Intravascular Papillary Endothelial Hyperplasia of the Central Nervous System
—Four Case Reports—

Sedat ÇAGLI, Nezih OKTAR, Tayfun DALBASTI, Sertaç İSLEKEL, Eren DEMİRTAŞ, and Nurcan ÖZDAMAR

Department of Neurosurgery, Ege University Faculty of Medicine, Bornova, Izmir, Turkey

Abstract

Four rare cases of intracranial intravascular papillary endothelial hyperplasia (IPEH) manifesting as cranial nerve disturbances occurred in 16-, 18-, 24-, and 28-year-old females. Magnetic resonance imaging showed all lesions as isointense with strong enhancement on T1-weighted images, and as hyperintense on T2-weighted images. All lesions were removed via craniotomies. Histological examination found vascular structures and papillary spaces lined with endothelial cells showing immunoreactivity for CD31. Complete removal was curative in two cases, whereas incomplete removal resulted in cure in one case and residual deficits in one case. Iatrogenic deficits should be avoided in IPEH treatment by surgery. Differentiation from neoplasm such as angiosarcoma depends on histological characteristics.

Key words: intravascular papillary endothelial hyperplasia, cavernous sinus, pterional craniotomy

Introduction

Intravascular papillary endothelial hyperplasia (IPEH) is generally considered to be a benign proliferation of endothelial cells with secondary thrombosis and fibrin deposition or an excessive reaction to a normal reorganization process in a thrombus. IPEH was first described as an intravascular papillary proliferation in the lumen of an inflamed hemorrhoidal plexus and named “vegetant intravascular hemangioendothelioma” in 1923. IPEH has since been described under many different names, including IPEH, intravascular angiomatosis, Masson’s pseudoangiosarcoma, Masson’s hemangioma, and Masson’s vegetant intravascular hemangiendothelioma. Today, the term IPEH is favored over the more traditional names because of the absence of assumptions about the pathogenesis of the lesion.

IPEH most commonly occurs in the skin and subcutaneous soft tissues, where it exhibits a benign clinical course, but has also occurred in the nasal cavity, pharynx, larynx, internal auditory canal, labyrinthine, heart valve, breast, digestive tract, liver, kidney, cervix, uterus, female urethra, and pelvic veins. Few cases of IPEH involving the central nervous system (CNS) have been reported and only two cases in the vertebral canal. This benign lesion is clinically important because of the presentation as a mass lesion, possible histological confusion with angiosarcoma, and tendency to recur if incompletely resected.

Here we report four cases of IPEH of the CNS and review the cases of IPEH located in CNS.

Case Reports

Case 1: A 16-year-old right-handed female presented with a 2-month history of diplopia and drooping left eyelid beginning one month previously. Physical examination disclosed she was alert and oriented with no general abnormality. Neurological and ophthalmologic evaluations revealed left oculomotor and abducens nerve pareses. T1-weighted magnetic resonance (MR) imaging demonstrated a lesion appearing slightly hyperintense, with strong and almost homogeneous enhancement after intravenous administration of gadolinium (Fig. 1).

A reddish, soft, and very vascular tumor was removed from the left wall of cavernous sinus...
through a left pterional craniotomy. The demarcation between the tumor and cavernous sinus was not clearly defined. The lesion could only be resected incompletely to preserve the intracavernous structures. Histological examination showed the lesion consisted of several ectatic, thin-walled vascular channels. The vascular spaces were lined by flat or plump endothelial cells without cellular atypia or mitotic figures (Fig. 2). Some areas contained distinctive papillary projections covered by endothelium. Fibrinoid structures were present in some vascular spaces and cores of papillary projections. Small areas contained somewhat large vascular spaces with thick fibrous septa that resembled those of cavernous hemangioma. Immunohistochemical staining showed the connective tissue of the core had strong reactivity for vimentin, but no immune reactivity for epithelial membrane antigen. The lining cells of the vascular spaces showed immunoreactivity for CD31.

After surgery, the patient had total left ophthalmoplegia that resolved completely during the next 6 months. Follow-up MR imaging obtained 3 years after surgery revealed a small residual lesion in the left cavernous sinus, but the patient’s clinical findings remained unchanged.

Case 2: A 18-year-old right-handed woman, who was otherwise healthy, was admitted to the hospital because of diplopia that began 5 months previously. Neurological and ophthalmologic examination revealed only right abducens nerve paresis. MR imaging showed a lesion measuring approximately 25 × 15 mm originating from the right cavernous sinus. T1-weighted MR imaging showed the lesion as isointense with strong and homogeneous contrast enhancement (Fig. 3). T2-weighted MR images showed the lesion as hyperintense.

A right pterional craniotomy was performed for the subtotal removal of the lesion from the right cavernous sinus. The cavernous sinus was opened with preservation of the anatomical intracavernous structure. Histological examination of the lesion...
found vascular spaces of various sizes containing organizing thrombus in the central and numerous papillary structures in the peripheral areas (Fig. 4A). The vascular spaces and papillary structures were lined with endothelial cells with immunoreactivity for CD31 (Fig. 4B). The fibrous tissue showed vimentin immunoreactivity but no immunoreactivity for epithelial membrane antigen.

The patient developed oculomotor and abducens nerve pareses on the surgically treated side, despite morphological preservation of the intracavernous structures. These deficits resolved partially during the next 3 years. Follow-up MR imaging showed some evidence of residual IPEH.

**Case 3:** A 28-year-old right-handed woman, previously healthy, presented with a one-year history of diplopia and a one-month history of drooping left eyelid. Neurological examination found disturbance of the first and second divisions of the left trigeminal nerve and the left abducens and partial left oculomotor nerves. MR imaging disclosed a lesion measuring approximately $20 \times 30$ mm originating from the left cavernous sinus and extending into Meckel’s cave. T$_1$-weighted MR imaging showed the lesion as isointense with strong and homogeneous contrast enhancement (Fig. 5A, B). T$_2$-weighted MR imaging showed the lesion as hyperintense (Fig. 5C).

The tumor was totally removed from the caver-
nous sinus within Meckel’s cave through a left pterional craniotomy. The cavernous sinus was opened, but the intracavernous structures were preserved anatomically intact. Histological examination showed this lesion was similar to the others, with very prominent papillary structures lined with endothelial cells and several thin-walled vascular channels. The endothelial cells contained no cellular atypia or mitotic figures. There were areas filled with fibrin and two dilated vessels were observed. Elastic fibers were seen in the walls of these vessels and in the fibrous tissue around the papillary structures.

After surgery, the patient experienced right ophthalmoplegia that resolved totally during the next 2 years. Follow-up MR imaging at this time showed no evidence of residual IPEH. The hyperintense lesion at the operation site was considered to be the remnants of fat packing placed during the surgery.

**Case 4**: A previously healthy, 24-year-old right-handed woman presented to the emergency department with a single grand mal seizure preceded by 2 months of steadily worsening headache. There was no history of head trauma. Physical examination disclosed she was alert and oriented with no general abnormality. She denied any motor or sensory difficulties. MR imaging showed a left parietal mass. T1-weighted MR imaging showed the mass as isointense, with strong and homogeneous contrast enhancement (Fig. 6). T2-weighted MR imaging showed the lesion as hyperintense.

The patient underwent left parietal craniotomy for resection of the left parietal lesion. The lesion was completely removed (Fig. 7).

The postoperative period was free of complications, and she had no neurological abnormalities. Follow-up MR imaging performed 6 months later found no evidence of residual IPEH. Two years later, follow-up MR imaging found no abnormalities.

**Discussion**

IPEH of the CNS is rare, with only 15 previously reported cases (Table 1). In general, intracranial IPEH does not seem to be...
<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Age, Sex</th>
<th>Clinical presentation</th>
<th>Neuroimaging findings</th>
<th>Location</th>
<th>Surgery</th>
<th>Radiotherapy and chemotherapy</th>
<th>Follow up</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 enhanced supratentorial lesions; angiography: avascular masses</td>
<td>bilateral temporal and bilateral parietal regions</td>
<td>subtotal</td>
<td>none</td>
<td>surgery for local recurrence 19 mos later; thereafter, 9 yrs free; no progression of other lesion</td>
</tr>
<tr>
<td>Chen and Kuo (1984)</td>
<td>3.5 mos, F</td>
<td>sign of raised ICP, epileptic seizures, Kasabach-Merritt syndrome</td>
<td>CT: frontal, large enhanced lesion</td>
<td>left frontoparietal region</td>
<td>biopsy</td>
<td>none</td>
<td>died 6 mos later</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: vascular mass</td>
<td>left parietooccipital region</td>
<td>complete</td>
<td>none</td>
<td>no follow up available</td>
</tr>
<tr>
<td>Sickler and Langford (1990)</td>
<td>12 days, F</td>
<td>increased head circumference, poor feeding, emesis, proptotic right eye</td>
<td>CT: mass with nonenhanced rim; angiography: vascular mass; MR imaging: hemorrhagic mass</td>
<td>right middle cranial fossa extending into frontoparietal region</td>
<td>subtotal</td>
<td>doxorubicin hydrochloride, dacarbazine</td>
<td>local recurrence at 2 mos and postoperative chemotherapy</td>
</tr>
<tr>
<td>Wen et al. (1991)</td>
<td>15 yrs, F</td>
<td>signs of raised ICP</td>
<td>MR imaging: small enhanced process within the confluens sinuum; angiography: avascular mass</td>
<td>torcular herophili</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)</td>
<td>27 yrs, F</td>
<td>unilateral deficit of CNs III, V, and VI; headache</td>
<td>CT and MR imaging: small enhanced lesion in the orbital fissure; angiography: vascularized mass</td>
<td>left fissura orbitalis superior</td>
<td>complete</td>
<td>none</td>
<td>no evidence of recurrence for 6 mos</td>
</tr>
<tr>
<td>Tsuji et al. (1994)</td>
<td>18 yrs, F</td>
<td>seizures, hemiparesis</td>
<td>CT and MR imaging: intracerebral hemorrhage</td>
<td>left frontal lobe</td>
<td>complete</td>
<td>none</td>
<td>no evidence of recurrence for 2 yrs</td>
</tr>
<tr>
<td>Kristof et al. (1997)</td>
<td>70 yrs, F</td>
<td>transient diplopia</td>
<td>MR imaging: small enhanced sellar mass; angiography: pathologic vascularization</td>
<td>left cavernous sinus</td>
<td>subtotal</td>
<td>46 Gy radiotherapy</td>
<td>enlargement of residual mass 3 mos later and postoperative radiotherapy, shrinkage of residual mass clinically inconspicuous 3 mos later on MR imaging</td>
</tr>
<tr>
<td></td>
<td>51 yrs, M</td>
<td>diplopia</td>
<td>MR imaging: small enhanced sellar mass; angiography: avascular</td>
<td>right cavernous sinus</td>
<td>subtotal</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td></td>
<td>24 yrs, F</td>
<td>intermittent diplopia, impairment of pituitary corticotrophic function</td>
<td>CT and MR imaging: small enhanced sellar mass</td>
<td>left sellar region</td>
<td>probably complete</td>
<td>none</td>
<td>inconspicuous for 4 mos</td>
</tr>
</tbody>
</table>

Contd.
Table 1, page 2

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Age, Sex</th>
<th>Clinical presentation</th>
<th>Neuroimaging findings</th>
<th>Location</th>
<th>Surgery</th>
<th>Radiotherapy and chemotherapy</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duong et al. (1997)</td>
<td>51 yrs, F</td>
<td>headache, lt visual field deficit</td>
<td>CT: multiple slightly hyperdense, enhanced masses with edema; MR imaging: T1/PD hypointense, enhanced, T2 hyperintense masses surrounded by hemosiderin rim and edema/hematoma</td>
<td>bil occipital, rt frontal, and lt parietal lobes</td>
<td>complete</td>
<td>none</td>
<td>no evidence of recurrence for 6 mos</td>
</tr>
<tr>
<td>Baylor et al. (1998)</td>
<td>27 yrs, M</td>
<td>rt side facial nerve paresis</td>
<td>CT: no mass lesion; MR imaging: enhanced, T2 hypo-to isointense mass/none</td>
<td>rt internal auditory canal and fallopian segment of facial nerve</td>
<td>complete</td>
<td>none</td>
<td>no follow up available</td>
</tr>
<tr>
<td>Avellino et al. (1999)</td>
<td>62 yrs, F</td>
<td>ear pain, facial nerve paresis, dysphagia</td>
<td>CT: enhanced mass; angiography: vascular mass; MR imaging: enhanced mass/aneurysm</td>
<td>lt CPA and middle cranial fossa region</td>
<td>subtotal</td>
<td>after 1st operation 45 Gy radiotherapy, after 2nd operation radiosurgery</td>
<td>2nd operation for local recurrence at 9 yrs and radiosurgery</td>
</tr>
<tr>
<td>Lesley et al. (2000)</td>
<td>46 yrs, F</td>
<td>rt ear pain extending into rt side of the face and neck, dysphagia</td>
<td>angiography: faint vascular blush and mass effect; MR imaging: T1 hypointense, enhanced, T2 hyperintense mass/aneurysm</td>
<td>rt PICA aneurysm</td>
<td>total</td>
<td>none</td>
<td>no evidence of recurrence for 1 yr</td>
</tr>
<tr>
<td>Stoffman and Kim (2003)</td>
<td>54 yrs, F</td>
<td>headache, speech difficulty</td>
<td>MR imaging: extradural partially hemorrhagic lesion in the lt petrous apex and Meckel’s cave</td>
<td>lt Meckel’s cave</td>
<td>subtotal</td>
<td>none</td>
<td>residual mass 10 mos postoperatively</td>
</tr>
<tr>
<td>Present Case 1</td>
<td>16 yrs, F</td>
<td>unilateral deficit of CNs III and VI</td>
<td>MR imaging: small enhanced lt intracavernous mass</td>
<td>lt cavernous sinus</td>
<td>subtotal</td>
<td>none</td>
<td>residual intracavernous mass 3 yrs later on MR imaging</td>
</tr>
<tr>
<td>Present Case 2</td>
<td>18 yrs, F</td>
<td>unilateral deficit of CN VI</td>
<td>MR imaging: small enhanced rt intracavernous mass</td>
<td>rt cavernous sinus</td>
<td>subtotal</td>
<td>none</td>
<td>residual intracavernous mass 3 yrs later on MR imaging</td>
</tr>
<tr>
<td>Present Case 3</td>
<td>28 yrs, F</td>
<td>unilateral deficit of CNs III, V, and VI</td>
<td>MR imaging: strongly enhanced lt intracavernous mass</td>
<td>lt cavernous sinus</td>
<td>total</td>
<td>none</td>
<td>no evidence of recurrence at 2 yrs on MR imaging</td>
</tr>
<tr>
<td>Present Case 4</td>
<td>24 yrs, F</td>
<td>seizure</td>
<td>MR imaging: enhanced lt parietal mass</td>
<td>lt parietal lobe</td>
<td>total</td>
<td>none</td>
<td>no evidence of recurrence at 2 yrs</td>
</tr>
</tbody>
</table>

associated with a specific age group, but does tend to occur in females (female/male 17/2). The age of presentation ranged from 12 days to 70 years. However, the male to female ratio was 1:1 in middle aged patients.7,24) Intracranial IPEH manifests as a variety of symptoms that largely depend on the location of the lesion including the signs of local compression and increased intracranial pressure.

Intracranial IPEH can develop within a preexisting vascular malformation or thrombus, such as the cavernous sinus, meninges, torcular herophili, superior orbital fissure, internal auditory canal, and aneurysm.5,6,9,22,26,34,37,40) Three of our cases were in the sellar region, and one in the parietal lobe. Multiple lesions may have included examples of IPEH in the setting of systemic cavernous angiomas: the pure form that occurs within a dilated vascular space most frequently located in the fingers, head and neck, and in the region between the elbows and hands; the mixed form that appears as a focal change in a hemangioma (most common), vascular malformation, or pyogenic granuloma, or is intramuscular in no particular sites; and the undetermined form, belonging to neither of the first two, which has an extravascular origin.15,20,29,34,36) The lesion had probably arisen within a cavernous angioma in our Case 1. Thrombotic material was seen in Cases 2, 3, and 4. In Case 2, there were no true vessels and probably the thrombus had arisen in the cavernous sinus. However, Case 3 had two large vessels and residual elastic fibers around the papillary projections.

Differentiation of IPEH from neoplasms, such as angiosarcomas, has been emphasized.5,20,31,33) Unlike other angiomatous tumors, the proliferation of endothelial cells in IPEH is confined to the vascular lumen. The paucity of mitosis, foci of necrosis, and solid cellular areas without vessel formation may also help to distinguish this entity from neoplasms. The 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 also missing. The whirling pattern of the reactive fibroblasts, clusters of arachnoid cap cells, and collagen may suggest the diagnosis of meningioma, but observation of papillary structures and factor VIII staining can be helpful. The vascular origin, hinted at by the relationship to cavernous angiomias and hemangiomas, is established by the presence of factor VIII reactivity.6,9,11,14,17,21,25,26,34–36)

IPEH was originally regarded as neoplastic because of the histological similarity with hemangiosarcoma, but is currently believed to be an unusual form of intravascular organizing thrombi or a reactive process, although the exact histogenesis remains controversial.3,5,10,13,18,33,35) Such endothelial proliferation was described as an unusual excessive reaction to the normal process of organization of a thrombus rather than a neoplasm in 1932.16) However, some authors continue to consider IPEH as a true neoplasm.9,20,38) The stages of the partitioning of intravascular thrombus into fine papillae by the “ingrowth” of endothelium have been elegantly described and illustrated.23) The majority of these lesions are intimately associated with thromboembolic material.1,2,4–6,11,15,17–20,22,26–30,32,34,35,37,38,40) IPEH can generally be observed as an unusual pattern of organization of arterial and venous thrombi or a focal incidental microscopic finding in hemangioma rather than true neoplastic change. IPEH may be closely related to and probably is a peculiar form of organizing thrombi.22) Northern blot and immunoblot studies revealed a 5–10 fold increase in basic fibroblast growth factor transcripts (7.0 and 3 kb) and a 10–20 fold increase in immunoreactive basic fibroblast growth factor protein.23) Therefore, the pathogenesis of IPEH involves an autocrine loop of endothelial basic fibroblast growth factor secretion stimulating endothelial cell protein. Immunohistochemically, IPEH reacts with factor VIII, CD31, CD34, and CD32, corresponding to the endothelial cell proliferative component.5,9,11,17,21,28,34–36)

IPEH can be divided into three different categories: the pure form that occurs within a dilated vascular space most frequently located in the fingers, head and neck, and in the region between the elbows and hands; the mixed form that appears as a focal change in a hemangioma (most common), vascular malformation, or pyogenic granuloma, or is intramuscular in no particular sites; and the undetermined form, belonging to neither of the first two, which has an extravascular origin.15,20,29,34,36) The lesion had probably arisen within a cavernous angioma in our Case 1. Thrombotic material was seen in Cases 2, 3, and 4. In Case 2, there were no true vessels and probably the thrombus had arisen in the cavernous sinus. However, Case 3 had two large vessels and residual elastic fibers around the papillary projections.

Differentiation of IPEH from neoplasms, such as angiosarcomas, has been emphasized.5,20,31,33) Unlike other angiomatous tumors, the proliferation of endothelial cells in IPEH is confined to the vascular lumen. The paucity of mitosis, foci of necrosis, and solid cellular areas without vessel formation may also help to distinguish this entity from neoplasms. The 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 also missing. The whirling pattern of the reactive fibroblasts, clusters of arachnoid cap cells, and collagen may suggest the diagnosis of meningioma, but observation of papillary structures and factor VIII staining can be helpful. The vascular origin, hinted at by the relationship to cavernous angiomias and hemangiomas, is established by the presence of factor VIII reactivity.6,9,11,14,17,21,25,26,34–36)

IPEH is generally hypervascular and is enhanced by gadolinium. T2-weighted imaging typically demonstrates the lesion as hypointense, whereas T1-weighted MR imaging generally shows IPEH as hyperintense, whereas T1-weighted MR imaging typically demonstrates the lesion as hypointense to isointense. Computed tomography enhancement is variable, but the lesion tends to appear at least slightly hyperdense.

The mainstay of therapy for intracranial IPEH has been, if possible, complete surgical resection. Nine of 19 cases were completely excised. Recurrence is rare, and total removal of the lesion is consistent with a clinical cure. IPEH generally recurs if resection is incomplete.1,19,27,34) Ten of 19 cases were incompletely excised surgically. Only four cases have recurred in the CNS: two were treated by radiation therapy and radiosurgery, one by chemotherapy, and one by second surgery (Table 1). No recurrent cases underwent complete resection. Two of our cases had incomplete surgical resection and no additional treatment. Follow-up MR imaging revealed a residual lesion in the cavernous sinus,
although the clinical findings remained normal. Some patients will have disease-free survival without adjuvant therapy for many years.

The clinical behavior, treatment, and prognosis of the IPEH in the skin and the subcutaneous soft tissue are difficult to compare with neural tissue sites. A lesion of the CNS cannot usually be completely removed without causing significant morbidity. This rare intracranial lesion does not have an accepted protocol for treatment. Complete resection was most probably possible in the present cases because of the small size and favorable location. Radiation was not considered appropriate. Adequate follow-up information is not yet available to allow comment on the effectiveness of the therapy. The postoperative courses detected no cases of metastasis or overt malignant behavior. The prognosis for the adults appears to be better than for neonates.

The present four cases and the 15 previous cases illustrate that 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. This entity must be clearly distinguished from neoplasms such as angiosarcoma. The paucity of mitoses, foci of necrosis, and solid cellular areas without vessel formation help to distinguish this entity from an angioma. Report of a fatal case. Arch Pathol Lab Med 108: 555–556, 1984

23. Levere SM, Barsky SH, Meals RA: Intravascular...
S. Çagli et al.


Address reprint requests to: S. Çagli, M.D., Ege Universitesi Tip Fakultesi, Nöroşirirji Anabilim Dah, Bornova Izmir 35100, Turkey.

e-mail: caglis@med.ege.edu.tr