*Neuropathology* 2006; **26**, 206–211 doi:10.1111/j.1440-1789.2006.00674.x

Case Report

# Papillary glioneuronal tumor radiologically mimicking a cavernous hemangioma with hemorrhagic onset

**Anna Maria Buccoliero,[1] Flavio Giordano,[3] Federico Mussa,[3] Antonio Taddei,[2] Lorenzo Genitori[3] and Gian Luigi Taddei[1]**

Departments of [1]Human Pathology and Oncology and [2]General Surgery, University of Florence and [3]Division of Neurosurgery, 'Anna Meyer' Pediatric Hospital, Florence, Italy

**Papillary glioneuronal tumor is a recently identified low-grade brain neoplasm classified as variant of ganglioglioma. Its salient morphological characteristics are the presence of pseudopapillary structures composed of blood vessels, often hyalinized, lined by uniform small astrocytes and a proliferation of neurocytic cells, eventually admixed with ganglioid and ganglion cells. We present a case of papillary glioneuronal tumor occurring in a 15-year-old female with an unusual hemorrhagic onset. The clinical, morphological and immunohistochemical features are discussed and the published literature is reviewed. This article proposes that papillary glioneuronal tumor should be included in the differential diagnosis of patients with tumoral related brain hemorrhage.**

**Key words:** central nervous system, immunohistochemistry, intracerebral hemorrhage, mixed neuronal-glial tumors, papillary glioneuronal tumor.

## INTRODUCTION

Mixed glio-neuronal tumors represent a group of brain neoplasms showing a wide morphological, immunohistochemical and ultrastructural spectrum of glial and neuronal differentiation. They especially occur in the supratentorial region of young people and often have an indolent prognosis. Among them, the papillary glioneuronal tumor has recently been identified as an infrequent low-grade tumor and classified as a variant of ganglioglioma. Typical morphological features are pseudopapillary structures composed of frequently thickened hyalinized blood vessels lined by uniform small astrocytes and a proliferation of neurocytic cells eventually admixed with ganglioid and ganglion cells. Rabdoid, minigemistocytic, and Olig2 (a recently established oligodendroglial marker) positive cells have been recognized too.[1–16]

In this article, we describe the clinical, morphological and immunohistochemical features of a new case of papillary glioneuronal tumor diagnosed in a young girl.

## CASE REPORT

### Clinical summary

MB, a previously healthy 15-year-old girl, was admitted to the intensive care unit (ICU) because of a sudden headache followed by aphasia and coma. First, computed tomography (CT) showed a massive intraparenchymal brain hemorrhage located in the left basal ganglia and temporal lobe with intraventricular bleeding and hydrocephalus (Fig. 1). Emergency external ventricular drainage was performed to treat the hydrocephalus and raised intracranial pressure. Cerebral angiography revealed no abnormal vascular circles, while T1–T2-weighed magnetic resonance imaging (MRI) supported the diagnosis of cavernous hemangioma. Shortly afterwards the brain hemorrhage spontaneously healed without further surgery. The patient was transferred to the ward and discharged 20 days later free of neurological complaints. The lesion was not operated on because of its deep and inaccessible site. During the follow-up, serial CT and MRI revealed a progressive cystic transformation of the hemorrhage cavity into the left temporal lobe extending in the region of the homolateral thalamus. The final radiological picture, 2 years later, con-

Correspondence: Anna Maria Buccoliero, MD, Dipartimento di Patologia Umana e Oncologia, Università degli Studi di Firenze, Viale G.B. Morgagni, 85, 50134 Firenze, Italia. Email: ambuccoliero@unifi.it

Received 25 July 2005; revised and accepted 22 September 2005.

sisted of a cystic-nodular lesion located in the deep left temporal lobe in the paraventricular region; the maximum diameter of the cystic lesion was about 35 mm, while the nodular one was about 25 mm. Contrast enhancement was nodular and showed only a small solid circular part of the lesion. The new radiological diagnosis was consistent with a brain tumor or vascular malformation, such as hemangioblastoma or cavernous hemangioma (Fig. 2).

Surgery was computer-assisted by Neuronavigator (Stealth Navigation System, Medtronic, Goleta, California, USA) after a previous brain-map of eloquent areas obtained with functional MRI. Gross total removal was achieved through a left parieto-occipital transventricular route. The postoperative period was uneventful. The patient was discharged from the ICU to the ward in 1-day surgery with normal neurological examination. Postoperative CT control confirmed radical removal without abnormal contrast enhancement. Thirty-two months after the first symptoms and 12 months after the surgery the patient is alive and well.

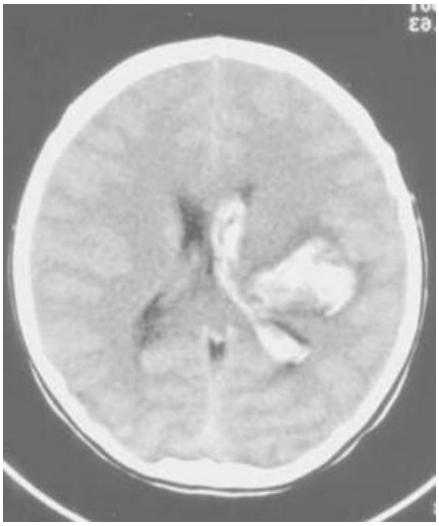

**Fig. 1** First computed tomography (CT): massive intraparenchymal brain hemorrhage located in the left basal ganglia and temporal lobe with intraventricular bleeding and hydrocephalus.

## Pathological findings

### *Methods*

Surgical samples were routinely fixed in neutral buffered formol, embedded in paraffin and stained with HE for histopathological evaluation. Immunohistochemical studies (standard Streptavidin-biotin technique) were performed. The primary antibodies used were: monoclonal antibody directed against KI-67 (clone Mib-1, 1:80 dilution; IMMUNOTECH, Marseille, France), GFAP (clone ZCG29, prediluted, Zymed Laboratory, San Francisco, California, USA), neuron specific enolase (NSE; clone MIG-N3, prediluted, BioGenex, San Ramon, California, USA), synaptophysin (SP; clone Snp 88, prediluted, BioGenex) and antibody against neurofilaments (NF; PAN clone DA2; FNP7; RMb020.11, 1:20 dilution, Zymed Laboratory). Microwave antigen enhancement was utilized for all the used antibodies. Immunohistochemical staining was performed on NEXES automated immunostainer (Ventana Medical Systems, Tucson, Arizona, USA).

The proliferation index was determined estimating the percentage of the Ki-67 positive neoplastic cells in the total tumoral cells in the most positive areas.

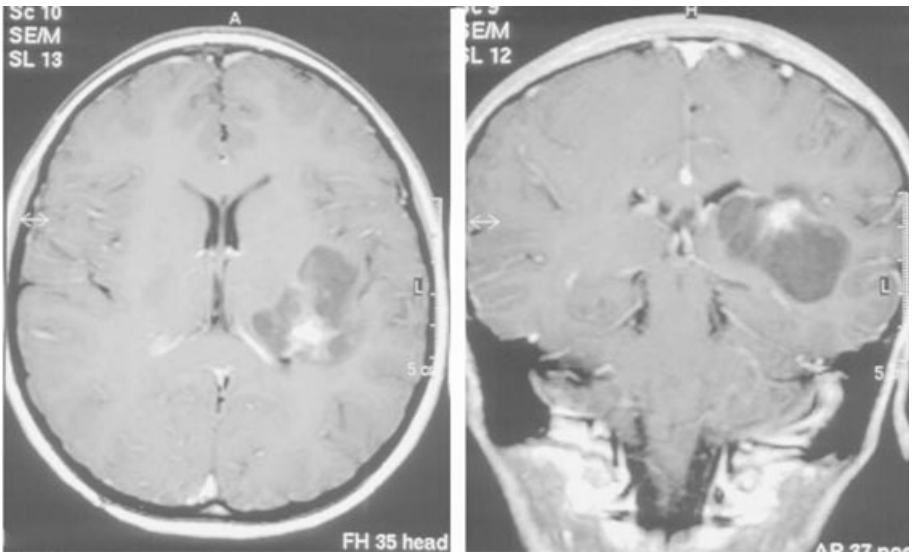


**Fig. 2** Axial (right) and coronal (left) MRI of the lesion before its surgical excision. The cystic-nodular tumor was paraventricular, located in the left deep temporal lobe and posterior thalamus; homogeneous gadolinium enhancement is seen in the nodular part.

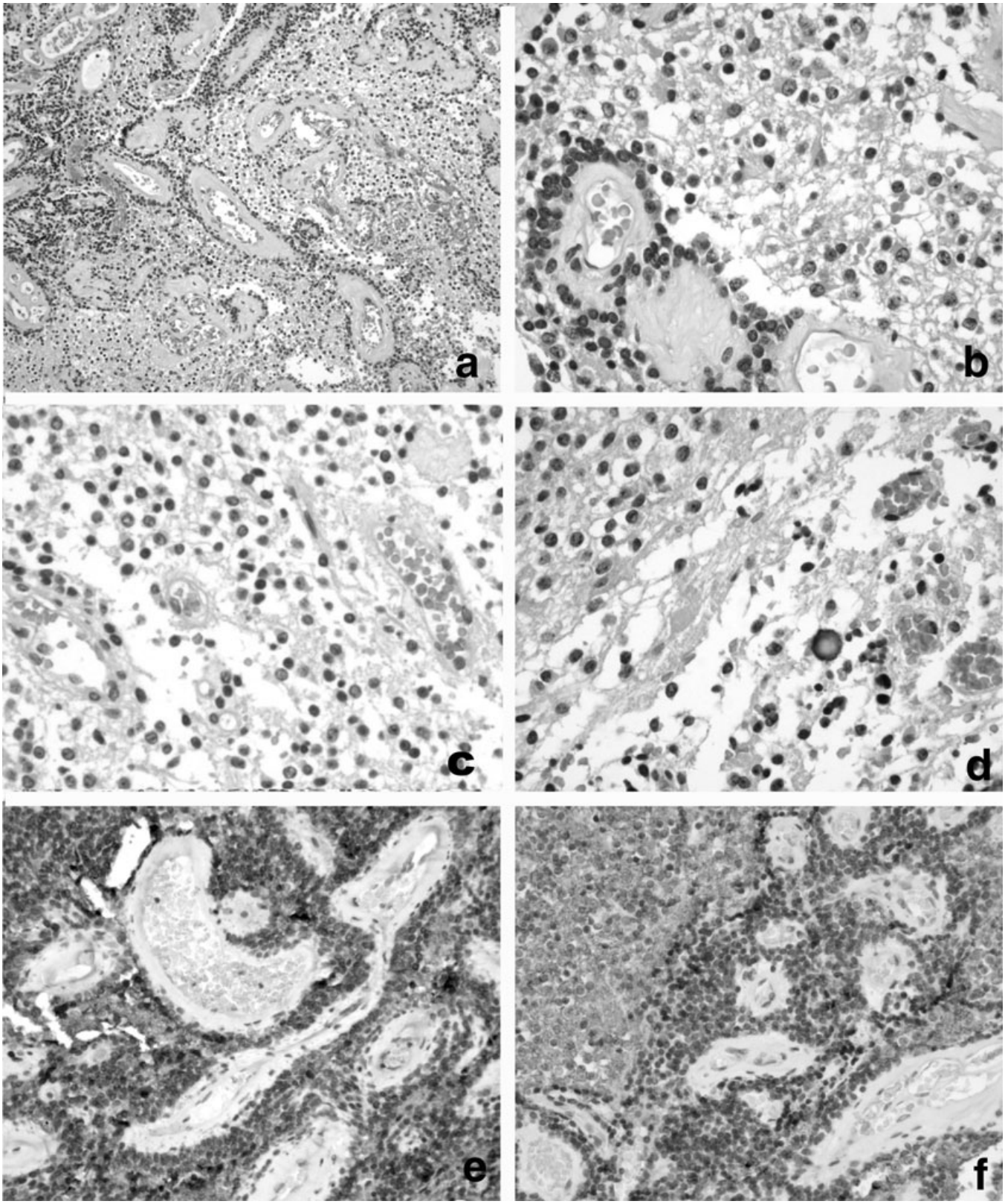


**Fig. 3** Histological and immunohistochemical features: (a–d) double architectural patterns, pseudopapillae composed of thickened and hyalinized blood vessels sheathed by a single or multistratified layer of small cells and solid areas consisted of neurocytic cells; (c,d) thin walled vessels; and (d) microcalcifications in the solid areas (HE; original magnification: a ×100; b–d ×200); GFAP (e, pseudopapillary and solid areas) and SP (f, solid areas only) positive immuno-stain (original magnification: e,f ×200).

**Table 1** Papillary glioneuronal cases reported in the international Literature

| Reference | Sex/ age | Symptoms/duration | Site/size (cm)† | Neuroimaging characteristics | | Therapy‡ | Follow-up§/ months |
|---|---|---|---|---|---|---|---|
| | | | | Lesion | Enhancement pattern | | |
| Komori 1998 | M/13 | Headache, nausea, memory loss, difficulty in comprehension and expression/8 months | Temporal left/7 | Cystic with mural nodule, calcifications | Heterogeneous | GTR | NER/45 |
| | F/30 | None | Parietal left/3 | Solid and cystic | Heterogeneous | GTR | NER/43 |
| | M/11 | Seizure/1 day | Temporal left/7 | Cystic, calcifications | Ring enhancement | PR RT | NER/12 |
| | F/27 | Seizure/1 day | Temporal right/4 | Solid and cystic, calcifications | Homogenous | GTR | NER/18 |
| | M/36 | Headache, transient visual field, impaired speech and comprehension/ 1 years | Parietal left/7 | Cystic with mural nodule | Homogenous | GTR | NER/6 |
| | F/19 | Mood swings, impaired comprehension and expression/2 years | Temporal left/1.5 | Solid | Equivocal | GTR | NER/12 |
| | F/35 | Seizure, headache/1 day | Temporal left/4 | Solid and cystic, calcifications | Ring enhancement | GTR | NER/12 |
| | M/52 | Headache/6 months | Frontal right/3 | Cystic with mural nodule | Homogeneous | GTR | NER/6 |
| | F/26 | Headache, tingling on the rightside/1 day | Frontal left/5 | Cystic with mural nodule | Homogeneous | GTR | NER/? |
| Bouvier-Labit 2000 | M/23 | Headache, visual disturbance, dorsalgias, impaired comprehension and expression/4 weeks | Parieto-occipital left/6 | Cystic with mural nodule | Heterogeneous | GTR | NER/84 |
| Prayson 2000 | M/18 | Headache, visual disturbance/2 months | Parieto-occipital left/5.3 | Cystic | Ring enhancement, scattered internal enhancement | GTR | NER/3 |
| Barnes 2002 | M/4 | Headache/6 months | Temporal left/3 | Solid | Heterogeneous | GTR | NER/30 |
| Broholm 2002 | M/16 | Consciousness lost, seizures/7 months | Frontal left/2.8 | Cystic with mural nodule | Ring enhancement, mural nodule enhancement | GTR | NER/6 |
| Tsukayama 2002 | F/75 | Vertigo, vomiting/ unclear | Frontal left/5 | Cystic with mural nodule | Homogeneous | PR | NER/20 |
| Lamszus 2003 | F/24 | Seizures/6 months | Parieto-occipital left/1 | Cystic | Absent | GTR | NER/3 |
| Borges 2004 | F/14 | Headache, decrease in musclestrength, seizure/18 months | Fronto-parietal left/5.5 | Cystic | Ring enhancement | GTR | NER/56 |
| Stosic-Opincal 2005 | F/16 | Nausea, vomiting, fever, headache/unclear | Parietal right/3.5 | Cystic | Ring enhancement and septations | PR | NER/36 |

†Greatest dimension
GTR, gross total resection; NER, no evidence of recurrence; PR, partial resection.

*Results*

Histological examination of the tumor revealed two different architectural patterns: pseudopapillary and solid. Pseudopapillae were composed of blood vessels, often thickened and hyalinized, sheathed by a single or multistratified layer of uniform small cells with ovoid-round nuclei and scant cytoplasm; solid areas consisted of isomorphous cells with round nuclei and wide, clear cytoplasm mimicking oligodendroglioma or neurocytoma. Thin walled vessels were numerous in the solid areas. Lymphocytic infiltrates, microcalcifications, hemosiderin deposits and microhemorrhagic areas were observed. The lesion did not show necrosis or mitoses. Reactive pilocytic gliosis with Rosenthal fiber and granular bodies, and wide cicatricial fibrous areas were identified along the peritumoral tissue (Fig. 3).

Immunohistochemical examination revealed both neuronal and glial differentiation. Specifically, the cells lining the pseudopapillae and the oligodendrocyte-like cells stained positively for GFAP, NSE and NF whereas the oligodendrocyte-like cells only stained positively for SP (Fig. 3).

The Ki-67 index was very low (about 1%).

## DISCUSSION

Papillary glioneuronal tumor is a low-grade uncommon neoplasm recently listed as a rare variant of ganglioglioma in the World Health Organization (WHO) classification of tumors of the nervous system.[1] It has been named in this way because of its papillary feature (due to the dehiscence of the cells about the vessels) and because of its double astrocytic and neuronal differentiation at either the morphological, immunohistochemical or ultrastructural level.

Papillary glioneuronal tumor was first described by Komori *et al.* in 1998 as a novel clinico-pathologic entity.[2] Nevertheless, morphologically similar tumors have been previously reported under many different names, i.e. pseudopapillary neurocytoma with glial differentiation, atypical extraventricular neurocytic neoplasm and pseudopapillary ganglioneurocytoma.[17–24]

To the best of our knowledge, 17 cases complete with clinical and histopathological data have been documented to date in the English language literature (one additional case lacked exhaustive clinical and histopathological data; six cases were reported in the Polish and Japanese literature).[2–12,15,16,24–26] The analysis of these cases supports the proposition that papillary glioneuronal tumor more often affects young people (mean age at the diagnosis: 26 years, range 4–75 years) without gender predominance (female : male ratio about 1:1). The first symptoms, commonly headache (59%) and seizures (35%), appear an average of 6 months (range 1 day-2 years) before diagnosis. It typically arises in the supratentorial region (all reported cases) primarily involving the left cerebral hemispheres (82%). Common neuroimaging characteristics are a cystic appearance (88%) and the presence of contrast enhancement (88%; ring enhancement 35%; homogeneous 29%; heterogeneous 24%). Follow-up data indicate a benign outcome with no evidence of recurrence during intervals ranging from 3 months to 7 years (Table 1).[2–12,15] Histopathological features of papillary glioneuronal tumor are similar in all reported cases, invariably reproducing the first description of this tumor by Komori.[2]

The main peculiarity of our case is the onset with a massive brain hemorrhage.

The frequency of intracranial hemorrhage in patients with intracranial neoplasms varies in the different series from 2% to 5%. It may occur in all central nervous system tumors to a varying degree and extent and may even be massive. These massive ones mostly occur in more malignant tumors, such as glioblastoma or metastases. Nevertheless, benign tumors, such as pituitary adenoma, pilocytic astrocytomas or meningiomas, may also bleed to the extent of a massive hemorrhage.[27–31]

Several mechanisms were advocated to explain the pathogenesis of brain tumor related hemorrhages: endothelial proliferation with subsequent obliteration of the lumen; thin walled or poorly formed vessels; perivascular necrosis with subsequent loss of vessel support; presence of intratumoral arteriovenous fistulae.[30,31]

In the present case, the hemorrhage could have resulted either from the presence of numerous thin walled vessels in the solid areas or from the abnormal hyalinized wall of the vessels in the papillary zones. Actually, in spite of an absence of previously reported papillary glioneuronal tumors showing massive brain hemorrhages, signs of previous bleeding (i.e., hemosiderin deposition, hemosiderin-laden macrophages) are often reported.[2–5,8] Consequently, we may suppose that hemorrages may occur with various gravity in papillary glioneuronal tumor.

In conclusion, papillary glioneuronal tumor should be included in the differential diagnosis of patients with tumoral related brain hemorrhage.

## REFERENCES

1. Kleihues P, Cavenee WK. *Pathology and Genetics. Tumor of the Nervous System. World Health Organization Classification of Tumours*. Lyon: IARC, 2000.
2. 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**: 1171–1183.
3. Bouvier-Labit C, Daniel L, Dufour H, Grisoli F, Figarella-Branger D. Papillary glioneuronal tumor: clinicopathological and biochemical study of one case with 7-year follow-up. *Acta Neuropathol* 2000; **99**: 321–326.
4. Prayson RA. Papillary glioneuronal tumor. *Arch Pathol Lab Med* 2000; **124**: 1820–1823.
5. Barnes NP, Pollock JR, Harding B, Hayward RD. Papillary glioneuronal tumour in a 4-year-old. *Pediatr Neurosurg* 2002; **36**: 266–270.
6. Broholm H, Madsen FF, Wagner AA, Laursen H. Papillary glioneuronal tumor – a new tumor entity. *Clin Neuropathol* 2002; **21**: 1–4.
7. Tsukayama C, Arakawa Y. A papillary glioneuronal tumor arising in an elderly woman: a case report. *Brain Tumor Pathol* 2002; **19**: 35–39.
8. Lamszus K, Makrigeorgi-Butera M, Laas R, Westphal M, Stravrou D. A parieto-occipital tumor. Neuropathology case. Available from URL: http://path.upmc.edu/cases/case323.html.
9. Borges G, Bonilha L, Menezes AS *et al.* Long term follow-up in a patient with papillary glioneuronal tumor. *Arq Neuropsiquiatr* 2004; **62**: 869–872.
10. Biernat W, Liberski PP. [Papillary glioneuronal tumor.] *Pol J Pathol* 2001; **52**: 111–112. (In Polish.)

11. Kordek R, Henning R, Jacobsen E, Kearney M. [Papillary glioneuronal tumor – a new variant of benign mixed brain neoplasm.] *Pol J Pathol* 2003; **54**: 75–78. (In Polish with English abstract.)
12. Ebato M, Tsunoda A, Maruki C, Ikeia F, Okada M. [Papillary glioneuronal tumor with highly degenerative pseudopapillary structure accompained by specific abortive glial cells: a case report.] *No Shinkei Geka* 2003; **31**: 1185–1190. (In Japanese with English abstract.)
13. McLendon RE, Provenzale J. Glioneuronal tumors of the central nervous system. *Brain Tumor Pathol* 2002; **19**: 51–58.
14. Cenacchi G, Giangaspero F. Emerging tumor entities and variants of CNS neoplasms. *J Neuropathol Exp Neurol* 2004; **63**: 185–119.
15. Stosic-Opincal T, Peric V, Gavrilovic S, Marcovic Z, Sener RN. Papillary glioneuronal tumor. *AJR Am J Roentgenol* 2005; **185**: 265–267.
16. Tanaka Y, Yokoo H, Komori T *et al.* A distinct pattern of Olig2-positive cellular distribution in papillary glioneuronal tumors: a manifestation of the oligodendroglial phenotype? *Acta Neuropathol* 2005; **110**: 39–47.
17. Kim DH, Suh YL. Pseudopapillary neurocytoma with glial differentiation. *Acta Neuropathol (Berl)* 1997; **94**: 167–191.
18. Tsuchida T, Matsumoto M, Shirayama Y, Imahori T, Kasai H, Kawamoto K. Neuronal and glial characteristics of central neurocytoma: electron microscopical analysis of two cases. *Acta Neuropathol (Berl)* 1996; **91**: 573–577.
19. von Deimling A, Janzer R, Kleihues P, Wiester OD. Pattern of differentiation in cortical neurocytoma: an immunohistochemical study of eleven biopsies. *Acta Neuropathol (Berl)* 1990; **79**: 473–479.
20. Westphal M, Stavrou D, Nausch H, Valldueza JM, Hermann HO. Human neurocytoma cells in culture show characteristics of astroglial differentiation. *J Neurosci Res* 1994; **38**: 698–704.
21. Biernat W, Zakrzewski K, Liberski PP. Case of the month. *Brain* 2000; **10**: 313–314.
22. Giangaspero F, Cenacchi G, Losi L, Cerasoli S, Bisceglia M, Burger PC. Extraventricular neoplasm with neurocytoma features. A clinicopathological study of 11 cases. *Am J Surg Pathol* 1997; **21**: 206–212.
23. Komory T, Sheithauer BW, Anthony DC, Scott RM, Okazaki H, Kobayashi M. Pseudopapillary ganglioneurocytoma. *J Neuropathol Exp Neurol* 1996; **55**: 654.
24. Shibuya M, Yamazaki H, Sugiyama M. [A case of papillary glioneuronal tumor.] *Brain Tumor Pathol* 2003; **20** (Suppl): 73. (In Japanese.)
25. Ishizawa T, Komori T, Ishizawa K *et al.* [A case of papillary glioneuronal tumor with rhabdoid cell components.] *Brain Tumor Pathol* 2004; **21** (Suppl): 65. (In Japanese.)
26. Tanaka Y, Hirato J, Makita Y, Nazato Y. [A case of papillary glioneuronal tumor.] *Brain Tumor Pathol* 2004; **21** (Suppl): 66. (In Japanese.)
27. Wakai S, Yamakawa K, Manaka S, Takakura K. Spontaneous intracranial hemorrhage caused by brain tumor: its incidence and clinical significance. *Neurosurgery* 1982; **10**: 437–444.
28. Schrader B, Barth H, Lang EW *et al.* Spntaneous intracranial haematomas caused by neoplasms. *Acta Neurochir* 2000; **142**: 979–985.
29. Licata B, Turazzi S. Bleeding cerebral neoplasms with symptomatic hematoma. *J Neurosurg Sci* 2003; **47**: 201–210.
30. Fujita K, Matsumoto S. [Intracerebral hemarrhage in brain tumors.] *No Shinkei Geka* 1980; **8**: 929–934. (In Japanese with English abstract.)
31. Lieu AS, Hwang SL, Howng SL, Chai CY. Brain tumors with hemorrhage. *J Formos Med Assoc* 1999; **98**: 365–367.