Psammomatous Cavernous Malformation Presenting as Drug-Resistant Epilepsy: Case Illustration and Review of Literature

Kanika Sharma1, Piyush Kalakoti1, John E. Shaughnessy1, Nestor De La Cruz2, Rimal H. Dossani1, Peimin Zhu3, Eduardo Gonzalez-Toledo4, Christina Ledbetter1, James B. Pinks ton5, Anil Nanda1, Rosario Maria Riel-Romero5, Alireza Minagar3, Christina Notarianni1, Hai Sun1

INTRODUCTION

Psammoma bodies (PBs) are whorled, laminated hyaline spherules containing calcium deposits. Intracranially, the presence of PBs is associated with variants of meningioma and pituitary lesions, as well as aging choroid plexus. Limited information exists on their presence in vascular malformation.

RESULTS: In this report, we describe a case of an adolescent male with drug-resistant epilepsy that was surgically managed at our regional epilepsy center. The epileptogenic focus was determined to be emanating from an indolent right insular lesion. Histopathologic evaluation showed the abundance of intravascular and perivascular PBs. Immunohistochemical evaluation confirmed the vascular origin using vascular markers. The unusual presence of PBs in a vascular lesion was unanticipated.

CONCLUSIONS: Based on our case, we present the clinicoradiologic characteristics, supplemented with intraoperative findings, for this unusual lesion. In addition, because of the unusual presence of PBs in vascular lesions, we provide the findings of a systematic literature review to show the association of PBs with intracranial vascular lesions.

Key words

Cavernoma
Drug-resistant epilepsy
Electrocorticography
Psammoma
Vascular malformation

Abbreviations and Acronyms

AED: Antiepileptic drug
EEG: Electroencephalography
ECoG: Electrocorticography
MR: Magnetic resonance
PB: Psammoma body
QoL: Quality of life

BACKGROUND: Psammoma bodies (PBs) are whorled, laminated hyaline spherules containing calcium deposits. Intracranially, the presence of PBs is associated with variants of meningioma and pituitary lesions, as well as aging choroid plexus. Limited information exists on their presence in vascular malformation.

RESULTS: In this report, we describe a case of an adolescent male with drug-resistant epilepsy that was surgically managed at our regional epilepsy center. The epileptogenic focus was determined to be emanating from an indolent right insular lesion. Histopathologic evaluation showed the abundance of intravascular and perivascular PBs. Immunohistochemical evaluation confirmed the vascular origin using vascular markers. The unusual presence of PBs in a vascular lesion was unanticipated.

CONCLUSIONS: Based on our case, we present the clinicoradiologic characteristics, supplemented with intraoperative findings, for this unusual lesion. In addition, because of the unusual presence of PBs in vascular lesions, we provide the findings of a systematic literature review to show the association of PBs with intracranial vascular lesions.

METHODS

A systematic review of the literature for relevant, peer-reviewed articles up to 15 March 2016 using the electronic databases MEDLINE and Google Scholar was performed. Boolean operators, “AND” and “OR” using the search terms “psammoma”, “vascular”, “malformation”, “hemangioma,” and “cavernous” were used in various combinations to narrow the scope of the review. The resulting citations were examined in their entirety by 2 authors (K.S. and P.K) independently. To filter relevant articles, retrieved articles were screened by reviewing each article title, abstract, or full texts as available. Bibliographies of identified publications and articles citing them were also scrutinized. Criteria implemented for screening included 1) articles documenting the presence of PB within vascular malformations; 2) vascular malformations in intracranial locations; and 3) articles limited to humans. Exclusion criteria applied to article selection included articles documenting the presence of PB with intracranial vascular malformation, our case serves to revisit this rare association and describe clinicopathologic correlates and radiologic and intraoperative findings of this unusual disease. In addition, we provide the results of a systematic review of the literature on intracranial vascular diseases associated with the presence of PB.
patient characteristics including age, gender, clinical presentation, vascular pathology, radiologic and histologic findings, management, and outcome. Our review is summarized in Table 1.6,7

CASE ILLUSTRATION

History and Examination
A 15-year-old African American, right-hand-dominant boy presented to our regional epilepsy center at the Louisiana State University, Shreveport, Louisiana, USA, for evaluation and management of drug-resistant epilepsy. At age 12 years (2011), the patient was alleged to have experienced his first seizure episode while playing video games at home. The seizure semiology was suggestive of a complex-partial type, starting with a brief aura lasting less than a minute with impaired consciousness. The patient was unresponsive to verbal or tactile stimuli and experienced head shaking while staring at the ceiling, with unilateral blinking of his right eye and fixed left eye glare. The episode lasted over 5 minutes, followed by loss of postural tone. Postictally, the patient reported tiredness and confusion. No facial grimacing, tongue biting, upward eye rolling, fever, or jerky limb movements were noted. The seizure episode recurred 2 days later with similar presentation, after which the patient was evaluated by a neurologist. Past medical history was unremarkable except for occasional migraine headaches. No documented delay in his developmental history or milestones was noted. Family history was negative for seizure disorders. Video electroencephalographic (EEG) studies at that time determined the epileptogenic focus to be emanating from the anterior and central region of the right temporal lobe. Frequent high-amplitude spikes were seen over the right frontotemporal areas, maximal over F8 and T4. These epileptiform abnormalities had a broad field and spread to T4 and T6 and occasionally to C4 and P4. A contemporary computed tomographic scan of the head showed an area of calcification, measuring 8 mm in maximal dimension in the insular region, adjacent to the sylvian fissure (Figure 1A). The spherical lesion was confirmed on magnetic resonance (MR) imaging (Figure 1B and C), and was contrast enhancing (Figure 1D). However, MR angiography proved inconclusive to distinguish if the lesion represented an aneurysm or a vascular malformation. At this point, medical management with oxcarbazepine 300 mg orally twice a day was initiated for seizure control; observation of the insular lesion with serial imaging on follow-up was deemed prudent.

Over the course of the next 3 years (2012–2014) since the onset, the patient was prescribed antiepileptic drugs (AEDs) in augmented dosages to curtail intermittent seizure episodes that initially averaged 5 or 6 times quarterly (2012) and progressed to every 2–3 days (2014). The seizure progression necessitated frequent emergency room visits with subsequent hospitalizations, negatively affecting quality of life (QoL) and predisposing to missed school days. No signs of cognitive decline or poor academic performance were noted. Potentially recognizable precipitating factors for seizure induction included stimulus overload (video games) and stress. Follow-up computed tomography (mid-2012) at 1 year since the first seizure depicted the presence of preexisting calcification, albeit with slight increment in size to 10 mm (Figure 1E). By mid-2014, the AED regimen comprised levetiracetam 1000 mg twice a day, extended release oxcarbazepine 2100 mg/day, and...
<table>
<thead>
<tr>
<th>Reference</th>
<th>Age (years), Sex</th>
<th>Presenting Symptoms</th>
<th>Neurologic Examination</th>
<th>Size (mm)</th>
<th>Vascular Disease</th>
<th>Neuroimaging</th>
<th>Management</th>
<th>Histopathologic Findings</th>
<th>Postoperative Complications</th>
<th>Follow-Up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ghosh and Saha, 2013</td>
<td>18, M</td>
<td>Left sided focal motor seizures</td>
<td>No deficits; unremarkable</td>
<td>30 × 24 × 13</td>
<td>Hemangioma calcificans</td>
<td>CT scan: well-circumscribed calcified lesion in the R frontoparietal area without any evidence of midline shift, mass effect, or perilesional edema</td>
<td>R frontoparietal craniotomy</td>
<td>Dilated, thin-walled vessels with intravascular presence of calcified laminated hyaline structures</td>
<td>None, patient remains seizure free until follow-up</td>
<td>6</td>
</tr>
<tr>
<td>Piplani et al., 2014</td>
<td>70, M</td>
<td>Unconscious after head trauma</td>
<td>GCS 9, increased ICP</td>
<td>72 × 34 × 57</td>
<td>Cavernous hemangioma</td>
<td>CT scan: hyperdense lesion associated with hemorrhage in the R temporal lobe, R basal ganglia, and R corona radiata. Effacement of Sylvian fissure compression of R lateral ventricle with midline shift of 6 mm towards the contralateral side</td>
<td>Craniotomy for clot evacuation</td>
<td>Dilated and congested vascular channels with presence of numerous psammoma bodies both intravascularly as well as in extravascular gial tissue: CD31 (+), CD34 (+), EMA (+), CK18 [—]</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Sharma et al., 2016, this study</td>
<td>16, M</td>
<td>Drug-resistant epilepsy of complex-partial type</td>
<td>No focal neuro deficits; unremarkable</td>
<td>10*</td>
<td>Cavernous malformation</td>
<td>MR: contrast-enhancing lesion in the R insular region, adjacent to the Sylvian fissure. SWAN sequence depicted classic blooming effect</td>
<td>Video-EEG monitoring; Neuronavigation-guided peritonal craniotomy for microsurgical resection of the lesion with intraoperative ECoG</td>
<td>Marked calcifications within the gliotic tissue with abundant blood vessels. Numerous perivascular and intravascular psammoma bodies visualized. GFAP (+), CD31 (+), CD34 (+), EMA (—)</td>
<td>None, patient remains seizure free</td>
<td>6</td>
</tr>
</tbody>
</table>

M, male; L, left; CT, computed tomography; R, right; GCS, Glasgow Coma scale; ICP, intracranial pressure; CD, cluster of differentiation; EMA, epithelial membrane antigen; CK, cytokeratin; NR, not recorded; MR, magnetic resonance; SWAN, susceptibility-weighted angiography; EEG, electroencephalogram; ECoG, electrocorticography; GFAP, glial fibrillary acidic protein.

*Maximal longitudinal diameter.
clobazam 10 mg twice a day. Despite modifications in the AED regimen and increment in dosages, the patient continued to have break-through seizures and was referred for possible surgical management of his drug-resistant epilepsy. Throughout the course of seizure progression, the patient remained neurologically intact with no focal deficits.

Presurgical Workup
Serial neuroimaging studies including MR and positron emission tomographic studies were pursued. A hypointense rim surrounding the lesion as noted on an axial MR gradient echo sequence was consistent with hemosiderin deposition, and a susceptibility-weighted angiography sequence (Figure 1F) showed the classic blooming effect of a cavernoma. A 4-vessel angiogram showed no evidence of aneurysm, stenosis, or vascular malformation (Figure 1G). Based on imaging characteristics, the lesion was suspected to be a vascular malformation. Intercital positron emission tomography showed decreased fluorodeoxyglucose uptake (hypometabolism) that coincided with the area of calcification (Figure 1H). Compared with previous imaging studies, the insular lesion remained stable in size. Fluid-attenuated inversion recovery sequences showed the popcorn appearance of the lesion, consistent with a cavernoma.

Scalp video-EEG monitoring performed for 2 days showed frequent interictal epileptiform discharges, over the right anterior temporal, central, and parietal head regions (Figure 2). One electroclinical seizure was captured during video-EEG monitoring characterized by ipsilateral head turning, head automatism, and confusion. On EEG, theta sharp waves were seen emanating from the T2 electrode spreading to C4 and P4 followed by higher-amplitude polymorphic delta transients lasting for 25 seconds. Neuroimaging and EEG findings yielded congruent findings, confirming the right insular lesion as the most plausible epileptogenic focus. In view of the patient’s poor seizure control with AEDs, the patient and family consented to resection of the lesion.

Surgical Management
The patient underwent a right-sided neuronavigation-guided pterional craniotomy for microsurgical resection of the calcified insular mass lesion, presumed to be a cavernous malformation (Supplementary Video). Intraoperative electrocorticography (ECoG) before and after resection, with neurophysiologic monitoring, was performed. Using an intradural approach, the sylvian fissure was split via

Figure 2. Neuroimaging studies: (A) computed tomography axial plane (2011) showing an area of calcification 8 mm in maximal diameter in the right insular region, adjacent to the sylvian fissure; magnetic resonance imaging confirmed the presence of a spherical lesion in (B) T2-weighted coronal brain volume imaging and (C) sagittal planes, with (D) contrast enhancement as visualized in axial T1-weighted sequence. (E) Follow-up computed tomography scan (2012) showing indolent growth to 10 mm in maximal diameter. (F) Axial susceptibility-weighted angiography sequences showing the classic blooming effect of a cavernomatous lesion. (G) A 4-vessel angiogram via a right internal carotid injection showing no evidence of aneurysm, stenosis, or vascular malformation. (H) Positron emission tomography scan showing a hypometabolic region (solid, black arrow), implying decreased fluorodeoxyglucose uptake congruent with the area of the lesion.
subarachnoid dissection. The right middle cerebral artery was visualized and traced posteriorly. Before the resection, the intraoperative ECoG recording from the electrodes placed on the cortex adjacent to the lesion on insular cortex showed frequent sharp waves, necessitating a small corticectomy adjacent to the lesion. No seizure recordings were perceived on other regions of the frontal lobe. A firm calcified mass was visualized after delineating from the surrounding tissues and subsequently resected en bloc (Supplementary Video). No evidence of sharp waves or abnormal cortical discharges was noted in the resection cavity. After adequate hemostasis, closure was performed in a routine fashion.

Histopathologic Studies
On gross examination, the resected mass consisted of 4 fragments of beige-tan tissue of firm consistency and measuring 1.7 cm × 1.5 cm × 0.6 cm in aggregate. Sections showed beige-tan solid cut surfaces with multiple crunchy spots. Microscopic sections showed marked calcifications within the gliotic tissue in a background of abundant blood vessels. Hematoxylin-eosin staining revealed the presence of numerous perivascular and intravascular PBs (Figure 3A). Immunohistochemistry staining confirmed the presence of PBs amid glial fibrillary acidic protein–positive cells (Figure 3B). Epithelial membrane antigen staining was negative (Figure 3C), thus ruling out psammomatous meningioma. Vascular markers such as the CD31 (Figure 3D) and CD34 (Figure 3E) showed positive staining of thin- and thick-walled vessels, thus confirming the vascular origin of the lesion. Correlating the clinicoradiologic and histopathologic findings, a diagnosis of psammomatous insular cavernoma was made.

Postoperative Course and Follow-Up
The postoperative inpatient stay was uneventful. Postresection MR imaging showed postsurgical changes with complete resection of the lesion (Figure 4A and B). With no episodes of seizure during the inpatient stay, the patient was discharged home on postoperative day 4 and prescribed daily doses of levitiracetam (1500 mg twice a day), clobazam (10 mg twice a day), and oxcarbazepine (2400 mg) to ensure seizure control. At 6 months follow-up, the patient remained seizure free without any focal neurologic deficits. We have begun to decrease the doses of his AEDs with the hope that he will remain seizure free without any medications.

DISCUSSION
We describe a rare case of an adolescent boy presenting with drug-resistant epilepsy. Seizure semiology in our patient was classic for a complex-partial type,

Figure 3. Histopathologic studies. (A) Section stained with hematoxylin-eosin showing the presence of numerous perivascular and intravascular psamomma bodies at (A) low- [×20] and (B) high-power [×40] magnification. The pointers (solid, black arrow) show isolated whorled laminated basophilic appearing psamomma bodies present intravascularly. No evidence of mitosis or necrotic area was seen. Immunohistochemical markers confirmed the presence of negatively stained psamomma bodies amid (C) glial fibrillary acidic protein–positive glial cells [×40]. (D) negative epithelial membrane antigen stained cells [×20] and positively stained vessel walls with vascular markers (E) CD31 [×40] and (F) CD34 [×40]. The pointers (solid, black arrow) in (E) and (F) show negatively stained psamomma body in the lumen of a blood vessel with positively stained endothelium.
The presence of intravascular and peri-vascular PBs in a cavernomatous lesion is unique to our case. Intracranial presence of PBs is strongly linked with specific variants of meningiomas and some pituitary lesions. The maiden depiction of PBs as a pathologic feature in intracranial meningioma was proposed by Virchow in 1847. The nomenclature derives its origin from the Greek word "πέτρικος" (petρίκος), implying “sandlike,” hinting at the presence of granules within the tumor. Over the years, various hypotheses about the formation of PBs have been proposed, albeit widely debated and poorly understood. Traditionally, PBs are believed to be a product of dystrophic calcification, a localized process that occurs in damaged (dead or dying) tissues without derangement of calcium metabolism. In a review of the existence of PBs in various diseases, Das proposed that PBs could overtly signify an active biological process aimed at limiting tumor growth and spread as opposed to dystrophic calcification. However, no definitive consensus on this viewpoint has been reached. Nevertheless, with enhanced knowledge pertaining to the presence of PBs in various systemic conditions, its usefulness as a significant diagnostic marker in narrowing the scope of differentials by correlating pertinent clinical features cannot be undermined.

To our knowledge, the presence of PBs in intracranial vascular lesions is rare. To assess the magnitude of this association, we performed a comprehensive review of the literature. The retrieved search results were limited to 2 solitary reports documenting the association of PBs with vascular malformations (Table 1).

CONCLUSIONS

With a paucity of literature on the rarity of association of intracranial vascular malformations with PBs, our case serves to...
support this association. Future reports documenting the association of PBs with vascular lesions are encouraged to clarify this association, if at all. In cases of calcified cavernous malformations, vigilant monitoring using serial imaging is recommended to monitor growth. Prompt surgical intervention coupled with intraoperative electrocorticography can aid in optimal resection with minimal morbidity and maximal chance for seizure freedom.

REFERENCES
2. Virchow R. Entwicklungsgeschichte des Krebes. Virchows Arch. 1847;71:94 [In German].

Conflict of interest statement: The authors declare that the article content was composed in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received 14 April 2016; accepted 27 May 2016
Citation: World Neurosurg. (2016) 93:120-126.
http://dx.doi.org/10.1016/j.wneu.2016.05.093
Journal homepage: www.WORLDNEUROSURGERY.org
Available online: www.sciencedirect.com
1878-8750/$ - see front matter © 2016 Elsevier Inc. All rights reserved.

Communicating through Clinical Images
Progress in neurosurgery has paralleled advances in lesion localization and imaging technologies. WORLD NEUROSURGERY is launching a new section to convey the nuances of our specialty through imagery: Communicating through Clinical Images. This is also a conduit by which neurosurgeons worldwide may communicate exciting discovery and experience through a common language, i.e. captivating clinical images. We thus encourage the submission of images or videos from cases that portray interesting, engaging and somewhat rare depiction of neurosurgical disease.

Submission criteria (please choose ‘Clinical Images’ as your article type):

- Text: One electronic document, double spaced
- Title: The title should be clear and concise
- No more than three authors, with name, highest academic degree, affiliations, address and email for each
- The legend should contain no more than 150 words, and include relevant patient history/physical examination, clinical course and response to treatment and if applicable, condition at follow-up.