Case Report
Features of intraventricular tanycytic ependymoma: report of a case and review of literature

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Abstract: Tanycytic ependymoma is the rarest variant of ependymoma and occurs primarily in the spinal cord. Intracranial cases are even rarer. Only 9 ventricular and 5 subcortical tanycytic ependymoma have been reported in the literature. Amongst the 9 ventricular cases, only one tumor arose from the third ventricle. We report here another case of tanycytic ependymoma arising from the third ventricle completed with immunohistochemical, ultrastructural, and molecular pathology study. The patient was a 44-year-old male who presented with headache, nausea and visual disturbances of a few months duration. Neuroradiological findings showed a well-defined mass arising from the posterolateral wall of third ventricle. Histologically the tumor was composed of monotonous spindle cells arranged in fascicles without definitive perivascular rosettes. The tumor cells were diffusely positive for glial fibrillary acidic protein and epithelial membrane antigen, showed faint immunoreactivity for synaptophysin but were negative for neurofilament proteins and Ki-67 was less than 1%. Molecular studies showed absence of isocitrate dehydrogenase gene 1 and 2 mutation. A diagnosis of tanycytic ependymoma (TE) was made. From literature review with our current case included, intraventricular tanycytic ependymomas ranged from 1.8 to 4.0 cm. The age of patients ranged from 3.5 to 75 years with a mean age of 37.5 and a male predominance. The tumors occurred as well-defined, solitary ventricular mass without significant peritumoral edema with or without cystic changes. Histopathology and immunohistochemical profile are rather similar among different tumors. The immediate to short term outcome is excellent but long term follow up data is lacking.

Keywords: Ventricular tumor, tanycytic ependymoma, subependymoma, ependymoma, astrocytoma

Introduction
Tanycytic ependymoma (TE) is a grade II tumor in the World Health Organization Classification [1]. It is the rarest variant of ependymoma being encountered in surgical neuropathology. This tumor is believed to be derived from a specialized population of ependymal cells known as tanycytes [2-4] that are believed to be the primitive progenitor cells in the phylogenetic development of ependymal cells and glial cells [3]. In their review of 43 ependymomas and 71 astrocytomas, Friede and Pollak coined the term ‘tanycytic variant of ependymoma’ for neoplasms showing tissue structure reminiscent of the evolution of piloid astrocytes from ependymoglia or tanycytes [3]. TE should be differentiated from other neuroepithelial neoplasms with spindle cell features including pilocytic astrocytoma, diffuse astrocytoma and schwannoma.

TE is the least common of ependymal tumors and is seen most commonly in the spinal cord. Only 9 ventricular and 5 subcortical TEs have been reported in the English literature. The rarity of these tumors poses a diagnostic challenge. Amongst these ventricular cases, only one TE arising from the third ventricle has been reported. We are reporting here the second case in the English literature completed with immunohistochemistry, electron microscopy, molecular pathology studies, and a review of literature.
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Case presentation

Clinical history

The patient was a 44 year-old female who presented to the neurosurgical service of our institute with complaints of minimal headache, double vision, nausea, and difficulty in maintaining balance for the past six months. The patient denied vomiting, falls, seizures or weakness. The patient also has a history of depression but no other constitutional conditions.

Neuromaging

Magnetic resonance imaging (MRI) (Figure 1) revealed a well-defined, intra-axial mass, $1.8 \times 1.7 \times 1.6$ cm, arising from the left lateral wall of the third ventricle. The tumor showed local mass effect on the hypothalamus and significantly narrowed the third ventricle. There is no herniation or midline shift. This mass is isointense to gray matter and hypointense to white matter on pre-contrast axial spoiled gradient echo (SPGR) imaging (A). The mass does not enhance (B, axial post-contrast SPGR imaging) and is hyperintense on axial pre-contrast T2 weighted imaging (C). Axial pre-contrast FLAIR imaging shows no peritumoral vasogenic edema (D).

Figure 1. MRI with and without contrast enhancement shows a well-circumscribed solid intra-axial mass ($1.8 \times 1.7 \times 1.6$ cm) arising from the left posterolateral wall of the third ventricle. The lesion exerts local mass effect on the hypothalamus and significantly narrows the third ventricle. There is no herniation or midline shift. This mass is isointense to gray matter and hypointense to white matter on pre-contrast axial spoiled gradient echo (SPGR) imaging (A). The mass does not enhance (B, axial post-contrast SPGR imaging) and is hyperintense on axial pre-contrast T2 weighted imaging (C). Axial pre-contrast FLAIR imaging shows no peritumoral vasogenic edema (D).
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Intraventricular tanycytic ependymoma significantly narrowed the third ventricle without any herniation. The mass was iso- to hyperintense to the cortex and hyperintense to white matter on pre-contrast axial spoiled gradient echo (SPGR) imaging (Figure 1A) and did not enhance with gadolinium administration (Figure 1B). It was isointense to the cortex on T2-weighted images (Figure 1C). No significant peritumoral vasogenic edema was demonstrated on fluid attenuated inversion recovery (FLAIR) images (Figure 1D).

Surgery

The patient underwent a complete resection of the tumor via an image guided transcortical approach. A gross total resection was achieved by using a cavitronic ultrasonic aspirator. He developed hydrocephalus after operation and a ventriculoperitoneal shunt was placed. The patient remained disease free and stable after one year.

Pathology

Small fragments of sample ranging from 0.1 to 0.2 cm in greatest dimension were sent for intraoperative consultation and a preliminary diagnosis of glial tumor with a possibility of subependymoma was made.

The subsequent resection specimen, 3.5 × 2.0 × 0.6 cm in toto, consisted of multiple pale tan soft tissue fragments admixed with a substantial amount of blood. Histologic examination with hematoxylin and eosin stain revealed frag-

Figure 2. (A) On hematoxylin and eosin stained sections, the tumor cells are rather monotonous and spindle shaped with vague fascicle formation. (B) The nuclei are small and hyperchromatic. (C) No definitive perivascular coronary arrangement is present. (D) The tumor cells are diffusely positive for GFAP. (E) The tumor cells are diffusely positive for EMA but not dot shaped immunoactivity is present (Inset in E). (F) The tumor cells are negative for neurofilament proteins but entrapped axons are well demonstrated. (G) The tumor cells are weakly positive for synaptophysin. Entrapped neurons are positive for synaptophysin. (H and I) are immunohistochemistry for Ki67 for high and low labeling index respectively. Original magnification in (A, D-I) is 20 ×, (B) is 40 ×, (C) and inset in (E) is 60 ×.
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Figure 3. Electron microscopic examination reveals cytoplasmic processes containing dense arrays of glial-type filaments. Ultrastructural features specifically associated with ependymal differentiation are not detected, possibly due to suboptimal preservation resulting from prior paraffin embedment. Original magnification is 5,000 ×.

ments of neoplastic glial cells with bland nuclei and moderate to substantial amount of pale eosinophilic cytoplasm. The neoplastic cells were spindly and reminiscent of astrocytes (Figure 2A and 2B). The nuclei were small, hyperchromatic, and lacked significant pleomorphism (Figure 2C). No definitive perivascular coronary arrangement, rosette, or tubule formation was noted. Neither mitosis nor necrosis was identified. On immunohistochemistry, the neoplastic cells were strongly and diffusely positive for glial fibrillary acidic protein (GFAP) (Cell Marque, California) (Figure 2D), and epithelial membrane antigen (EMA) (Cell Marque, Arizona) (Figure 2E), weakly positive for synaptophysin, (Ventana, CE, Arizona) (Figure 2G) but negative for neurofilament proteins (Invitrogen, CE, California) (Figure 2F). Scant neoplastic cells were weakly positive for p53 (Ventana, Arizona). The Ki-67 (Mib-1), (Ventana, Arizona) labeling index was less than 1% (Figure 2I). All immunohistochemistry was performed with a Benchmark autostainer (Ventana, Arizona) as per instructions from the vendor.

Electron microscopy (EM) was performed on material retrieved from paraffin embedded material and demonstrated cytoplasmic processes containing dense arrays of glial-type intermediate filaments. These features are consistent with glial differentiation (Figure 3). Features of ependymal differentiation such as serpentine cell junctions, cytoplasmic microvilli, and perivascular elastin accumulations were not identified. No dense core (neurosecretory) granules were noted. The study was suboptimal due to the small size of the available sample and the artifacts due to formalin fixation and paraffin embedding.

A diagnosis of tanycytic ependymoma was made based on histological, immunohistochemical, and ultrastructural evidence.

DNA was isolated from the paraffin embedded material with or without prior microdissection and then amplified in 2 separate polymerase chain reaction and sequenced using separate pyrosequencing to determine the presence or absence of mutations in codon 132 of the isocitrate dehydrogenase gene (IDH) 1 and codon 172 of the IDH2 gene. No mutation was detected.

Discussion

TE, a rare variant of ependymoma was first described by Friede and Pollak [3] in 1978. It was recognized as a new pathological entity in the year 2000 World Health Organization (WHO) classification of brain tumors [5]. These tumors are WHO grade II tumors with a relatively better prognosis than other grade 2 ependymomas [6, 7].

TE is the most uncommon variant of ependymal tumor and usually arises in the spinal cord. Only 9 ventricular and 5 subcortical TE have been reported in the English literature. Amongst the ventricular cases, 4 of them arose in the lateral ventricle, 3 of them arose in the fourth ventricle, 1 involved the foramen of Monro and 1 involved both lateral and third ventricle. Our case would be the second case that involves the third ventricle. With the current case included, the age of patients ranged from 3.5 to 75 years of age with a mean age of 37.5. Seven of the 10 cases occurred between the ages of 34 to 55 years. Overall, we noted a male predominance with male to female ratio of 7 to 3 (Table 1). The immediate and short term prognosis of these tumors seems to be excellent but data for long term follow up are lacking (Table 1). Lieberman et al [8] reported a “tanycytoma” arising from the ventricle. However, that tumor has features of a pilomyxoid astrocytoma as per their description and is therefore not includ-
### Table 1. Reported cases of ventricular tanycytic ependymomas in the English literature

<table>
<thead>
<tr>
<th>Author &amp; year</th>
<th>Age (year)/Sex/Location/Imaging/Outcome</th>
<th>EM/IHC/Ki-67*/Mol. Path.</th>
</tr>
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<tbody>
<tr>
<td><strong>Current case</strong></td>
<td>General: 44/Female/3rd ventricle. Imaging: Well-circumscribed non-enhancing solid mass, 1.8 × 1.7 × 1.6 cm. Isointense on T1-weighted images and hyperintense on T2-weighted images. No significant edema around tumor on FLAIR. Outcome: No recurrence at 1 year.</td>
<td>EM: Demonstrated features of glial differentiation but no demonstrable evidence of ependymal differentiation, no dense core granules identified. IHC: GFAP-diffuse positivity, EMA-diffuse positivity, Synaptophysin-weak positivity, Neurofilament-negative. Ki-67-1**: &lt; 1%. Mol. Path: No mutation of IDH1 or 2 genes.</td>
</tr>
<tr>
<td>Zhang et al., 2008 [12]</td>
<td>General: 38/Male/Anterior horn of lateral ventricle. Imaging: well-defined 3.5 × 2.3 × 2.4 cm solid-cystic mass. Hypointense on T1-weighted images and heterogeneous on T2-weighted images. Outcome: Patient was further treated with radiation therapy and remained stable after 8 months.</td>
<td>EM: Not reported. IHC: GFAP-positive, S-100-positive, vimentin and nestin-strongly positive, EMA-dot like positivity, Synaptophysin and NeuN***-negative Ki-67: &lt; 0.5%. Mol. Path: Not reported.</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Reference</th>
<th>General</th>
<th>Imaging</th>
<th>IHC</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Du et al., 2009 [2]</td>
<td>36/Male/Lateral ventricle.</td>
<td>4.0 cm round, well-defined mass, hypointense on T1-weighted images and hypertense on T2-weighted images.</td>
<td>GFAP-strongly positive, EMA-positive, S-100-negative, Synaptophysin-negative, CD34-negative, Pan-cytokeratin-negative.</td>
<td>Patient was able to leave the hospital after two weeks.</td>
</tr>
<tr>
<td>Daneyemez et al., 1999 [16]</td>
<td>42/Male/Lateral ventricle-temporal horn.</td>
<td>Cystic space occupying lesion. Size and other radiological properties were not reported.</td>
<td>Not reported.</td>
<td>Not reported.</td>
</tr>
<tr>
<td>Arvanitis et al., 2013 [11]</td>
<td>40/Male/Lateral ventricle-anterior horn.</td>
<td>2.5 × 2.2 × 1.6 cm heterogeneously enhancing mass with cystic and calcific components. Properties on T1- or T2-weighted images were not reported.</td>
<td>GFAP-positive, S-100-positive, EMA-negative.</td>
<td>Not reported.</td>
</tr>
</tbody>
</table>

ed in this study. Interestingly, this tumor is negative for EMA, a marker that is typically expressed in tumors with ependymoma family.

In addition to the current case, the size of the tumors was available in the 3 cases arising from the lateral ventricle and the case that involved the lateral and third ventricle. The greatest dimension of tumor ranges from 1.8 to 4.0 cm with the current case being the smallest (Table 1). One likely reason for the tumor’s small size at presentation could be due to its presence in a strategic location, thereby leading to hydrocephalus related manifestations.

Imaging studies were performed in all but the three TEs arising in the fourth ventricles. All of these tumors appeared as a solitary, round to oval well-defined mass. Cystic change was noted in three and calcification in one of the reported cases. These tumors are hypointense or isointense on T1-weighted images with minimal or no enhancement. T2-weighted images range from heterogeneous to hyperintense. Similar to the current case, peritumoral edema as judged by T2-weighted or FLAIR images is minimal or none (Table 1).

The cell of origin for these neoplasms is believed to be the primitive progenitor cells known as the ependymoglial cells, also called “tanycytic” glia or tanycyte [3, 4]. Tanycytes are elongated bipolar cells that are primarily present in the circumventricular organs with predominance in the ventral portion of third ventricle and around the central canal in the spinal cord [9]. Their close association with both cerebrospinal fluid (CSF) and blood vessels suggest their functional role in transport and exchange of substances between CSF and either blood or neuropil [5, 10].

The histopathology among different reported tumors is similar. TEs exhibit low to moderate cellularity. While the distribution of nuclei can be homogeneous, TEs may contain nuclear dense zones and hypocellular fibrillary zones. The nuclear dense zones are composed of elongated spindle cells that are often confused with the piloid cells of pilocytic astrocytoma. These tumors generally lack true ependymal rosettes but may show few ill-defined perivascular rosettes. Kawano et al [6] described two types, one with no ependymal rosettes and inconspicuous perivascular rosettes referred to as the “pure type” and the other that contains true rosettes and perivascular rosettes partially in the tumor, known as the “mixed type”. The present case demonstrated “pure type” histology with bland looking spindle shaped neoplastic cells without evidence of perivascular or true rosettes. Mitotic figures, high grade pleomorphism, and necrosis were absent.

In the 5 reported cases (including our case), that include information on immunohistochemical profile, strong immunoreactivity for GFAP was demonstrated. These tumors were positive for $100 in 2 out of the 3 reported cases. Interestingly, immunoreactivity for synaptophysin was demonstrated in 1 out of the 3 cases, including the current case, when immunohistochemistry for synaptophysin was included. Immunohistochemistry for EMA is positive in 2 out of the 3 cases, including the current case, when it was performed. Ki67 labeling was reported in one of the reported case and was low. The labeling index in the current case is also low and is 1%.

Electron microscopy was reported in 5 publications of TEs with one of them arising from the ventricle [11]. Ultrastructural features of ependymal differentiation were demonstrated [4, 6, 10, 11]. Interestingly, the case reported by Arvanitis et al [11] was negative for EMA. Although Friede et al [3] provided an exhaustive study on the ultrastructural features of ependymoma and were the first to coin the term “tanycytic variant” of ependymoma, ultrastructural studies specifically on the 11 cases that they classify as tanycytic variant was not included in their original article. Langford and Barré [4] however, have provided a detailed study on the ultrastructural features of spinal TEs. These tumors showed characteristic ependymal features, including intracytoplasmic intermediate filaments, prominent intercellular junctions, numerous slender surface microvilli, and microvilli-lined lumina. Electron microscopy was also performed in the current case. While ultrastructural evidence for glial differentiation was present, no ultrastructural evidence for ependymal differentiation was noted. In contrast, the current case is diffusely positive for EMA which supports its ependymal differentiation. The failure to demonstrate ultrastructural evidence of ependymal differentiation in the current case might have resulted from suboptimal technical quality due to the necessity of retrieving sam-
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samples from formalin fixed paraffin embedded samples. Mutation analysis for IDH1 and 2 genes was performed only in the current case and, as anticipated, no mutation was demonstrated.

In summary, cerebral TE are most common in adults in the 4th to 6th decade with a male predominance. They are exclusively supratentorial and more common in ventricles. They are typically small tumors that are under 4 cm in greatest dimension, usually solid but may contain cystic component and calcification. Imaging features include hypointense to isointense on T1-weighted images, non-enhancing to heterogeneously enhancing, and with little if any peritumoral edema on T2-weighted or FLAIR images.

Tanycytic ependymomas pose a diagnostic dilemma especially when the tissue submitted for histopathological examination is small. It must be differentiated from other spindle cell neoplasms such as pilocytic astrocytoma, fibrillary astrocytoma and schwannoma [2, 9, 12]. The diagnosis of Tanyctic ependymoma and its differential diagnosis from other spindle cell neoplasms are primarily based on histological features of tanycytic tumor cells and immunohistochemical features.

Pilocytic astrocytomas may be confused with tanycytic ependymomas but the former usually demonstrate a more variable histology within the same tumor and often contains Rosenthal fibers and eosinophilic granular bodies. Astrocytomas with fibrillary morphology often show microcysts and mucinous degeneration that are not seen in TE. Positive immunoreactivity for EMA can be demonstrated in TE but not in pilocytic astrocytoma or astrocytoma with fibrillary morphology. Electron microscopy helps in this differential diagnosis with tanycytes showing microvilli, cilia, cell junctions, intracytoplasmic filaments and absence of basal lamina [9, 11, 12]. Tumor cells of pilocytic astrocytoma, fibrillary astrocytoma and schwannoma are surrounded by basal lamina [11].

Diffuse astrocytomas typically lack immunoreactivity for EMA and ultrastructural features of ependymal differentiation. These tumors are often, but not always, positive for mutations of IDH1 and IDH2. Our case report is the first one to include the pyrosequencing results demonstrating absence of IDH1 and IDH2 mutations in tanycytic ependymoma tumor sample. It should also be noted that mutations of IDH1 and IDH2 are typically absent in ependymal tumors [13].

Schwannoma is differentiated from TE on the basis of light microscopy and immunohistochemistry. Intraventricular tumor is an extremely uncommon site for schwannoma. TE is a compact mass of elongated cells without loose areas (Antoni B areas) and Verocay bodies, as are seen in Schwannoma. In addition, tanyctic TE cells are more uniform and their nuclei more oval compared with those of schwannoma cells [9]. While TEs are positive for EMA and GFAP, schwannomas are negative for these markers.

Tanycytic ependymomas are treated by complete resection followed by radiological surveillance [12, 14]. These tumors have a low MIB-1 labeling index and p53 expression [7] as compared to other subtypes of ependymomas, suggestive of a favorable prognosis. Accurate recognition of tanyctic variant of ependymoma requires a high index of suspicion and use of ancillary studies to differentiate these neoplasms from other spindle cell mimickers.

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Disclosure of conflict of interest

None.

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References


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