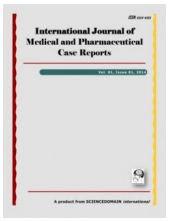

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Papillary Glioneuronal Tumor: A Case Report and a Brief Review

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Authors' contributions

This work was carried out in collaboration between all authors. Authors AHJ and SBN wrote the draft of the manuscript and managed the literature searches. Author NMR designed the figures, managed literature searches and contributed to the correction of the draft. Author AAO provided the case and supervised the work. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Aims: Papillary glioneuronal Tumor (PGNT) is a rare, recently recognized glioneuronal tumor. To date only about 68 cases of PGNT have been reported. Although it has been regarded as a grade 1 neuronal – glial tumor by World Health Organization, aggressive cases have been reported and so, they can be challenging to diagnose and to treat as their relatively unclear clinical course. In this article, we summarize the clinical and pathological findings of this new entity.
Presentation of Case: The patient was a 23-year-old man with headaches and right hemiparesis who had a tumor arising in close proximity of the anterior horn of the left lateral ventricle. No mitotic activity was identified, confirmed by Ki-67 labeling of about 1%. There was no evidence of recurrence during 64 month follow-up. A brief review of the other reported cases also has been included.
Discussion and Conclusion: Although PGNT has been regarded as a grade 1 tumor, aggressive

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cases have been reported and their behavior has not been related to histological grading. So, all cases need to be reported to make further knowledge about its biological behavior.

Keywords: Papillary glioneuronal tumor; brain tumor; central nervous system; hemiparesis.

ABBREVIATIONS

PGNT: Papillary Glioneuronal Tumor.

1. INTRODUCTION

Papillary glioneuronal tumor (PGNT) is a rare brain tumor that shows mixed neuronal and glial differentiation, firstly reported by Komori et al. [1]. In 2007, the World Health Organization (WHO) classified this lesion as a grade 1 neuronal-glial tumor because of its biphasic neurocytic and glial components and indolent clinical course [2]. According to our data, to date only about 68 cases of PGNT have been reported in world literature; thus these tumors are relatively infrequent lesions, and so, they can be challenging to diagnose for the practicing pathologist and to treat for the clinician as they have relatively unclear clinical courses. In this article, we summarize the clinical and pathological findings of this new entity.

2. PRESENTATION OF CASE

The patient was a 23 year old man who presented with intermittent headaches and right hemiparesis of upper and lower extremities during the 10 days before admission. He had no noticeable past medical history. Magnetic resonance imaging (MRI) showed a thick wall cystic lesion with a mural nodule in close proximity of the anterior horn of the left lateral ventricle (Fig. 1). There was mild peri-tumoral edema. Based on imaging, tumors like glioblastoma multiform, ganglioglioma and pleomorphic xanthoastrocytoma were considered but no stereotactic biopsy was taken before the main operation. The patient subsequently underwent an uneventful left frontoparietal craniotomy, with total resection of the tumor nodule and cystic wall. The resected mass was about 2.5 × 2 × 1 cm^3 in dimension.

The patient's symptoms were improved, post operatively. Pathological study of the removed tumor showed pseudopapillary structures which were composed of hyalinized blood vessels lined, predominantly, by a single layer of ovoid to cuboidal cells with small nuclei. At the first look, tumors with papillary architecture such as ependymoma, choroid plexus papilloma, astroblastoma, papillary meningioma as well as PGNT were included in the differential diagnosis list. Closer examination revealed populations of small and relatively uniform round cells possessed round nuclei with a prominent nucleolus and fine granular cytoplasm, mimicking neurocytes, occupying the intervening regions between the pseudopapillae (Fig. 2). This feature is not familiar to any of the differential diagnosis list except for PGNT. Furthermore, the tumor did not show rosette or pseudorosette structures, epithelial features or foci with meningothelial appearance which are diagnostic clues toward ependymoma, choroid plexus papilloma and papillary meningioma, respectively. There was no mitotic activity, confirmed by Ki-67 labeling of about 1%. Immunohistochemically, the cuboidal cells around the vascular cores were positive for GFAP and S-100 protein and negative for neuronal markers, revealing their astrocytic differentiation. Small neurocytic cells scattered in interpseudopapillary areas showed synaptophysin positivity (Fig. 3). Until the presentation of this article (64 months after the surgery) the patient is alive and well.

3. DISCUSSION

Three new entities have been added to the group of glioneuronal tumors in the most recent update of the WHO classification of tumors of the central nervous system. They are papillary glioneuronal tumor, rosetted glioneuronal tumor with neuropil-like islands, and rosette-forming glioneuronal tumor of the fourth ventricle [2]. In this classification PGNT has been regarded as a grade 1 tumor. PGNT firstly introduced by Komori T et al in 1998 as a new variant of a mixed glioneuronal tumor [1].

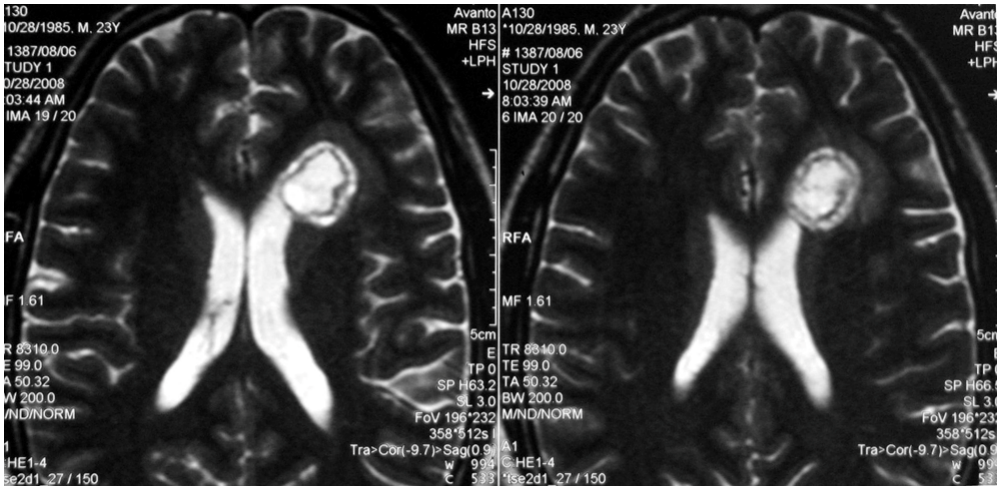

Fig. 1. Magnetic resonance imaging examination showed a thick wall cystic lesion with a mural nodule in close proximity of the anterior horn of the left lateral ventricle

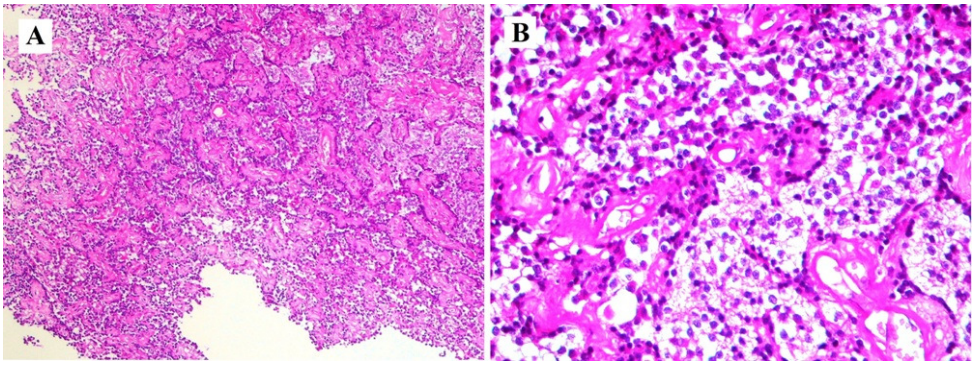

Fig. 2. A, Pseudopapillary architecture with hyalinized vascular cores surrounded by cellular interpapillary zones (hematoxylin-eosin, magnification✖100). B, the papillae are covered by 1–2 layers of glial cells. In The interpapillary zone there are neurocytomatous cells with uniform round nuclei, fine chromatin pattern, and perinuclear clearing (hematoxylin-eosin, magnification ✖400)

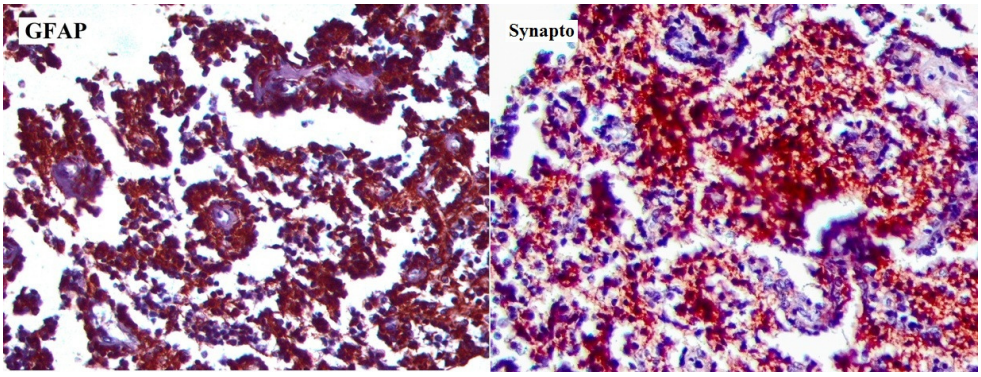

Fig. 3. The pseudopapillae formed by glial fibrillary acid protein positive cells and synaptophysin positive neuronal cells forming solid areas. GFAP = Glial Fibrillary Acid Protein, Synapto = Synaptophysin

To our knowledge, 68 cases of PGNT have been reported to date. Regarding the published articles by Xiao H et al and Myuang Jk et al. who reviewed 42 and 18 cases, respectively, by adding the data of 8 newer cases (which have not been included in that reviews) and our case, the following information has been yield (Table 1) [3-8]. The PGNT was occurring more commonly in young peoples and 76.8% of affected patients were under the age of 30 years, with the mean age of 24.7 years. It affected both men and women and there was no obvious sex predominance (M: F=1.16: 1). Headache and seizure were the most common presentations (occurred in 69% and 32% of patients, respectively), followed by nausea/vomiting, visual disturbances, and cognitive and memory difficulties (Table 1). There was a large variety of symptoms associated with tumor location.

There was an anatomical predilection to frontal lobes in cerebral hemispheres. The other frequent tumor locations were temporal and parietal lobes. However, they can be seen as intra ventricular or bilateral masses [3,4,7,8]. The tumors were usually presented as cysts with mural nodules or as mixed solid and cystic lesions. Even though, cases have been reported mimicking massive intraparenchymal brain hemorrhage and cavernoma on imaging [6,9]. Peritumoral edema was rare and calcification was seen, uncommonly.

Histologically, the papillary glioneuronal tumor consists of two distinctive components. The GFAP-positive glial component, which grows in a pseudopapillary pattern, composed of cuboidal cells covering hyalinized vessels. These pseudopapillae are separated by a diffuse proliferation of small to medium-sized, synaptophysin-positive neuronal cells, in a sheet-like fashion [2,3,4]. As what we observed in our patient, the PGNT displays moderate cellularity and is typically devoid of necrosis, microvascular proliferation, and mitoses (evidenced by low MIB-1 labeling). However, changes indicative of anaplasia including necrosis, capillary endothelial proliferation, dedifferentiation and high mitotic activity and MIB-1 indices (10-15%) have been recorded [4,5,7,10-14]. The mentioned observations may cause some worry about the clinical course of the disease but these features were not necessarily associated with unfavorable behavior [4,5,7,12]. On the other hand histological benignity did not assure an indolent clinical course [5]. Thus, additional data are required to elucidate the significance of histological characteristics [4]. Beside these features, degenerative changes like Rosenthal fibers, calcification, foam cell collection, hemosiderin laden macrophages or mild lymphocytic infiltrate were also common in this neoplasm [4,5,15]. All of these degenerative changes were absent in the present case. There have been also cases contained mini gemistocytic cells, oligodendroglial like areas and gangliod cells, in addition to typical components [5,8,14,16].

The origin of tumor is in doubt. Immunohistochemical expression of PDGFR alpha, olig2 and Nestin and the fact that most PGNTs were near to ventricular system, support of a proposed origin of this tumor type from common progenitor cells in the subependymal plate [2,4,17]. Co-localization of glial and neuronal markers was demonstrable on confocal microscopy with expression of stem cell markers (Nestin and CD133) suggesting possible origin from neuroepithelial stem cell with biphenotypic differentiation [18]. Further studies are needed to clarify the histogenesis of PGNT.

Regarding the genetic alterations, one study revealed structural alterations involving only chromosome 7 with breakpoints at 7p22 a region where glial and neuronal linked genes (RAC1 and NXPH1) are known to be located [19], while the results of Myuang Jk et al. [4] who did array CGH study on 2 PGNT cases, were not consistent with the previous data. They found multiple gain and loss foci. By the way, IDH-1/IDH-2 alterations known to be found in various glial tumors and BRAF gene mutations that were seen in some gliomas and gangliogliomas, have not showed similar changes in their studied cases of PGNT. In addition, deletion of 1p/19q and amplification of EGFR were not observed in their 4 cases [4]. Thus they concluded that PGNT seems to have no cytogenetic changes similar to conventional glial tumors. Similarly, by means of fluorescence in situ hybridization (FISH) and IHC, Agarwal S et al, did not find 1p or 19q deletion and immunoreactivity for IDH1 and EGFR in their four cases [5]. In a recent study by Bridge JA et al, a novel translocation, t(9;17)(q31;q24), was identified in three PGNTs. Using a FISH-based positional cloning strategy, they revealed SLC44A1, a member of the choline transporter-like protein family, and PRKCA, a protein kinase C family member of serine/threonine-specific protein kinases, as the 9q31 and 17q24 breakpoint candidate genes, respectively [20]. They finally suggest that the

Table 1. Summary of clinical presentations of PGNT

	Xiao et al's review (n=42)	Myuang et al's review (n=18)	Recent reports and our case (n=9)	Total (n=69)
Age				
Mean	26y	18.4y	32.2y	24.7y
Range	4-75 y	4-75 y	4-74 y	4-75 y
< 30y	73.80%	94%	66.60%	76.80%
Gender (M:F)	1.1:1	1.1:1	1.25:1	1.16:1
Symptoms				
Headache	26 (62%)	7 (39%)	7 (78%)	40 (58%)
Seizure	10 (24%)	10 (56%)	2 (22%)	22 (32%)
Visual disturbance	6 (14%)	2 (11%)	1 (11%)	8 (11.6%)
Nausea/vomiting	5 (12%)	2 (11%)	3 (33%)	11 (16%)
Comprehensive & Memory difficulties	4 (10%)		1 (11%)	7 (10%)
Hemiparesis	2 (5%)	1 (6%)	2 (22%)	5 (7%)
Other Symptoms*	2 (5%)	3 (16%)	4 (44%)	9 (13%)
None/Not available	7 (17%)		1 (11%)	8 (11%)

**Other symptoms include vertigo/ataxia, syncope, muscle spasm, dysphasia, stagger and sensorium alteration*

novel fusion oncogene SLC44A1-PRKCA is the defining molecular feature of PGNT that may be responsible for its pathogenesis [20].

4. CONCLUSION

We report a case of PGNT in a 23 years old male with hemiparesis and a cystic mass in front of left ventricle. The PGNT is a supratentorial rare tumor which mostly affects young people. And it usually presents with headache and a lesion with cystic features on imaging. The present case was a grade 1 neuronal- glial tumor, and as expected, it showed benign appearing histology, and no recurrence developed during 64 month follow-up. Nevertheless, aggressive cases of this entity have been reported [5,12] and their behavior has not been related to histological grading. As a result, all cases of this lesion need to be reported making further knowledge about its biological behavior.

CONSENT

All authors declare that 'written informed consent was obtained from the patient for publication of this case report and accompanying images'.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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