Intravascular papillary endothelial hyperplasia of the sellar region

Report of three cases and review of the literature

RUDOLF A. KRISTOF, M.D., DIRK VAN ROOST, M.D., HELMUT K. WOLF, M.D., AND JOHANNES SCHRAMM, M.D.

Departments of Neurosurgery and Neuropathology, University of Bonn, Germany

Intravascular papillary endothelial hyperplasia (IPEH) is considered a reactive proliferation of endothelium associated with thrombosis. The occurrence of IPEH in the cranial cavity is exceedingly rare. In this article, the authors report three cases of IPEH that originated from the cavernous sinus and extended into the sellar contents. The lesions were resected incompletely in two cases and completely in one case. The IPEH in one of the patients was incompletely resected and exhibited further growth on magnetic resonance imaging 3 months postoperatively; local radiation therapy was instituted. This led to shrinkage of the lesion over an additional follow-up period of 3.5 years. In a review of the literature, the authors located seven other cases of intracranial IPEH. The authors conclude that clinically symptomatic intracranial IPEH should be completely resected whenever possible, because it can cause considerable morbidity and mortality and because it is prone to progression or recurrence.

KEY WORDS • intravascular papillary endothelial hyperplasia • intravascular angiomatosis • Masson’s pseudoangiosarcoma • sellar process • cavernous sinus process

Intravascular papillary endothelial hyperplasia (IPEH) is generally considered an unusual form of thrombus organization with excessive papillary endothelial proliferation, which is usually confined to the lumen of preexisting vessels or vascular malformations2–4, 7,8,16,23–25, and which rarely occurs in organizing hematomas.16,22 Accordingly, this lesion, which histologically bears some resemblance to organizing thrombi and to angiosarcoma,3,4,7,12,18,21 exhibits a benign biological behavior if it is located in the extracranial soft tissues. However, recurrences of IPEH after incomplete resection of the lesion-bearing vascular malformation have also been reported.7,8,11,12

Here we report three unusual cases of IPEH in the sellar region and review the findings of seven other cases of IPEH located elsewhere in the cranial cavity.

Case Reports

Case 1

This 70-year-old woman, who was otherwise healthy, was admitted to the hospital because of a transient episode of diplopia that occurred 3 months previously.

Examination. The patient’s neurological and ophthalmological evaluation revealed no pathological finding. Magnetic resonance (MR) imaging disclosed the presence of a 1.8 × 2.5–cm mass occupying the left cavernous sinus with extension into and above the sellar lumen and along the left optic nerve. This mass was isointense to slightly hyperintense on T1-weighted MR images, although it enhanced strongly and almost homogeneously after intravenous administration of gadolinium (Fig. 1 upper left and right). Carotid angiography demonstrated a faint blush from the early arterial to the late venous phases. Dynamic pituitary function tests revealed no significant impairment. Because of the radiological features of the lesion, the diagnosis of meningioma or pituitary adenoma seemed unlikely.

Operation. At craniotomy, a reddish, soft, and very vascular tumor was removed from below the compressed optic nerve, the sellar lumen, and the dorsal aspect of the cavernous sinus. The demarcation between the tumor and the pituitary gland was clearly defined. To preserve the intracavernous structures, the lesion could only be resected incompletely.

Pathological Examination. Histologically, the lesion was initially believed to be a capillary angioma. At reevaluation 4 years later, the diagnosis of IPEH was established (Fig. 2 upper left).

Postoperative Course and Treatment. In spite of morphological preservation of the intracavernous structures, a decrease in the patient’s visual acuity, a temporal hemianopia, and an oculomotor nerve palsy became evident on the surgically treated side. These deficits resolved partial-
Intravascular papillary endothelial hyperplasia

Examination. The patient’s neurological and ophthalmological evaluations revealed a palsy of the right abducens nerve as the only abnormality. Magnetic resonance imaging disclosed a process measuring approximately 1.2 × 1.5 cm, which originated from the right cavernous sinus and extended into the sellar lumen, thereby displacing the pituitary gland and stalk. On T₁-weighted MR images, the process was isointense with respect to the brain and slightly hypointense compared to the pituitary gland; contrast enhancement was strong and homogeneous (Fig. 1 center left and right). On T₂-weighted and proton-weighted images, the lesion appeared to be hyperintense. Carotid angiography revealed no pathological vascularization. Pituitary dynamic testing was normal. A diagnosis of meningioma or pituitary adenoma was again considered unlikely in view of the lesion’s radiological features and the clinical findings.

Operation. At transsphenoidal surgery, the process appeared reddish and strongly vascularized; its intrasellar portions were removed and the intracavernous parts were resected incompletely. There was a clearly defined demarcation between the tumor and the pituitary gland.

Pathological Examination. Histologically, the process was initially diagnosed as a vascular malformation without further specification. At reevaluation 6 months later, the diagnosis of IPEH was established (Fig. 2 upper right).

Postoperative Course. The patient’s postoperative course was uneventful; the abducens nerve palsy resolved and pituitary function remained normal. Four months later, follow-up MR imaging revealed a small residual lesion in the cavernous sinus, although the patient’s clinical and endocrinological findings remained normal.

Case 3

This 24-year-old woman, who was otherwise healthy, presented with a 1.5-year history of intermittent episodes of diplopia that were short in duration.

Examination. The patient’s neurological and ophthalmological evaluations were normal. Computed tomography (CT) scanning revealed a space-occupying sellar process measuring 1.5 × 2 cm that was slightly hyperdense on noncontrast-enhanced CT scans and showed contrast enhancement. The process displaced the pituitary gland, possibly infiltrated the left cavernous sinus, and eroded the surrounding bone structures. Magnetic resonance imaging confirmed the CT findings, especially regarding infiltration of the cavernous sinus (Fig. 1 lower left and right). Assessment of the patient’s pituitary function revealed a moderate impairment in corticotropic function.

Operation. With the expectation of finding an infiltrating, hormone-inactive pituitary adenoma, we performed transsphenoidal surgery. Intraoperatively, the relatively firm and bloody mass was thought to be a meningioma. It was well demarcated from the intrasellar structures and was adherent to the cavernous sinus. The cavernous sinus was opened and its contents were carefully dissected from the lesion, which was believed to be completely removed, although the persistence of small remnants could not be definitively ruled out.

Fig. 1. On noncontrast-enhanced T₁-weighted MR images, sites of IPEH are isointense (Case 1, upper left) to slightly hypointense (Case 2, center left) as compared to brain. Enhancement after administration of gadolinium is strong (Cases 1 and 2, upper and center right) to weak (Case 3, lower right). On T₂-weighted MR images, areas of IPEH are hyperintense (Case 3, lower left). The lesions extend from the cavernous sinus into the sellar lumen, thereby displacing the pituitary gland, and on to the suprasellar space and the sellar floor, which is eroded.
Pathological Examination. Histologically, the diagnosis of IPEH was established. Small parts of the lesion resembled a cavernous hemangioma (Fig. 2 lower left).

Postoperative Course. After surgery, the patient experienced a complete left ophthalmoplegia that resolved totally during the next 4 months. Her pituitary function normalized. Control MR imaging performed at this time was difficult to interpret because of postoperative artifacts; however, there was no definite evidence of residual IPEH.

Histopathology of Intravascular Papillary Endothelial Hyperplasia

The three lesions in our patients showed similar features. The specimens consisted of highly vascular connective tissue. There was a complex network of irregularly branching, thin-walled vascular structures with narrow lumina that were much smaller than those of a cavernoma. Small areas in Case 3 contained somewhat larger vascular spaces, which resembled those of a cavernous hemangioma. However, fibrotically thickened vascular walls, muscle fibers, and calcifications were not present. In all three lesions there were areas with pronounced papillary formations. The papillae consisted of connective tissue cores of varying thickness and cellularity; these cores were lined by a single layer of flat or slightly thickened endothelial cells without cellular atypia or mitotic figures. In other areas of the lesions, papillary formations were less conspicuous and there was an interconnective network of small caliber vessels embedded in a loose connective tissue, indicating a more advanced stage of the lesion. The complex architecture of the vascular spaces was highlighted in immunohistochemical preparations using the antibody CD43, which labels endothelial cells (Fig. 2 lower right). In some areas, the connective tissue cores contained abundant reticulin fibers and showed a strong immunoreactivity for vimentin. There was no immunoreactivity for epithelial membrane antigen, which would have been present in vascular meningiomas. Larger vessels with an arterial or venous architecture and brain parenchyma were not encountered in any of the specimens.
Intravascular papillary endothelial hyperplasia

Discussion

Intravascular papillary endothelial hyperplasia was first described in 1923 by Masson,13 who believed that it represented a true endothelial neoplasm. Although there is ongoing discussion as to the pathogenesis of IPEH, today most authors consider this lesion an unusual form of thrombus organization with exuberant proliferation. The tumourlike growth may be caused by disturbed local hemodynamics that induce progression of thrombus formation and subsequent development and growth of IPEH. Hormonal and local angiogenetic factors may play a role as well.16,17,23 The better understanding of the biological nature of this entity is reflected by its nomenclature, which has changed over time. Today, most authors favor the term IPEH over the more traditional names “Masson’s vegetant intravascular hemangiendothelioma,” “Masson’s pseudoangiosarcoma,” and “intravascular angiomatosis.”2-4,7-9,11,15,24,25

Histologically, the lesion consists of an intravascular proliferation of numerous papillae that are composed of a core of connective tissue and an endothelial surface. The endothelial cells may be plump. However, features of malignancy, such as nuclear pleomorphism, more than occasional mitotic figures, necrosis, multiple layers of endothelial cells, and infiltrating growth into adjacent structures, are missing. The majority of these lesions are intimately associated with thrombotic material.1-4,6-8,20-26 In cases of IPEH that fail to exhibit intravascular thrombosis, it is presumed that the whole preexisting thrombus is already and completely transformed into IPEH.1,8 The histopathological distinction of IPEH from angiosarcoma and hemangiomata may be difficult; however, it is of great importance to avoid unnecessary aggressive treatment.3-5,7-9,11,16,18,19

A primary or pure form of IPEH occurs in normal vessels (usually a vein, seldom an artery) and is distinguished from a secondary or mixed form that occurs in preexisting vascular malformations (usually a hemangiomata, rarely an arteriovenous or other vascular malformation) and in pyogenic granuloma.8,12 These two forms of IPEH occur with similar frequency.5,8,12,16 In a third, rare form, IPEH has been described in organizing hematoma as well.16,22

Intravascular papillary endothelial hyperplasias are uncommon lesions.3 The vast majority of more than 320 cases described to date16 were diagnosed in the skin of the head, neck, and the upper and lower extremities; however, they have also been found in muscles, digestive and urogenital tracts, mucosa of the upper respiratory tract, and the heart.1,4,7,8,11,12,16,17,25 The occurrence of multiple IPEHs has also been reported.3,9,21

Extracranial IPEH usually presents as a slow-growing nodule that may be tender and somewhat painful. The age at manifestation varies widely, and there seems to be a slight female predominance. At surgery, IPEH tends to bleed and often gives the impression of an organized hematoma. Complete resection seems to be curative. The few recurrences are thought to be due to incomplete resection of the underlying vascular malformation.3,8,12,16 Deleterious courses in extracranial IPEH have not been reported.

The intracranial occurrence of IPEH is exceedingly rare. To our knowledge, only seven cases have been described previously.6,9,10,14,15,20,24,25 Recently, the first spinal IPEH has been reported.17

We believe the present cases of IPEH are the first ones described in the sellar region. These cases occurred among 259 consecutive cases of space-occupying lesions of the sellar region that were surgically treated during a 5-year period. These figures indicate that the incidence of intracranial IPEH may have been underestimated.

Two of the present cases of IPEH were diagnosed retrospectively during a systematic review of unusual lesions involving the cavernous sinus. They were initially diagnosed as capillary angioma or vascular malformation without further specification. In the sellar region, angiomatos meningioma and vascular malformations, such as cavernous hemangiomata, arteriovenous angioma, and capillary hemangiomata, have to be considered in the differential diagnosis of IPEH. Histopathologically, there were no meningothelial elements in any of the lesions; this was confirmed by the absence of immunoreactivity for epithelial membrane antigen. The caliber of the vascular spaces was much smaller than that of cavernous hemangiomata and no vascular wall was fibrotically thickened or contained muscle fibers. Capillary hemangiomata are a heterogeneous group of lesions that are mostly associated with the skin and lack prominent papillary formations as seen in the present cases. Larger arterial or venous vessels were not seen in any of the cases. As the initial diagnostic difficulties in Cases 1 and 2 illustrate, the correct histopathological diagnosis of IPEH rests on the presence of a complex network of small-caliber vessels with papillary formations, knowledge of the intravascular origin of the specimen, and familiarity with this lesion.

Intracranial IPEH may show a variety of presenting symptoms that largely depend on the location of the lesion (Table 1). The age and sex of patients with intracranial IPEH resemble that of extracranial IPEH. The duration of symptoms is usually short and ranges from a few weeks to several months. The presenting clinical symptoms include signs of local compression and increased intracranial pressure. Some cases may become evident by intracerebral hemorrhage, which probably originates from an underlying vascular malformation and may be facilitated by the presence of IPEH.24 Seven of 10 cases of IPEH arose from dural structures, whereas in the other three cases the IPEH was situated in the brain parenchyma.

On CT and MR imaging, IPEH appears mostly homogeneous and contrast enhancing. Signs of recent hemorrhage may be present. Angiographically, IPEH can present as either a vascular or an avascular mass.

At surgery, intracranial IPEH usually presents as a well-demarcated oozing structure that often resembles a blood clot. The bleeding tendency may represent an intraoperative problem, especially when associated with a coagulation disorder, which may be caused by the lesion itself.6 In four of 10 cases, an underlying vascular malformation was documented histologically and in another three cases associated thrombosis was documented. These findings are consistent with the current opinion that IPEH is an unusual form of thrombus organization. In the other cases, no vascular malformation or evidence of thrombosis could be detected. One of these cases14 was remarkable in that there were multiple sites of IPEH with a neurocutaneous
distribution pattern and no underlying vascular malformation or thrombosis was found in multiple cutaneous and intracranial biopsies. This case again raises questions as to the pathogenesis of IPEH because it seems unlikely that multiple neurocutaneous vascular malformations or thrombi would simultaneously and completely change to IPEH.

Reviewing the patients’ postoperative courses and considering the nonneoplastic nature of IPEH, it appears surprising that four of six cases with incomplete resection showed evidence of recurrence or progression that required further treatment within 2 to 19 months from the first operation (our Case 1 and cases reported by Nagib, et al.,14 and Sickler and Langford20) or resulted in the death of the patient.6 Both cases of incompletely resected IPEH (our Case 2 and one presented by Wen, et al.26) remained inconspicuous over postoperative follow-up periods lasting 11 and 3 months, respectively.

In the cases with complete or probably complete IPEH resection (our Case 3 and three others8,10,17), the follow-up period was short (weeks–6 months), and thus the patients’ long-term courses cannot be finally assessed.

The natural course of intracranial IPEH is probably not worse than that of IPEH in other locations. However, the technical difficulty of surgical treatment of an intracranial lesion with a tendency to bleed is higher than that of a small lesion located in the skin or soft tissue, and bears a higher risk of incomplete resection or perioperative complications. The three cases reported here and the synopsis of seven other cases from the literature raise the question as to why some incompletely resected intracranial IPEH recur within a few months, whereas other lesions remain clinically silent over many years without treatment. Therefore, initial radical surgery should not be performed at the price of severe and irreversible neurological deficit.

### TABLE 1
Summary of clinical features of intracranial IPEH reported in the literature*

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Patient Age, Sex</th>
<th>Clinical Presentation</th>
<th>Neuroradiological Findings</th>
<th>Surgery</th>
<th>Underlying Vascular Malformation</th>
<th>Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nagib, et al., 1982</td>
<td>16 yrs, F</td>
<td>neurocutaneous disseminated form, epileptic seizures</td>
<td>CT: multiple intracranial enhancing supratentorial lesions angiography: avascular masses</td>
<td>probably subtotal</td>
<td>none, no thrombus detectable</td>
<td>op for local recurrence 19 mos later; thereafter, 9 yrs recurrence free; no progression of other lesions died 6 mos later</td>
</tr>
<tr>
<td>Chen &amp; Kuo, 1984</td>
<td>3.5 mos, F</td>
<td>signs of raised intracranial pressure, epileptic seizures, Kasabach–Merritt syndrome</td>
<td>CT: frontal, large enhancing lesion</td>
<td>biopsy</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td>Izukawa, et al., 1987</td>
<td>55 yrs, F</td>
<td>hemianopsia, sensory dysphasia, hemiparesis, epileptic seizures</td>
<td>CT: parietooccipital mass of mixed density, no enhancement angiography: avascular mass</td>
<td>complete</td>
<td>cavernous hemangioma</td>
<td>no follow up available</td>
</tr>
<tr>
<td>Sickler &amp; Langford, 1990</td>
<td>12 days, F</td>
<td>signs of raised intracranial pressure, coagulation disturbances</td>
<td>CT: large temporal mass, no enhancement MRI: areas suggestive of hemorrhage</td>
<td>subtotal</td>
<td>none</td>
<td>recurrent mass 2 mos later; treated by chemotherapy &amp; stabilized for a nonspecified time period</td>
</tr>
<tr>
<td>Wen, et al., 1991</td>
<td>15 days, F</td>
<td>signs of raised intracranial pressure</td>
<td>MRI: small enhancing process w/in the confusus sinuum angiography: avascular mass</td>
<td>subtotal</td>
<td>none</td>
<td>neuroradiologically, no progression for 6 mos; clinically inconspicuous for 11 mos</td>
</tr>
<tr>
<td>Patt, et al., 1992 &amp; Kaden, et al., 1993</td>
<td>27 yrs, F</td>
<td>unilateral deficit of CNs III, V, &amp; VI; headache</td>
<td>CT &amp; MRI: small enhancing lesion of the orbital fissure angiography: vascularized mass</td>
<td>complete</td>
<td>venous angioma</td>
<td>no evidence of recurrence for 6 mos</td>
</tr>
<tr>
<td>Tsujii, et al., 1994</td>
<td>18 yrs, F</td>
<td>seizures, hemiparesis</td>
<td>CT &amp; MRI: intracerebral hemorrhage angiography: negative</td>
<td>complete</td>
<td>AVM</td>
<td>no evidence of recurrence for 2 yrs</td>
</tr>
<tr>
<td>Kristof, et al., 1997 (present study)</td>
<td>70 yrs, F</td>
<td>transient diplopia</td>
<td>MRI: small enhancing sellar mass angiography: pathological mass vascularization</td>
<td>subtotal</td>
<td>none, no thrombus detectable</td>
<td>enlargement of residual mass 3 mos later; shrinkage of residual mass for the next 3.5 yrs after local irradiation clinically inconspicuous 3 mos later on MRI; small residual intracavernous mass inconspicuous for 4 mos</td>
</tr>
<tr>
<td></td>
<td>51 yrs, M</td>
<td>diplopia</td>
<td>MRI: small enhancing sellar mass angiography: avascular</td>
<td>subtotal</td>
<td>none, no thrombus detectable</td>
<td></td>
</tr>
<tr>
<td></td>
<td>24 yrs, F</td>
<td>intermittent diplopia, impairment of pituitary corticotropic function</td>
<td>CT &amp; MRI: small enhancing sellar mass</td>
<td>probably complete</td>
<td>probably cavernoma</td>
<td></td>
</tr>
</tbody>
</table>

* AVM = arteriovenous malformation; CN = cranial nerve; CT = CT scanning; MRI = magnetic resonance imaging.
For cases of IPEH that were not amenable to surgery, radiotherapy and chemotherapy have been used, but so far there is no sufficient evidence that these are beneficial.

References