Original Article

Clinicopathological Study of Recently Added Glioneuronal Tumors

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Abstract

Background: Glioneuronal tumors are pathologically heterogeneous group of tumors containing both glial and neural components or glial tumors with neural differentiation. In the year 2007, three new entities have been added to the repertoire of glioneuronal tumors by the World Health Organization (WHO) which include papillary glioneuronal tumor (PGNT) (WHO Grade I), rosette-forming glioneuronal tumor of the fourth ventricle (RGNT) (WHO Grade I), and glioneuronal tumor with neuropil-like islands (GTNIs) (WHO grade II/III). The present study summarizes the clinical and neuropathological features of these three glioneuronal neoplasms. **Materials and Methods:** This study included seven cases of newer glioneuronal tumors (four cases of PGNT, two cases of RGNT, and one case of GTNI) which were reviewed. **Results:** The clinical presentations (patient characters), radiology, squash preparations, histology, and immunohistochemical findings of these cases are discussed including some of the morphological variations and follow-up. **Conclusion:** Glioneuronal tumors show considerable morphological and clinical diversity with some unique features. As these neoplasms are low grade and well manageable, the knowledge of their clinical presentation and histological diagnosis is essential for treatment. The present study is an attempt toward this.

Keywords: *Glioneuronal, neuropil, rosette forming, synaptophysin*

Introduction

Glioneuronal tumors are pathologically heterogeneous group of tumors containing both glial and neural components or glial tumors with neural differentiation.[1-3] They form an important category of central nervous system (CNS) neoplasms and ganglioglioma, constitute the most common and earliest described entity of this group.[4] This group also includes other neoplasms, namely, gangliocytoma, desmoplastic infantile astrocytoma and ganglioglioma, dysembryoplastic neuroepithelial tumor (DNET), central neurocytoma, cerebellar liponeurocytoma, and paraganglioma of the filum terminale.[1,2] During the past decade, pathologists have introduced several morphologically distinctive neoplasms to the category of mixed glioneuronal tumors. In the year 2007, three new entities were added to the repertoire of glioneuronal tumors by the World Health Organization (WHO). These include papillary glioneuronal tumor (PGNT) (WHO Grade I), rosette-forming glioneuronal tumor of the fourth ventricle (RGNT) (WHO Grade I), and glioneuronal tumor with neuropil-like islands (GTNIs) (WHO grade II/III).[2,3] In the most recent update of the World Health Organization (WHO) classification of CNS tumors 2016, one more entity has been added to the list and has been termed "diffuse leptomeningeal glioneuronal tumor".[1] It is becoming evident that the group of neuronal and glioneuronal tumors in reality represents a rather heterogeneous group of lesions in histology, clinical presentation, and natural history. The present study attempts to add to the list of newly described glioneuronal tumor entities (PGNT, RGNT, and GTNI) and summarizes the clinical, imaging, and neuropathological features of three glioneuronal neoplasms, namely, PGNT, RGNT of the fourth ventricle, and glioneuronal tumor with neuropil-like islands.

Materials and Methods

We reviewed all cases between 2008 and 2015 that belonged to the category of glioneuronal tumors (tumors microscopically and immunohistochemically showing distinctive glial and neuronal components) and retrieved seven cases of newer glioneuronal tumors (PGNT, RGNT,

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and GTNI) from the pathology archives of our institution. Of these seven cases, the final diagnosis was PGNT in four cases, RGNT in two cases, and GTNI in one case.

All patient-specific information was kept confidential. Formalin-fixed, paraffin-embedded tissue was used for routine histological and immunohistochemical studies. Immunohistochemistry was performed on representative sections using polymer-based technique and the antibodies used included the following prediluted (ready to use) primary antibodies: glial fibrillary acid protein (GFAP) (clone EP13, RM, PathnSitu, Livermore, CA) synaptophysin (Syn) (clone DAK-SYNAP, MM, DAKO, Carpinteria, CA), p53 (Clone DO-7, MM, DAKO, Carpinteria, CA), and Ki-67 (Clone G M001, MM, PathnSitu, Livermore, CA). The slides were stained using the DAKO Envision secondary antibody (DAKO, Carpinteria, CA). The markers were studied with the appropriate positive controls.

Results

The clinical presentations (patient characters), radiology, squash preparations, histology, and immunohistochemical findings of these seven cases were listed in Table 1.

For convenience of analysis, the patients were grouped into three categories:

1. Group I: PGNT
2. Group II: RGNT
3. Group III: GTNI.

Table 1: Clinicopathological summary of seven cases in the present study

Age/sex (years)	Clinical features	Duration of symptoms (months)	Site	Radiological findings	Squash smear diagnosis	Histology	Immunohistochemistry			
							GFAP	Syn	p53	Ki-67 (%)
36/male	Multiple episode of generalized tonic-clonic seizures	6	Right frontal lobe	T1-hypointense T2-hyperintense No contrast enhancement No perilesional edema Solid and cystic area	Low-grade glioma	PGNT	+	+	-	1.5
54/female	Multiple episodes of complex partial seizures	3	Right medial temporal and parahippocampal region	T1-hypointense T2-hyperintense with cystic patchy enhancement	Low-grade glioma	PGNT	+	+	-	2
8/male	Multiple CPS	3	Right parietooccipital	Nonenhancing solid, subcortical	Low-grade glioma favoring pilocytic astrocytoma	PGNT	+	+	-	1
16/male	Multiple CPS	4	Left medial temporal	T1-hypointense T2-hyperintense subcordial solid	Low-grade glioma	PGNT	+	+	-	1.5
24/male	Raised ICP with headache vomiting alexia	4	Fourth ventricle and vermis	Iso to hypointense on T1 and hyperintense on T2	Pilocytic astrocytoma	RGNT	+	+	-	2.5
12/male	Raised ICP	7	Fourth periventricle and cerebellum	Solid cystic with T1-mild enhancement	Low-grade neoplasm favoring glioneuronal tumor	RGNT	+	+	-	<1
43/male	Raised ICP no laterally sign	2	Posterior corpus callosum	T1-hypointense T2-hyperintense with patchy enhancement infiltrative nature	Glioma with nuclear atypia	GTNI	Glial component +	Neuronal component +	+	1-7

ICP: Intracranial pressure, PGNT: Papillary glioneuronal tumor, GTNI: Glioneuronal tumor with neuropil-like islands, RGNT: Rosette-forming glioneuronal tumor, GFAP: Glial fibrillary acid protein, Syn: Synaptophysin, CPS: Complex partial seizures, +: Positive, -: Negative

Group I: Of the seven cases included in the present series, four cases were PGNT. The intraoperative diagnosis (squash preparation) was low-grade glial neoplasm in all four cases with one case being further categorized as pilocytic astrocytoma. On histology (PGNT), all cases revealed a biphasic pattern comprising neurocytic and glial components. The neurocytic component is characterized by monomorphic cells with round dark staining nuclei and scant cytoplasm forming rosettes and perivascular pseudorosettes showing positivity for Syn. The other component being glial in nature with evidence of papillary and pseudopapillary configuration which was positive for GFAP. Case 1 and 3 had pilocytic-like glial component with rosenthal fibers and eosinophilic granular bodies (EGBs). Case 1 in addition showed endovascular proliferation. Areas of pericellular halos resembling oligodendroglioma with foci of microcalcifications were evident in the glial component in Case 2. None of the cases had necrosis/mitosis. Ki-67 immunostain revealed a proliferative index ranging from 0.1% to a maximum of 2% and p53 was negative. Representative images shown in Figure 1.

Group II: Two cases were diagnosed as RGNT on squash smear during intraoperative consultation, one of the cases was diagnosed as low-grade glioneuronal tumor while the other as pilocytic astrocytoma. Histology revealed in both the cases a moderately cellular neoplasm composed of sheets of astroglial cells with oval and spindled nuclei with piloid processes along with rosenthal fibers and EGBs showing positivity for GFAP. The stroma was loose, myxoid with microcystic changes. Cells with small round, regular nuclei with speckled chromatin were seen arranged as perivascular pseudorosettes showing positivity for Syn. No evidence of necrosis/mitosis/endovascular proliferation was noted. Ki-67 ranged from 0.5% to a maximum of 2.5% in Case 5 and p53 was negative. Representative images shown in Figure 2.

Group III: One case of GTNI was diagnosed, which during intraoperative consultation was called as glial neoplasm with nuclear atypia. Histology revealed neurocytic cells with small and round nuclei with no atypia. The prominent features of GTNI were the presence of rosetted neuropil islands surrounded by neurocytic cells. This component showed Syn positivity. The cells in the gliomatous component showed mild to moderate pleomorphism and were diffusely positive for GFAP. No necrosis/endovascular proliferation was noted in the tumor with occasional mitotic figures in the glial component. Ki-67 in the glial component showed a maximum of 7% with positivity for p53 (40%) whereas Ki-67 was very low in neurocytic component being <1% and p53 was negative. Representative images shown in Figure 3.

Some of the pertinent clinical features of patients were presented in Table 1 and also copies of radiological studies or preoperative imaging reports were available for review and were mentioned in Table 1. Gross total excision of the tumor was performed in all the seven cases. Follow-up of these cases ranged from 20 to 80 months and all the patients are doing well with no evidence of recurrence.

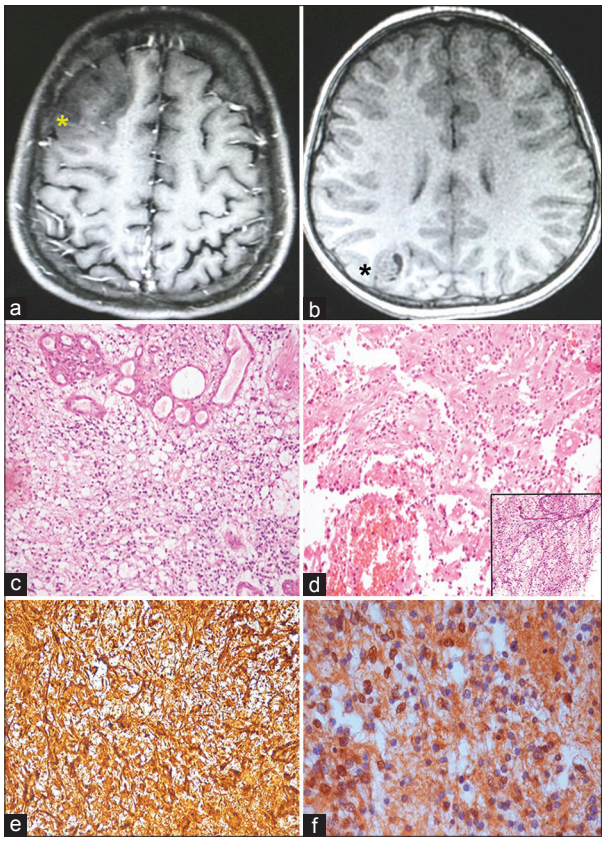

Figure 1: (a and b) Magnetic resonance imaging brain (axial view) showing the lesion (asterix) of Cases 1 and 3. (c and d) Microphotograph showing a biphasic pattern with glial component (c) and neurocytic (d) component having a papillary configuration. Inset: Microphotograph of squash smear showing delicate vascular endothelial strands with round cells with perivascular distribution of cells (H and E, ×200). (e) Microphotograph showing glial component with positive immunohistochemical staining for glial fibrillary acid protein (×400). (f) Microphotograph showing the neuronal component with positive staining for synaptophysin (×400)

Discussion

The 2007 World Health Organization Classification of Tumors of Central Nervous Systems expanded the classification of tumors of mixed glioneuronal type by adding three new entities to the group. These are PGNT, RGNT of the fourth ventricle, and rosetted glioneuronal tumor with neuropil-like islands. These neoplasms are relatively rare and the exact prevalence is not known. More number of such cases are being added with advent of immunohistochemistry and its awareness enabling us to readily identify neuronal differentiation in tumors which morphologically resemble glial neoplasm. In the most recent (2016) update of the WHO classification of tumors of the central nervous system has retained, these three entities with an addition of diffuse leptomeningeal glioneuronal tumor as a new entity.[1,2]

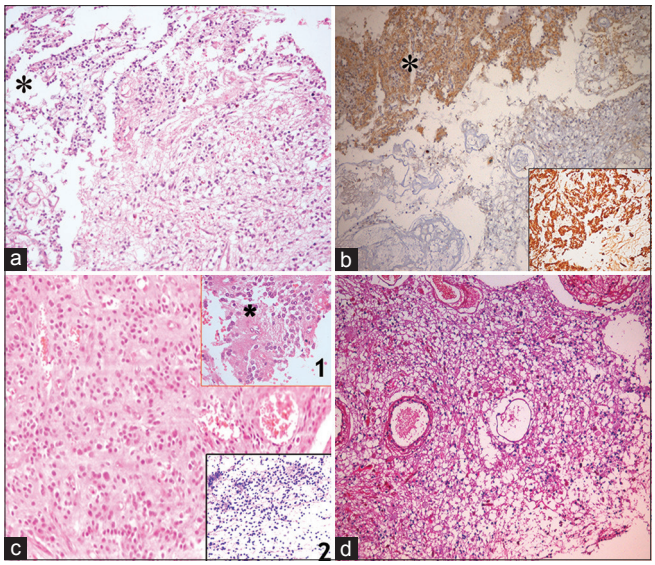

Figure 2: (a) Microphotograph showing a biphasic pattern with glial component and neurocytic (asterix) component having a pseudopapillary configuration (H and E, ×200). (b) Microphotograph showing neurocytic component with positive immunohistochemical staining for synaptophysin (asterix, ×200) and negative staining by glial component. Inset: Microphotograph showing positive staining for glial fibrillary acid protein (inset, ×200) of the glial component. (c) Microphotograph (H and E, ×200) showing neurocytic (N) component with Homer Wright and perivascular rosettes. Inset 1: Highlighting the rosettes (asterix). Inset 2: Microphotograph of squash smear with vague rosettes (H and E, ×200). (d) Microphotograph (H and E, ×200) showing glial component (g) with Rosenthal fibers

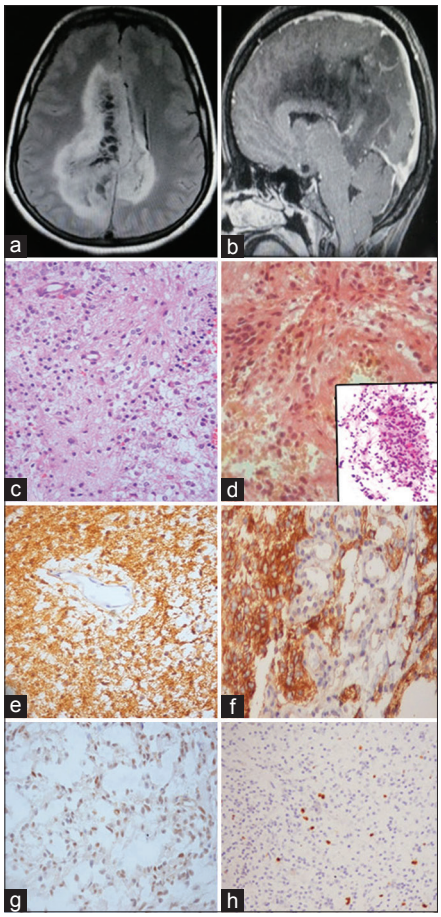

Figure 3: (a) Magnetic resonance imaging T2-weighted axial fluid-attenuated inversion recovery image (Case 6) showing large hyperintense solid-cystic bihemispheric lesion along superior aspect of corpus callosum. (b) Magnetic resonance imaging T1-weighted contrast sagittal (Case 6) showing nonenhancing lesion arising from superior aspect of corpus callosum. (c and d) Microphotograph showing round to oval cells dispersed in a delicate fibrillary stroma (H and E, ×100 and × 200). Inset: Microphotograph of squash smear showing round to oval cells with anisonucleosis and dispersed in a delicate fibrillary background (neuropil like) (H and E, ×200). (e) Microphotograph showing glial fibrillary acid protein positive staining in the neoplastic glial areas (×200). (f) Microphotograph showing synaptophysin-stained neuropil islands (×200). (g) p53 immunostaining (×200). (h) Ki-67 immunostaining showing proliferative index up to a maximum of 7% (×200)

PGNT was described first by Komori *et al*. in 1998 as a new variant of a mixed glioneuronal tumor.[5] These are slow-growing indolent tumors and are considered as Grade I. Majority of these lesions are found in young adults, but there has been a few cases described in children and elderly. Neuroimaging for other reasons has detected incidental mass in asymptomatic patients.[6] There is a slight predilection for male gender. There is no association with any heritable syndrome. Nonspecific headache, seizures, nausea, and vomiting are common clinical presentation. Focal neurological deficit, visual, or speech disturbance are also noted.[5]

In our study, male: female ratio was 2.5:1. There was a wide distribution of age with a mean of 27.5 years and a median of 24 years, the youngest patient being 8 years and the eldest being 54 years. Parietooccipital lesion presented with partial seizure. The above features were in concordance with the literature.[6] The glial component is astrocytic and is characterized by pseudopapillary formation and conspicuous hyalinized vasculature. The vessels are enclosed by uniform, single, or pseudostratified layer of small cuboidal cells with round vesicular nuclei without atypia and scant cytoplasm. These cells are uniformly immunoreactive for GFAP and S-100 antibodies. In some cases, they show immunostaining with Syn antibodies.[7-9] The interpapillary spaces contain small round neuronal cells with perinuclear halos, resembling oligodendroglioma that have been shown to stain for Olig2 and Syn antibodies. Other striking finding is the presence of rosenthal fibers in most of the cases. Proliferative indices such as Ki-67 have uniformly been low.[7] The histogenesis of PGNT is uncertain. Multipotent precursor cells capable of divergent glioneuronal differentiation from stem cells have been suggested because of its common periventricular location and origin from subependymal stem cells.[5] The more superficially located ones have probable origin from the secondary germinal layer.[5] Radiological characteristics in magnetic resonance imaging (MRI) such as occurrence of a cystic lesion with mural nodule, mixed solid-cystic lesions (39%) with ring-like enhancement facilitate the diagnosis.[5] The PGNT being a WHO Grade I tumor has a benign course and an excellent prognosis, especially after

gross total tumor resection. There are, however, examples of more aggressive glioneuronal tumor described in the literature.[10,11]

RGNT, initially described as DNET of the cerebellum, is considered as a separate entity based on distinctive morphology, location, age distribution, and biologic behavior.[12] This tumor typically arises in the midline of the cerebellum, wall or floor of the fourth ventricle, and/or cerebral aqueduct and may show parenchymal extension.[3,13] This tumor predominantly affects young adults with a mean age of 29.2 years, with the youngest being 6-year-old, and the oldest being 59 years of age.[14] There is a female preponderance (female:male ratio, slightly more than 2:1).[14-16] In our study, both 12- and 24-year-old male patients had posterior fossa involvement.

On computed tomography scans, the lesions are in midline location, relatively well circumscribed with solid, cystic, or mixed and enhance focally with contrast.[12,13] MRI features are T1-isointensity/hypointensity and T2-hyperintensity with no contrast enhancement.[3,12,13] Similar to the PGNT, the incidence of this lesion in the general population is not known because of the less number of cases reported in the literature. The most common presenting manifestations are headache and ataxia, followed by visual disturbances and vertigo.[13] Imaging studies show a relatively circumscribed, solid mass demonstrating high-signal intensity on T2-weighted images and low intensity on T1-weighted images. RGNT has distinct histological biphasic appearance with neurocytic rosettes/perivascular pseudorosettes and glial elements that resemble a pilocytic astrocytoma. The neurocytic component is composed of cells with small and regular nuclei and speckled chromatin forming perivascular pseudorosettes and miniature neurocytic rosettes with a delicate neuropil matrix. Cytologic atypia and mitotic activity are generally absent.[9] On immunostaining, Syn labels both the neuropil matrix and perivascular pseudorosettes. Occasionally, ganglion cells may be present. Vascular proliferative changes may be focally evident. Ultrastructural studies confirm the presence of both astrocytic and neurocytic cell components. The astrocytic component is labeled by GFAP and S-100.[12,13] Ki-67 proliferation indices are low.[3,12,13] The RGNT resembles pilocytic astrocytoma, a major differential diagnostic consideration. Pilocytic astrocytoma typically consists of cells with spindled morphology that are clearly astrocytic and other areas in which the cells may be more rounded. However, there is no evidence of neural differentiation in the rounded cells of pilocytic astrocytoma. On imaging, the pilocytic astrocytoma tends to be a cystic lesion with an enhancing mural nodule. Clinical follow-up in limited cases are reported to have a favorable prognosis which correlates with the WHO grade I designation.[3,12,13] Even though benign, the deep location around the ventricle may impart significant neurologic injury at surgery.[12,13]

The other neoplastic entity included and reviewed is GTNIs (rosetted glioneuronal tumor) which is WHO grade II or III. One of the first descriptions of GTNI was made in1999, where the author reported four cases of neuronal tumor of adult cerebrum that was marked by neuropil-like or rosetted islands.[17] The above tumor consists of glial cells and neuropil-like islands that typically contain neurocytic cells and occasionally mature emerging neurons.[17] The lesion is considered to be a variant of astrocytoma, WHO Grade II or III.[3] Most cases reported in the literature have been located in the cerebrum with the exception of a single spinal cord tumor. It is considered that GTNIs occur more commonly in adult patients and predominantly localize in brain hemispheres.[18-21] Tumor localization in the spinal cord is less frequent.[22,23] The clinical presentation includes seizures, focal neural deficits, or signs of increased intracranial pressure.[17,22,24] Our series had a single case of 43-year-old female presented with seizures. According to Teo *et al*., GTNIs are represented by well-circumscribed hypodense tumors which neither shows necrosis nor cyst formation.[17] T1-weighted MRI shows a decreased tumor signal intensity as compared to that of the brain cortex. Contrast-enhanced MRI shows that the tumor poorly accumulating the contrast agent. T2-weighted MRI shows hyperintense signals. Morphologically, the tumor is composed of cells resembling a fibrillary, gemistocytic, or protoplasmic astrocytoma. Within the neoplasm are relatively circumscribed, round to oval islands of a neuropil-like matrix rimmed by rounded oligodendroglial-like cells, which show immunoreactivity with neurocytic markers such as Syn or NeuN.[9] A few mitotic figures may be evident. Vascular proliferation and necrosis are uncommon. The gliomatous component shows strong staining affinity to GFAP antibody and also immunoreactive for p53. Ki-67 proliferation indices that can be variable reaching up to 18%.[18-21] The present case showed positivity for p53 with a proliferative index ranging from 1% to a maximum of 7% in the gliomatous component of the tumor.[18] In most of the previously reported literature on usual glioneuronal neoplasms, there has been only rare evaluation of p53 immunoreactivity. p53 nuclear protein is well known to suppress cell proliferation in tumor growth. Mutations in the p53 gene often increase the stability of the gene product, allowing for immunohistochemical detection. p53 abnormalities are well known to occur in astrocytomas. This neoplasm appears to represent a distinct phenotype of glioneuronal tumor and does not show phenotypic characteristics typical of more commonly encountered, well-defined glioneuronal tumors such as gangliolgioma and DNET. The clinical outcome of this tumor seems to correspond to the grade of the astrocytoma component. Inclusion of this lesion in the section of anaplastic astrocytoma in the WHO classification implies that these tumor may, in fact, represent a variant of diffuse astrocytoma with aberrant neuronal differentiation rather than a distinct glioneuronal

tumor.[2] The 3-year survival rate varies from 50% to 75%.[17,25] Complete surgical resection followed by adjuvant (chemo and radiation) therapy is a method of choice for treating GTNI.[17,25,26]

Conclusion

Glioneuronal tumors show considerable morphological and clinical diversity, some of which are incompletely understood. The present study highlights the diverse clinicopathological spectrum and certain unique features of the newer glioneuronal tumors. The present study has tried to add to expand number of newly added glioneuronal neoplasms and thus would aid in gaining experience of the clinical and pathological profile of these neoplasms. This would help in avoiding misdiagnosis of some of the overlapping features of glioneuronal tumors with some of the glial neoplasms. Further analysis of a larger cohort with incorporation of molecular genetics and ultrastructure with extensive clinical follow-up would be needed for better understanding of the natural history, histogenesis, and pathobiology of these neoplasms. This would contribute to offer a stronger and better diagnostic, therapeutic, and prognostic profile.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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