Rare Variants of Ependymoma: A Report of Four Cases and a Review of the Literature

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CASE SERIES

Introduction
Ependymomas are brain tumors with a wide spectrum of morphological patterns. The importance of morphological diagnosis cannot be overemphasized, even in the molecular era. Molecular interpretation is heavily dependent on the morphological diagnosis and misinterpretation of the latter will affect the former. Although new molecular classification of ependymal tumors proved to be a better predictor of prognosis, morphological recognition of these rare variants as ependymoma is essential to guide subsequent molecular tests.

The World Health Organization (WHO) classification of ependymoma focuses on a few variants (i.e., cellular, papillary, clear cell, and tanycytic ependymoma), while only listing other, rare variants. The updated 2016
WHO classification of CNS tumors, focusing on the integrated pathological and molecular subgrouping for better understanding of the biological behavior of ependymomas, adopted the RELA fusion-associated group as a distinct entity of ependymoma\(^\text{[3]}\). Molecular testing essential for this new classification was not available. However, the main aim of this study is morphological recognition of these rare variants. The current report presents 4 unusual cases that expand the current state of knowledge regarding rare variants of ependymoma, illustrate the combination of different patterns in the same ependymoma tumor, and highlight the unusual locations of rare variants with peculiar architectures.

**Materials and Methods**

Prior to the study, approval was obtained from the Research Committee of the Biomedical Ethics Unit of the Faculty of Medicine of King Abdulaziz University (Jeddah, Saudi Arabia). I searched the archive of the pathology department for any cases with a pathological diagnosis of ependymoma during the period 2006-2016. I excluded common cases, and only selected those with unusual or rare morphological or radiological features. Four cases of surgically resected glial tumors with ependymal differentiation were reviewed. The clinical data (sex, age at onset, and surgical intervention), imaging study findings, and pathological findings of these cases were retrospectively reviewed. All included patients were followed up until May 2016.

Tissue sections were cut to a thickness of 4 μm and stained using standard procedures. The sections were routinely treated with the hematoxylin and eosin (H&E) stain. Automated immunohistochemistry (IHC) was carried out on paraffin sections using the Ventana Autostainer (Benchmark XT, Ventana Medical Systems, Inc.; Oro Valley, AZ, USA) and visualized with the ultraView Universal Diaminobenzidine (DAB) Detection Kit (Ventana Medical Systems, Inc., AZ, USA). The following primary antibodies were included: glial fibrillary acidic protein (GFAP; EP672Y; Cell Marque, Rocklin, CA, USA), R132 IDH1 (Dianova, Hamburg, Germany; H09 clone, monoclonal, predilute), epithelial membrane antigen (EMA; E28, Ventana Medical Systems Inc.; predilute), CD99 (O13; Ventana Medical Systems, Inc.; predilute), synaptophysin (SYN; SP11; Ventana Medical Systems, Inc.; predilute), neurofilament protein (2F11; Cell Marque; predilute), S100 (4C4.9; Ventana Medical Systems, Inc.; predilute), Ki-67 (30-9; Ventana Medical Systems, Inc.; prediluted), p53 (DO-7; Ventana Medical Systems, Inc.; predilute).

**Results**

Twenty-two cases of ependymoma were found in our archive and reviewed. The pathological features in four cases had previously unreported combinations of patterns that were observed in individual tumors, rare locations and architectures or rare patterns. The clinical characteristics and radiological findings of the 4 cases are summarized briefly in Table 1. The following sections of this report will concentrate on the pathological features of the cases.

| Case | Age/Sex | Symptoms | Imaging | Management | Follow-up |
|------|---------|----------|---------|------------|-----------|
| 1    | 7 yr/F  | Seizure and vomiting for 5 months. Two previous resections (at ages 4 and 5.5 yr) at the same side, performed in a different country with no available data | MRI: Right frontal, well circumscribed, solid and cystic with enhancement of the cyst wall | GTR | No recurrence, 3 months |
| 2    | 18 months/M | Seizure for 7 months with no relevant prenatal, intranatal, or postnatal history | CT: Large interhemispheric solid mass with scattered cystic changes (Fig. 2a) and postcontrast enhancement | GTR | No recurrence, 12 months |
| 3    | 19 yr/F | Left-sided weakness, headache, and vomiting for 1 day | MRI: Right frontal, well circumscribed, solid and cystic with variable enhancement. | STR and radiotherapy | Recurred after 4 months, followed by another STR and no subsequent recurrence for 2 months (to date) |
| 4    | 5 yr/M | Headache and vomiting for 3 months | MRI: Right frontal, solid, not well circumscribed with heterogeneous enhancement | GTR | Multiple intracranial metastasis, 2 years |

CT: Computed tomography; GTR: gross total resection; MRI: magnetic resonance imaging; STR: sub-total resection.

Table 1. Clinical history and imaging characteristics of the 4 reported cases.
Case 1

The investigated specimen was the result of the third resection (in 3 years) of the tumor from the same site, most likely representing residual tumor from a previous, incomplete resection. The previous resections were performed in another country, and little information was available regarding the surgical intervention.

The histological features of this neoplasm showed heterogeneous areas of glial neoplasm with different forms of ependymal differentiation, including subependymoma, classic ependymoma, and astroblastoma, along with scattered dysplastic neurons. The tumor was well demarcated from the adjacent brain and was arranged in solid sheets and infiltrative nodules (Fig. 1a). The nodules could be separated into 2 types depending on the glial cells in the background, but both types were associated with multiple microcysts. The glial cells in the first type of nodule were characterized by eccentric nuclei and glassy cytoplasm resembling gemistocytes (Fig. 1b). In contrast, the glial cells in the second type of nodule and most solid areas formed variable cellular clusters of bland-looking, oval nuclei with dense fibrillary background (Fig. 1c). The focal areas of low cellularity with dense fibrillary and microcystic background appeared very similar to subependymoma. GFAP immunostain highlighted the differences between the glial cells in these 2 nodule types, with dense cytoplasmic staining in the first type and fibrillary staining in the second type (Fig. 1d). There were focal areas of classic ependymoma with perivascular pseudorosette formation (Fig. 1e). Further, there were other areas with neoplastic glial cells that formed non-tapering cytoplasmic processes radiating around blood vessels, which is characteristic of astroblastoma (Fig. 1f). CD99 immunostain showed background staining in areas with the fibrillary background, as well as characteristic dot-like cytoplasmic staining in the neoplastic cells, confirming the ependymal differentiation in the neoplastic cells (Fig. 1g). In contrast, EMA immunostaining was negative.

The other interesting components in this neoplasm were the scattered, haphazard arrangement of dysplastic neurons with large eosinophilic cytoplasm and the peripheral distribution of Nissl substances (Fig. 1h). The dysplastic neurons were more numerous in the solid areas, while only a few were located inside the nodules. These neurons showed cytoplasmic reactivity for phosphorylated neurofilament and synaptophysin immunostain (Fig. 1i). Other features of ganglioglioma-like eosinophilic granular bodies and significant perivascular lymphocytes were not identified. There was no significant mitosis, no necrosis, and no endothelial proliferation. The Ki-67 proliferative index was approximately 3-5%. IDH1, CD34, and P53 immunostaining were negative. Molecular testing for BRAF V600E mutation was not available.

In this case, the differential diagnoses were glioma with a different type of ependymal differentiation and dysplastic neurons (WHO grade II) and ganglioglioma with the glial part represented by a different type of ependymal differentiation (WHO grade I). This differential is described in greater detail in the Discussion section.

Case 2

The interesting aspect of this tumor was the extra-axial location, which was observed on computed tomography scanning (Fig. 2a) and raised differential diagnoses of meningioma and metastasis. Histopathological examination of the tumor showed clear demarcation of the tumor from the cortical ribbon, which confirmed the extra-axial location of the tumor (Fig. 2b). The tumor was arranged in solid sheets, lobules, and papillary projections (Fig. 2c, 2d). Perivascular arrangement was prominent, with glial processes radiating toward the central blood vessels (Fig. 2e). There was no hyalinization of the blood vessels. The neoplastic cells were round to oval with fine granular chromatin. There was a small focus of necrosis with no peripheral palisading, no endothelial proliferation, and only a few mitoses. The Ki-67 proliferative index range from 5 to 10%. Immunostaining with GFAP showed diffuse strong immunopositivity in the tumor cells, while EMA showed only focal dot-like staining in the cytoplasm (Fig. 2f). The histological diagnosis was ependymoma with papillary and lobular configuration (WHO grade II/III).

Case 3

Histological examination showed sheets of monotonous round neoplastic cells with numerous giant cells arranged in solid sheets that were separated into small nests by branching blood vessels. There were small rims of nuclear-free zones around these blood vessels, but none of the conspicuous perivascular pseudorosette formation that is typical of classical ependymoma (Fig. 3a). The neoplastic cells had infiltrated the adjacent cortex in small tight clusters. The small round...
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Figure 1. Ependymoma with dysplastic neurons/ganglion cells. (a) Multiple, well-demarcated nodules of the neoplasm infiltrate through the brain (hematoxylin and eosin [H&E]; original magnification: 40x). The brain parenchyma is highlighted by synaptophysin immunostain, which is similar to the staining pattern of phosphorylated neurofilament immunostain (inset: synaptophysin; original magnification: 40x). There are 2 types of nodules, both of which are formed by glial cells and microcysts: (b) The first type contains glial cells with eccentric nuclei and glassy cytoplasm resembling gemistocytes (H&E, original magnification: 400x); (c) The second type of nodules show fibrillary background and clusters of bland-looking oval nuclei in a distribution that is similar to the architecture of the subependymoma (H&E, original magnification: 400x). (d) Solid sheets of fibrillary areas are interrupted by well-demarcated small nodules of the first type (glial fibrillary acidic protein [GFAP] immunostain; original magnification: 200x) (inset: GFAP; original magnification: 400x). (e) Focal areas show classic ependymoma with perivascular pseudorosettes formation (H&E, original magnification: 200x); (f) Focal areas show astroblastic differentiation with neoplastic cells that form thick non-tapering processes around blood vessels (H&E, original magnification: 200x). (g) CD99 shows background staining in areas with the fibrillary background, as well as characteristic dot-like cytoplasmic staining in the neoplastic cells (CD99; original magnification: 400x); (h) Dysplastic neurons are numerous. Most of the dysplastic neurons are outside of the nodules and are associated with the areas with fibrillary background (H&E; original magnification: 400x); (i) Dysplastic neurons show cytoplasmic reactivity for phosphorylated neurofilament as well as greater reactivity with synaptophysin immunostain (SMI31; original magnification: 400x) (inset: SMI31; original magnification: 400x).
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Figure 2. (a) A post-contrast computed tomography (CT) scan shows a large, interhemispheric, extra-axial, lobulated, solid-enhancing mass with few cysts; (b) There is clear demarcation of the tumor from the cortex (hematoxylin and eosin [H&E]; original magnification: 20x); (c) Multilobular architecture of the ependymoma (H&E; original magnification: 40x); (d) Papillary configuration of the ependymoma (H&E; original magnification: 40x); (e) Perivascular arrangement of the tumor cells with glial processes radiating toward the blood vessels (H&E; original magnification 100x) (inset: H&E; original magnification: 400x); (f) Tumor cells show strong glial fibrillary acidic protein immunostaining (GFAP; original magnification 200x) and dot-like immunoreactivity for epithelial membrane antigen (inset: EMA; original magnification: 400x).
neoplastic cells showed perinuclear clearing and were evenly distributed, creating an overall impression of oligodendroglioma (Fig. 3b). Giant cells were numerous and present in most of the tumor. Their chromatin was similar to the smaller cells, but they had irregular nuclear membranes and inconspicuous nucleoli (Fig. 3c). EMA immunostain highlighted the characteristic, dot-like cytoplasmic staining of ependymoma in many of the neoplastic cells, including the giant cells (Fig. 3d). GFAP was immunopositive in approximately 50% of the neoplastic cells, including the giant cells, and showed perinuclear and/or short process staining (Fig. 3e). Endothelial proliferation was present, but necrosis was absent. The mitotic index was 15/10 high-power fields. The Ki-67 proliferative index was approximately 35% focally, and Ki-67 staining was observed in some of the giant cells. IDH1 and synaptophysin immunostaining were negative.

The tumor recurred at the same location 3 months after the subtotal resection. The diagnosis was anaplastic clear cell ependymoma with giant cells (WHO grade III). The morphological features of the newly resected specimen were similar to those of the previous sample.

Case 4
This neoplasm showed characteristic morphological features of ependymoma when under low-power examination, including being well demarcated from the adjacent white matter and perivascular nuclear-free areas (Fig. 4a), as well as showing focal clear cell changes (Fig. 4b). Significant mitoses and focal endothelial proliferation were present, but necrosis was absent, which is consistent with WHO grade III anaplastic ependymoma.
The interesting feature of this neoplasm was the arrangement of the tumor cells into small tight clusters. These clusters were formed by epithelioid ependymal cells with central fused cytoplasmic processes, but no central lumen. The arrangements of these epithelioid cells resembled giant cells, which is considered characteristic of epithelioid ependymoma (H&E, original magnification: 400x) (inset: H&E; original magnification: 400x). Epithelial membrane antigen (EMA) immunostaining of these giant/epithelioid cells shows intense staining in the inner portion of the cytoplasm (EMA, original magnification: 400x) (inset: EMA; original magnification: 400x). Glial fibrillary acidic protein (GFAP) immunostaining highlights the background and a few reactive astrocytes between the neoplastic cells, but most of the neoplastic cells are immunonegative (GFAP, original magnification: 400x). S100 highlights only the reactive astrocytes, whereas the neoplastic cells and the background are immunonegative (inset: S100, original magnification: 200x).

Discussion

Ependymoma has many different morphological variants with widely different cell morphologies, such as tanycytic (elongated cells that resemble astrocytes), clear (resembling oligodendrocytes), epithelioid, lipomatous, pigmented, large pleomorphic, and other variants. The many possible morphological variants may lead observers to confuse cases of ependymoma with diffuse glioma. However, most of these variants characteristically feature tumors that are well circumscribed from the adjacent brain tissue, which excludes diffuse glioma and limits the differential diagnoses to a few glial tumors that have well-circumscribed borders (e.g., pilocytic astrocytoma and ganglioglioma). Other important diagnostic features...
of ependymoma are perivascular pseudorosettes formation, true ependymal rosettes, and the formation of ependymal canal-like structures. Perivascular pseudorosettes are the most common feature that is found in ependymoma, and are formed by the tapering of the cytoplasmic process toward blood vessels.

Most ependymoma are immunopositive for GFAP, which highlights the perivascular accentuation in pseudorosettes. However, clear cell variants have shown variable staining in the few cases that have been reported. Although EMA and CD99 immunostaining are commonly applied in cases of ependymoma, their results should be interpreted with caution. CD99 is highly sensitive, but is not specific, while EMA has variable sensitivity and specificity, depending on the type of staining in the neoplastic cells. The sensitivity of EMA is much lower than that of CD99, and can be negative (as was observed in Case 1 of this study) or only focally positive (as was observed in Case 3 of this study). Cytoplasmic dot- and ring-like EMA stainings correspond to microrosettes ultrastructurally. Dot-like staining can be seen in glioblastoma, while ring-like staining is considered specific to ependymoma.

The first case in this report was very complicated and addresses 3 topics that are important to ependymoma: the presence of mixed types of ependymal differentiation in the same tumor, the presence of neuritic differentiation in ependymoma, and the relationship of the ependymoma with the adjacent brain tissue. The different types of ependymal differentiation in Case 1 included subependymoma, classic ependymoma, and astroblastoma. The mixture of subependymoma and ependymoma has been reported previously and the WHO grade was assigned to the higher component. However, to the best of my knowledge, astroblastoma has not been reported previously with this mixture. Lehman included all of these tumors under the umbrella of tumors of primarily ependymal differentiation. The combination of types in this case supports a common origin from precursor cells (i.e., radial glia) with different morphologies that represent the different stages of ependymal cell development.

Neuronal differentiation in ependymoma has been documented in 3 forms. The most common form is based on IHC staining (and not on morphological features), especially including neurofilament light polypeptide and, less commonly, other forms of IHC such as NeuN. This type of neuronal differentiation has been associated with a supratentorial location and better prognosis (i.e., longer progression-free survival). The second type of neuronal differentiation is based on the presence of morphological neuronal differentiation in the form of neuropil-like islands. Together, these 2 types have been regarded as ependymoma with neuronal differentiation. The third type, is based on the presence of dysplastic neurons, as were found in Case 1 of this report. This form of ependymal differentiation has been regarded as ganglioglioma with the ependymal differentiation represented in the glial component of the tumor, rather than ependymoma with neuronal differentiation. Another possible interpretation for this mixture is ependymoma with dysplastic neurons. The latter possibility is favored in the first case because the predominant component was represented by glioma with ependymal differentiation, and because the dysplastic neurons were only scattered in the tumor. The lack of eosinophilic granular bodies despite extensive sampling in the current case—and in contrast with previously reported cases—is also contrary to ganglioglioma. BRAF V600E mutation, which can be positive in ganglioglioma, was not analyzed in the first case. Although this issue is difficult to solve, it should not affect the diagnosis in the current case. As in general, the grade and the behavior of ganglioglioma is based on the glioma component (in this case of ependymoma, WHO grade II), and it is therefore better to consider the case as being ependymoma with dysplastic neurons. The behavior of this tumor (2 recurrences in 3 years) is also more compatible with ependymoma than with WHO grade I ganglioglioma.

The third important feature of Case 1 was the presence of multinodular growth with well-circumscribed infiltrative nodules. Although ependymomas are usually well circumscribed brain tumors, different types of infiltration have been described and are compatible with the diagnosis of ependymoma. Similar multinodular growth has been described in a new entity of neuronal tumor, but is not associated with the features of ependymoma. To the best of my knowledge, no similar case in the previous literature has included these features. In conclusion, Case 1 is best regarded as ependymoma with dysplastic neurons (WHO grade II).

The second case addresses important concepts regarding the location of ependymoma.

Ependymoma usually occurs near the ventricular system and in the spinal cord; however it has...
been described in all locations in the neuro-axis\textsuperscript{[2]}. Supratentorial ependymoma has been described outside the ventricular system and, in rare cases, can be entirely centered within the cerebral cortex (i.e., cortical ependymoma)\textsuperscript{[16]}. Pathological assessment of cortical ependymoma has revealed a close resemblance to another low-grade glioma (i.e., angiocentric glioma). Although these diseases show distinct histopathological features, they share a relatively favorable outcome and behave like WHO grade I tumors\textsuperscript{[19,20]}. Intracranial extra-axial ependymoma (IEAE) is a rare tumor with only 16 previously reported cases in the literature\textsuperscript{[19,20]}, and only 2 cases reported in children\textsuperscript{[19]}.

The second case represents the youngest affected patient. The age of onset of previous cases has ranged from 10 to 81 years, with a mean of 38.4 years (12 cases in men and 4 in women)\textsuperscript{[19,20]}. The clinical presentations mainly depended on the location of the tumor (8 supratentorial and 8 infratentorial); however, headache and vomiting were the most common presenting features. Other features have included hemiparesis, facial pain, seizure, and visual field defect\textsuperscript{[19,20]}. As IEAE is a rare neoplasm, it was not included in the radiological differential diagnosis of our case or the previously reported cases. In most cases, the radiological differential diagnosis depends on the tumor location. For supratentorial tumors, the radiological differential diagnosis has mainly been meningioma, and has included schwannoma in cases of cerebellopontine angle tumors.

Histological examination of Case 2 was diagnostic of ependymoma, but included unusual histological features. A predominant lobular architecture and papillary projections were present, consistent with the papillary variant of ependymoma. Because previous studies have focused on the unusual location of the tumor, the tumor histopathology has only been described briefly in some cases. Other reports with more detailed pathological descriptions have noted the presence of papillary architecture in 4 cases of ependymoma\textsuperscript{[22,23]} and the presence of lobular architecture in no cases of ependymoma. Most cases were of WHO grade II, and only 1 case was diagnosed as WHO grade III ependymoma\textsuperscript{[22]}. Because papillary ependymoma is a rare variant of ependymoma\textsuperscript{[22]}, the relatively high frequency of this variant in IEAE (5/17 cases) indicates a morphological correlation with the location in ependymoma.

The prognosis of ependymoma is especially dependent on the location of the tumor, extent of resection, and age of the patient\textsuperscript{[22]}. The locations of these tumors make them more accessible to total resection and hence provide a better prognosis. This is similar to cortical ependymoma, which has been suggested to behave more like a WHO grade I tumor\textsuperscript{[18]}. Follow-up data were available in 8/16 reported cases, with no recurrence in 7 cases (range of follow up, 6 months to 2.5 years). In the remaining case that was followed up, recurrence developed after 4 months, even though the tumor was completely resected and the pathology showed WHO grade II ependymoma\textsuperscript{[19]}. In resemblance with cortical ependymoma, IEAE arises in areas where normal ependymal cells are absent. This supports the theory that the origin of these tumors is progenitor glial cells that differentiate toward ependymal cells. However, other proposed hypotheses cannot be excluded, such as the development of these tumors from heterotopic ependymal cell rests during fetal development\textsuperscript{[19]}.

Case 3 included a combination of 2 rare variants of ependymoma that, to the best of my knowledge, has not been reported previously: clear cell and giant cell ependymoma. Giant cell ependymoma is rare variant of ependymoma, with only 21 cases reported in the literature\textsuperscript{[26]}. It may occur anywhere in the central nervous system, but has a predilection to the spinal cord, and can be of both WHO grade II and III\textsuperscript{[26]}. Giant cell ependymoma is characterized by marked pleomorphic and bizarre nuclei, representing degenerative atypia. Clear cell ependymoma with clear perinuclear halo, round nuclei, and focal positivity for GFAP mimics oligodendroglioma and is easily misdiagnosed as such if clear cell ependymoma is not included in the differential diagnosis. Because the differential diagnosis for clear cell ependymoma is oligodendroglioma, the presence of pleomorphic giant cells can be misinterpreted as polymorphous oligodendroglioma of Zülch\textsuperscript{[27]}. However, the fact that the tumor was well demarcated from the adjacent brain and the presence of EMA immunopositivity were diagnostic for ependymoma, rather than oligodendroglioma.

The last case was a rare variant of ependymoma: epithelioid ependymoma. The tumor was characterized by the presence of tight clusters of epithelioid cells that coalesced to form multinucleated giant cells with no central lumen\textsuperscript{[24]}. The few previously reported cases
have been associated with diffuse myxoid background, have lacked perivascular pseudorosette formation, and have shown variable GFAP staining. The current case had diffuse fibrillary background with no mucinous changes, and was diffusely immunopositive for GFAP. Although the processes of the neoplastic cells did not form typical perivascular pseudorosettes, the arrangement of the clustered epithelioid cells left nuclear-free zones around the blood vessels, thereby giving the impression of perivascular pseudorosette formation.

In conclusion, the 4 cases that have been described in this report expand the current state of knowledge regarding rare variants of ependymoma and the combinations of different patterns that can be found in the same tumor. Further, the reported cases highlight the unusual locations that are possible for this neoplasm.

Conflict of Interest
The author has no conflict of interest.

Disclosure
The author did not receive any type of commercial support either in forms of compensation or financial for this study. The author has no financial interest in any of the products or devices, or drugs mentioned in this article.

Ethical Approval
Obtained.

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أعمال مجازية نادرة لورم البطانة العصبية

مراد عبدالكريم التركستاني
قسم علم الأمراض، كلية الطب، جامعة الملك عبد العزيز
جدة - المملكة العربية السعودية

المستخلص. ورم البطانة العصبية يمثل نوع من أنواع أورام الدماغ ولديه مجموعة واسعة من الأنماط المجهرية والتي تتشابه مع أورام الدماغ الأخرى مما من الممكن أن يؤدي إلى التشخيص الخاطئ. في هذا البحث تم دراسة الشكل المجهرى لجميع أورام البطانة العصبية للدماغ في أرشيف قسم علم الأمراض في مستشفى جامعة الملك عبد العزيز في الفترة 2002-2016. تم التوصيل لأربعة أنماط مجهرية نادرة لهذا الورم من أصل 23 حالة. في هذا المقال تم الشرح المجهري التفصيلي لهذه الحالات الأربع مما يساعد في إثراء المنشورات العلمية في الأنماط المجهرية النادرة لهذا الورم حيث أن بعضها لم يتم عرضه من قبل مما يسهل التعرف عليها.