DOI: 10.21608/pajn.2023.190113.1086

Case Report

Papillary Glioneuronal Tumor: A Case Report

Shankar Ayyappan Kutty,[1] Naimah Aljasem,[2] Priya Vadekkatt Sambhukumar[3]
[1]Department of Neurosciences, NMC Specialty Hospital, Abu Dhabi, UNITED ARAB EMIRATES
[2]Department of Histopathology, NMC Royal Hospital, Khalifa City A, Abu Dhabi, UNITED ARAB EMIRATES
[3]Department of Anesthesia, NMC Specialty Hospital, Abu Dhabi, UNITED ARAB EMIRATES

Received: 28 January 2023 / **Accepted:** 23 March 2023 / **Published online:** 19 June 2023

BACKGROUND: Papillary glioneuronal tumors (PGNT) are rare, with only around 130 reported cases since this tumor was first described in the fourth edition of the World Health Organization (WHO) classification of tumors of the central nervous system.

CASE PRESENTATION: We report the case of a 41-year-old male who presented with a right frontal tumor. The only presenting complaint was seizures. A cystic tumor with an enhancing nodule was found on magnetic resonance imaging (MRI) and this was excised via a craniotomy. Intra-operatively the cyst contents were thick and mucinous, the nodule was vascular and the cyst walls were made up of compressed white matter.

CONCLUSION: Papillary glioneuronal tumor is a low grade (WHO grade I) tumor that usually affects younger patients. They are usually periventricular in location and the presence of thick cyst contents may warn that the lesion is not a hemangioblastoma or dysembryoplastic neuroepithelial tumor (DNET). When in doubt, a frozen section may help to decide if the cyst wall should be excised. These tumors have a good prognosis if total excision is achieved.

KEYWORDS: Glioneuronal tumor, Mixed neuronal-glial tumor, Neuroepithelial tumor, Papillary.

INTRODUCTION

Papillary glioneuronal tumors (PGNT) are rare, with only around 130 cases being reported since this tumor was first described in the fourth edition of the WHO classification of tumors of the central nervous system published in 2007.[1,2] The term papillary glioneuronal tumor was first used by Komori et al. in 1998 to describe a new variant of mixed neuronal-glial tumor.[3] However, the first report of the new tumor, which eventually came to be classified as PGNT, was made by Kim et al. in 1997.[4] These tumors have a predilection for the frontal and temporal lobes and are often found in those below 35 years of age, though diverse locations such as cerebellum and suprasellar cistern, and ages ranging from 4-75 years have been reported.[5]

We report the case of a 41-year-old male who presented with a right frontal tumor which was reported as a papillary glioneuronal tumor on histopathology. The clinical presentation, radiological features and histopathological characteristics of these rare tumors are discussed.

CASE PRESENTATION

A 41-year-old Spanish national was brought to the emergency department with a history of one episode of generalized tonic-clonic seizures an hour earlier. There was a history of frequent headaches over the previous month and his acquaintances had noticed that he had become more lethargic and withdrawn over the same time period. He was drowsy after the attack and had intermittent incontinence of urine, but he was completely indifferent about it. On examination, he had papilledema and pronator drift on the left side.

Correspondence:
Shankar Ayyappan Kutty
Department of Neurosciences, NMC Specialty Hospital, Abu Dhabi, UNITED ARAB EMIRATES
Email: shankar.ayyappan@nmc.ae

An emergent MRI of the brain was done which showed a very large cystic mass with an enhancing mural nodule in the right frontal region, causing compression of the adjacent brain with subfalcine and transtentorial herniation **(Fig. 1).** The lesion was hypointense on T1 weighted images and hyperintense on T2 weighted and fluid attenuated inversion recovery (FLAIR) images. The ipsilateral lateral ventricle was partly effaced, and the contralateral lateral ventricle was dilated. Midline shift was approximately 11mm.

The patient was taken up for emergency craniotomy and excision of the lesion. At surgery, a cyst containing xanthochromic, thick and partly mucinous fluid was encountered 2-3mm beneath the cortical surface. Posteriorly, the frontal horn was bulging into the cyst. Antero-medially, a reddish, well-circumscribed, encapsulated lesion was seen in the cyst wall, with a good plane with the adjacent brain. Multiple vessels were seen entering and leaving the lesion. This lesion was removed in toto and measured about 2.5cm in size. Postoperatively, the patient made an uneventful recovery. The apathy and behavioral changes regressed completely.

The histopathology examination revealed a well-circumscribed tumor with biphasic pattern; glial and neuronal components associated with vascular proliferation with patchy marked perivascular hyalinization forming pseudopapillary architecture. The neuronal component showed neurocytes, occasional

ganglion and ganglioid cells within the interpapillary zone. Immunohistochemistry showed that the glial fibrillary acidic protein (GFAP) was positive for tumor cells **(Fig. 2).** Synaptophysin was positive for the cytoplasm of ganglion cells and fibrillary stroma **(Fig. 3).** S100 was negative for the nuclei of ganglion cells. Epithelial membrane antigen (EMA) was negative, Panck was non-contributory, cluster of differentiation 34 (CD34) was positive for vascular tumor and Inhibin was negative. Ki67 was less than 1%. The specimen was compatible with a diagnosis of mixed neuronal glial tumor such as PGNT.

The patient was followed up with annual scans done in Spain . The scan done one year after surgery did not show any residual lesion but the second one done two years after surgery showed a tiny area of enhancement anterior to the left frontal horn **(Fig. 4).**

Regional Research Ethics committee approval was obtained (vide approval number NMC/RREC/AUH/2021/0009) and the patient's written consent for publication was taken when he visited the hospital to collect the histopathology report.

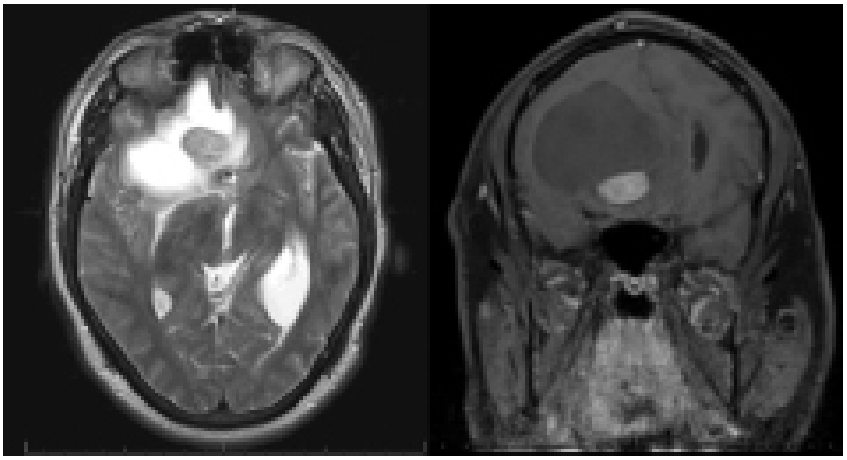

Fig 1: (A) Axial T2 weighted MRI showing the nodule with surrounding cyst in the right frontal region. (B): Coronal T1 weighted MRI showing contrast enhancement in the nodule.

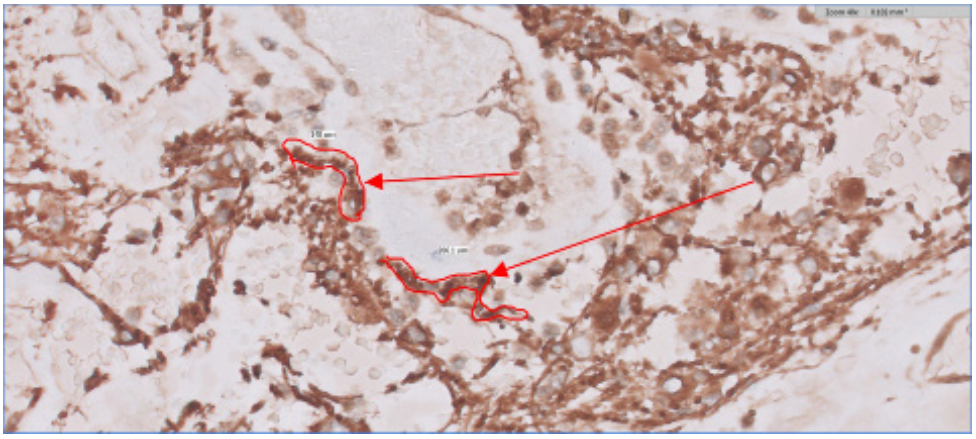

Fig 2: GFAP staining at 40x magnification showing flat to cuboidal cells covering hyalinized vessels.

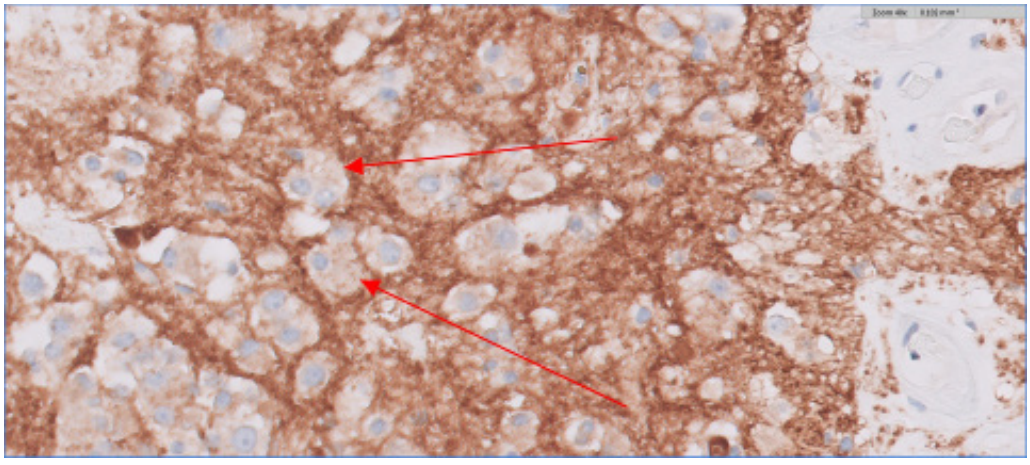

Fig 3: Synaptophysin staining at 40x magnification showing ganglion cells.

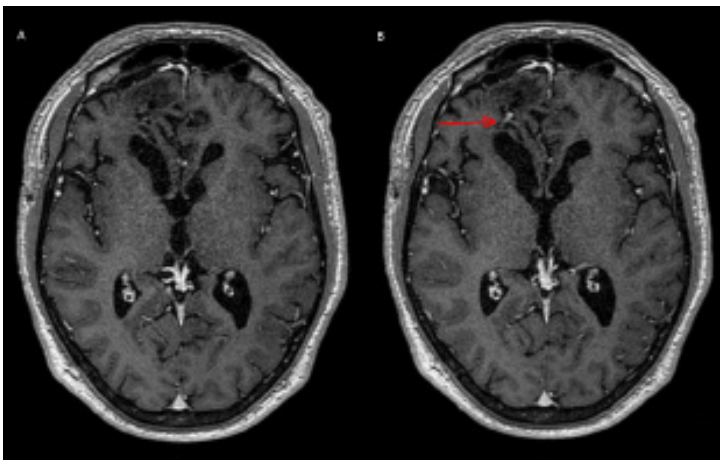

Fig 4 (A,B): Axial T1 weighted contrast enhanced MRI done one year and two years after surgery, showing no evidence of any enhancing lesion in (A) and a tiny area of enhancement in (B) (red arrow).

DISCUSSION

PGNT is designated as a low grade (WHO grade I) tumor that usually involves the supratentorial compartment (95% of cases) and primarily affects younger patients.[4] In their series of 16 cases, Li et al. reported a mean age of 23.8 years.[6] Schlamann et al. in their extensive meta-analysis noted that after a median follow up of 1.5 years, progression-free survival rate was 86±5%.[5] Exceptionally, PGNT may present as an aggressive variant, with a high Ki67 index (>5%) and a tendency to recur.[7] Goethe et al. reported a recurrence of PGNT one year after subtotal excision, which continued to progress despite radiotherapy and temozolomide. Molecular testing revealed a telomerase reverse transcriptase (TERT) promotor mutation, a fibroblast growth factor receptor 3-transforming acidic coiled-coil containing protein 3 (FGFR3-TACC3) oncogenic fusion, and a copy number loss in cyclin-dependent kinase inhibitor 2A/2B (CDKN 2A/2B). The authors concluded that molecular analysis of these tumors may help to identify those at risk of recurrence.[8] Similar recurrences have been reported by other authors as well.[9] These patients may need radiotherapy and/or chemotherapy.[7]

The most common clinical presentation is headache, followed by seizures. Focal neurological deficits are rare or delayed as the tumor usually occurs in the frontal or temporal lobes.[6] Deficits, incidence of partial excision, and recurrences are more common in lesions involving the parietal lobe, due to the eloquent nature of the brain in this region.[10] A rare instance of a patient presenting with intracerebral hemorrhage, mimicking a bleeding cavernous malformation, was reported by Buccoliero et al.[11] Another case of intratumoral hemorrhage in a toddler was also reported recently.[12]

Radiologically, the tumor usually appears as a cyst with a solid nodule, though lesions which consist only of an enhancing cyst or only of a solid nodule may also occur.[6] On MRI, periventricular lesions that are isointense on T2 weighted images and hypo-isointense on diffusion-weighted imaging (DWI) may offer some specificity to PGNT.[13] Where the cyst wall is found to enhance on imaging, it may be necessary to excise the wall to prevent recurrence. Alternatively, the wall may be biopsied intra-operatively to confirm the presence or absence of tumor cells.[10] In our case, since the wall was not enhancing with contrast, and since during surgery it appeared to consist only of white matter, only the mural nodule was excised.

The histopathological picture is a biphasic one, consisting of papillary and solid components, with a mixture of glial and neuronal cellular elements. The pseudopapillae are composed of hyalinized vessels covered by GFAP positive astrocytes and synaptophysin positive neuronal cells.[6] Our patient had a typical appearance on histopathological evaluation. A number of studies have looked at the genetic variations in these tumors. Hou et al. reported that only 11 out of 28 cases diagnosed histologically as PGNT showed a distinct deoxyribonucleic acid (DNA) methylation and showed a characteristic protein kinase C alpha (PRKCA) fusion, indicating the need for molecular analysis for confirming the diagnosis of PGNT in the future.[14] Solute carrier family 44 member 1- protein kinase C alpha (SLC44A1-PRKCA) fusion seems to be a specific characteristic of PGNT with a high diagnostic value and detectable by fluorescence in situ hybridization (FISH).[15] Capper et al. noted that there have been no reports of v-raf murine sarcoma viral oncogene homolog B1 (BRAF) V600E mutation in PGNT while 40% of gangliogliomas are positive for this mutation, and this may help to distinguish between these two conditions.[16] Multiple genetic mutations continue to be reported in cases of glioneuronal tumors, and their usefulness in formulation of diagnosis or prognosis can be ascertained only as more data becomes available. For example, fibroblast growth factor receptor 1 tyrosine kinase domain (FGFR1 N546K) mutation in PGNT was reported by Gessi et al. in 2014,[17] while gene fusion of CAP-GLY-domain-containing linker protein 2-mesenchymal–epithelial transition factor (CLIP2-MET) resulting from aberrant chromosome 7 abnormalities was reported by Chowdhury et al. in 2020,[18] and a novel G

protein-coupled receptor 37 like 1-PRKCA (GPR37L1-PRKCA) fusion was reported by Ahn et al.[19] While high Ki67 has been conclusively associated with a poor prognosis, the definitive genetic markers that correlate with higher recurrence rates are still an ongoing field of study, and the need to send all tissue samples for genetic analysis when feasible cannot be over-emphasized.

Total excision of the tumor is considered curative in most cases. Hence, it is important to consider this diagnosis when unexpected findings occur intraoperatively in tumors where a possible differential diagnosis is PGNT, such as the finding of thick mucinous cyst content in our case whereas the expected finding was a xanthochromic fluid as in a hemangioblastoma or metastasis. When PGNT is a differential diagnosis, every attempt must be made to totally excise the lesion when feasible, as incomplete excisions are associated with a poorer long-term prognosis. Where recurrences occur, they are usually in cases where excision was hampered by the adjacent eloquent cortex, as mentioned above, and these cases have been treated with radiotherapy. The close association between the ventricular system and the tumors, as was noted in our case, has been commented on by several authors, and it is thought to be due to the possible origin of these tumors from the neuroglial progenitor cells in the subependymal plate as postulated by Komori et al.[3] These tumors need to be followed up for a long time since enlargement of the lesion has been reported as late as 10 years after the initial diagnosis.[20,21]

CONCLUSION

As awareness about this entity is spreading, more cases are being reported from around the world. It is important to consider the diagnosis of PGNT in patients presenting with supratentorial enhancing nodules associated with a cyst, as this will emphasize the need for total excision during surgery, which is usually curative. As more cases are reported, we also gain greater insight into the variations in clinical presentation, radiological findings and histopathological as well as genetic changes associated with these rare tumors. In the present case, the patient made a complete recovery after surgery, and coupled with the fact that total excision of the tumor was achieved, we expect an excellent long-term prognosis.

List of abbreviations

BRAF: v-raf murine sarcoma viral oncogene homolog B1.
CD: Cluster of differentiation.
CDKN: Cyclin-dependent kinase inhibitor .
CLIP2: CAP-GLY-domain-containing linker protein 2.
DNA: Deoxyribonucleic acid.
DNET: Dysembryoplastic neuroepithelial tumor.
DWI: Diffusion-weighted imaging.
EMA: Epithelial membrane antigen.
FGFR1 N546K: Fibroblast growth factor receptor 1 tyrosine kinase domain.
FGFR3: Fibroblast growth factor receptor 3.
FISH: Fluorescence in situ hybridization.
FLAIR: Fluid attenuated inversion recovery.
GFAP: Glial fibrillary acidic protein.
GPR37L1: G protein-coupled receptor 37 like 1.
MET: Mesenchymal–epithelial transition factor.
MRI: Magnetic resonance imaging.
PGNT: Papillary glioneuronal tumor.
PRKCA: Protein kinase C alpha.
SLC44A1: Solute carrier family 44-member 1.
TACC3: Transforming acidic coiled-coil containing protein 3.
TERT: Telomerase reverse transcriptase.
WHO: World Health Organization.

Disclosure

The authors report no conflict of interest in the materials or methods used in this study or the findings specified in this paper.

Funding

The authors received no financial support for the research, authorship, and/or publication of this paper.

REFERENCES

1. Ahmed AK, Dawood HY, Gerard J, et al. Surgical resection and cellular proliferation index predict prognosis for patients with papillary glioneuronal tumor: Systematic review and pooled analysis. *World Neurosurg.* 2017;107:534-541.

2. Louis DN, Ohgaki H, Wiestler OD, et al. The 2007 WHO classification of tumours of the central nervous system. *Acta Neuropathol.* 2007;114(2):97-109.

3. Komori T, Scheithauer BW, Anthony DC, et al. Papillary glioneuronal tumor: A new variant of mixed neuronal-glial neoplasm. *Am J Surg Pathol.* 1998;22(10):1171-1183.

4. Kim DH, Suh YL. Pseudopapillary neurocytoma of temporal lobe with glial differentiation. *Acta Neuropathol.* 1997;94(2):187-191.

5. Schlamann A, von Bueren AO, Hagel C, et al. An individual patient data meta-analysis on characteristics and outcome of patients with papillary glioneuronal tumor, rosette glioneuronal tumor with neuropil-like islands and rosette forming glioneuronal tumor of the fourth ventricle. *PLoS One.* 2014;9(7):e101211.

6. Li D, Wang JM, Li GL, et al. Clinical, radiological, and pathological features of 16 papillary glioneuronal tumors. *Acta Neurochir (Wien).* 2014;156(4):627-639.

7. Agarwal S, Sharma MC, Singh G, et al. Papillary glioneuronal tumor-a rare entity: Report of four cases and brief review of literature. *Childs Nerv Syst.* 2012;28(11):1897-1904.

8. Goethe EA, Youssef M, Patel AJ, et al. Recurrent papillary glioneuronal tumor. *World Neurosurg.* 2019;128:127-130.

9. Carangelo B, Arrigucci U, Mariottini A, et al. Papillary glioneuronal tumor: Case report and review of literature. *G Chir.* 2015;36(2):63-69.

10. Rocka S, Neverauskiene L, Nelson EL, et al. Papillary glioneuronal tumor: A case report. *Cureus.* 2019;11(3):e4215.

11. Buccoliero AM, Giordano F, Mussa F, et al. Papillary glioneuronal tumor radiologically mimicking a cavernous hemangioma with hemorrhagic onset. *Neuropathology.* 2006;26(3):206-211.

12. Tavallaii A, Keykhosravi E, Rezaee H. Acute presentation of papillary glioneuronal tumor due to intra-tumoral hemorrhage in a toddler: An odd presentation of a rare pathology. *Br J Neurosurg.* 2020 Aug 12:1-6.

13. Tan W, Huang W, Xiong J, et al. Neuroradiological features of papillary glioneuronal tumor: A study of 8 cases. *J Comput Assist Tomogr.* 2014;38(5):634-638.

14. Hou Y, Pinheiro J, Sahm F, et al. Papillary glioneuronal tumor (PGNT) exhibits a characteristic methylation profile and fusions involving PRKCA. *Acta Neuropathol.* 2019;137(5):837-846.

15. Pages M, Lacroix L, Tauziede-Espariat A, et al. Papillary glioneuronal tumors: Histological and molecular characteristics and diagnostic value of SLC44A1-PRKCA fusion. *Acta Neuropathol Commun.* 2015;3:85.

16. Capper D, Preusser M, Habel A, et al. Assessment of BRAF V600E mutation status by immunohistochemistry with a mutation-specific monoclonal antibody. *Acta Neuropathol.* 2011;122(1):11-19.

17. Gessi M, Abdel Moneim Y, Hammes J, et al. FGFR1 N546K mutation in a case of papillary glioneuronal tumor (PGNT). *Acta Neuropathol.* 2014;127(6):935-936.

18. Chowdhury T, Lee Y, Kim S, et al. A glioneuronal tumor with CLIP2-MET fusion. *NPJ Genom Med.* 2020;5:24.

19. Ahn JS, Ervin J, Cummings TJ, López GY, Wang SJ. Papillary glioneuronal tumor with a novel GPR37L1-PRKCA fusion. *J Neuropathol Exp Neurol.* 2021;80(10):1004-1006.

20. Fujita Y, Kinoshita M, Ozaki T, et al. Enlargement of papillary glioneuronal tumor in an adult after a follow-up period of 10 years: A case report. *J Surg Case Rep.* 2018;2018(6):rjy123.

21. Lavrador JP, Kandeel HS, Kalb A, et al. 5-ALA fluorescence in a WHO grade I papillary glioneuronal tumour: A case report. *Acta Neurochir (Wien).* 2020;162(4):813-817.