the absence of "atypical findings" in our series, such as postural changes in proptosis, bruit, phlebolith formation, intermittency and intralesional hemorrhages, to the lack of contamination of our case material by these other types of tumors.

We have indicated that the natural history of orbital cavernous hemangioma may be quite variable. Many patients may have manifestations of tumor growth for more than 10 years without developing non-optically correctable visual loss, whereas others may have visual loss that is not optically correctable within a few months of symptom onset. Visual disability in this disease is due primarily to induction of marked hyperopia which cannot be practically managed optically, or to compression of the optic nerve or its vascular supply. Diplopia is uncommon and corneal compromise may never occur.

The patient who may benefit most from surgery is the one with true visual loss secondary to optic-nerve compression; however, the location of the lesion in such a case makes uncomplicated delivery more difficult. The patient who is optically correctable to 20/20 may have more than a cosmetic indication for surgery, if the degree of anisometropia is intolerable. However, it should be borne in mind that this patient will retain, on the average, almost 75% of his relative hyperopia after surgery. In addition, such a patient has a risk of reduced vision after surgery. The magnitude of that risk seems to be diminishing as our diagnostic and surgical techniques improve. The lateral orbitotomy (Krönlein procedure) will usually be adequate for excision and the general complications of this procedure should be recalled. If the patient understands the above risks and wishes to be relieved of a social and psychological stigma, then excision seems justified on this basis alone.

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References


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