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Case Report

Adult cerebral high-grade glioneuronal tumor with perivascular or pseudopapillary growth co-existing with low-grade tumor: a case report

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Abstract: An unusual, small cell-predominant, high-grade glioneuronal tumor in the occipital lobe of a 49-year-old man that co-existed with a low-grade tumor is reported. The tumor consisted of two distinct components: the major component was a dense proliferation of primitive small cells showing bidirectional neuronal and glial differentiation; and the minor component consisted of a proliferation of well-differentiated astrocytes intermingled with mature neuronal cells. In the former component, perivascular pseudorosette-like or pseudopapillary growth reminiscent of ependymoma or papillary glioneuronal tumor (PGNT), respectively, was prominent, and hypertrophic astrocytic cells were located just outside the central blood vessels. Small cells were immunoreactive for Olig2, synaptophysin, and, less frequently, for glial fibrillary acidic protein. The low-grade component included Rosenthal fibers, hemosiderin deposition, and perivascular lymphocytic infiltration, thus closely resembling ganglioglioma. Cytogenetic studies did not demonstrate any mutations or rearrangements of the genes *IDH1*, *IDH2*, *H3F3A*, *BRAF, FGFR1*, or *TERT* promoter. The tumor recurred and spread along the ventricular surface three years after total removal. The small cell-predominant, high-grade component was considered to have evolved from the ganglioglioma-like, low-grade component. The histopathologic resemblance of the high-grade component to PGNT was a special feature.

Keywords: Adult, cerebrum, glioneuronal tumor, perivascular growth

Introduction

Glioneuronal tumors of the central nervous system form a heterogeneous group consisting of many different entities that share a common feature, i.e., mixed neuronal and glial cell proliferation [1]. Their incidence is relatively low, but they show a wide variety of pathologic features, as well as biological behavior, and the underlying genetic abnormalities are also diverse. In particular, glioneuronal tumors arising in adulthood and showing malignant clinical behavior are rare and poorly characterized [1, 2]. The details of each case are therefore needed, instead of hastily assigning them to the existing categories.

The clinicopathologic and cytogenetic findings of an unusual case of high-grade glioneuronal tumor that co-existed with a low-grade tumor in the occipital lobe of a middle-aged man are reported. Primitive small cells comprising the high-grade component showed bidirectional neuronal and glial differentiation and formed perivascular pseudorosette-like or pseudopapillary structures resembling those seen in ependymoma or papillary glioneuronal tumor (PGNT), respectively.

Clinical history

The patient was a 49-year-old male office worker, who had noticed mild clumsiness of the left hand and frequent minor problems while driving a car in the last month. He had never had epileptic seizures. He consulted a physician because of headache and dizziness starting three days earlier. Head computed tomography (CT) showed a mass lesion in the right occipital lobe, and he was referred to our hospital.

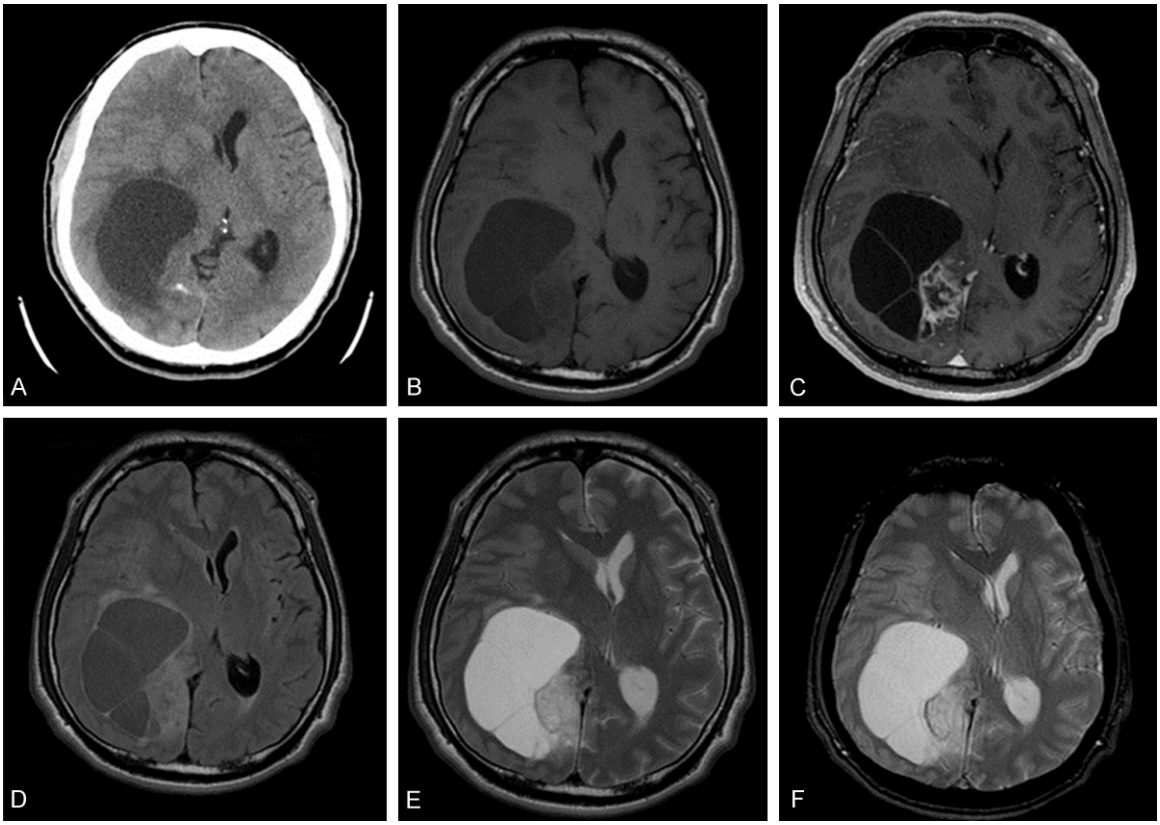

Figure 1. Preoperative head CT (A) and MRI (B-F). A large cystic tumor occupying the medial region of the right occipital lobe is seen. A heterogeneously enhanced, mural nodule-like, solid component is located on the medial wall of the unilocular cyst. (A: CT, B: T1-weighted image, C: T1-weighted image with contrast enhancement, D: Fluid-attenuated inversion recovery image, E: T2-weighted image, F: T2-star image).

On admission, visual disturbance (left homonymous hemianopsia) and mild paresis of the left upper limb were noted, and CT and magnetic resonance imaging (MRI) demonstrated a large cystic tumor, measuring 73 × 70 × 63 mm^3, that involved the right occipital cortex and white matter and had a mural nodule-like, solid component, measuring 43 mm in diameter, on the medial aspect (**Figure 1**). The solid portion was heterogeneously enhanced. Perilesional edema was associated with the tumor, causing midline shift.

After drainage from the cystic portion, the patient underwent partial occipital lobectomy (**Figure 2A**). A pathologic diagnosis of high-grade glioma was made, and the patient received postoperative chemotherapy (temozolomide and bevacizumab) and radiation therapy (60 Gy in 30 fractions over 6 weeks). The patient's postoperative course was uneventful, but a small enhancing nodular lesion appeared at the operative site 15 months later (**Figure 2B**), and he underwent re-operation following gamma-knife surgery. Pathologic examination of the resected tissue showed delayed radiation necrosis without residual or recurrent tumor, and chemotherapy was resumed. However, multifocal hyperintensity lesions involving the lateral ventricular wall appeared on MRI four months later (**Figure 2C**), and left hemiparesis, cognitive impairment, and somnolence gradually developed. At the time of this writing (48 months after the first operation, the patient now being 53 years old), the patient is following a slowly downhill course under best supportive care.

Pathological findings

The tumor was intra-axial and located in the medial portion of the right occipital lobe, involving both the cortex and white matter. It was predominantly cystic and contained a mural nodule-like, solid portion. The solid portion was slightly hard and yellow-brown in color, but

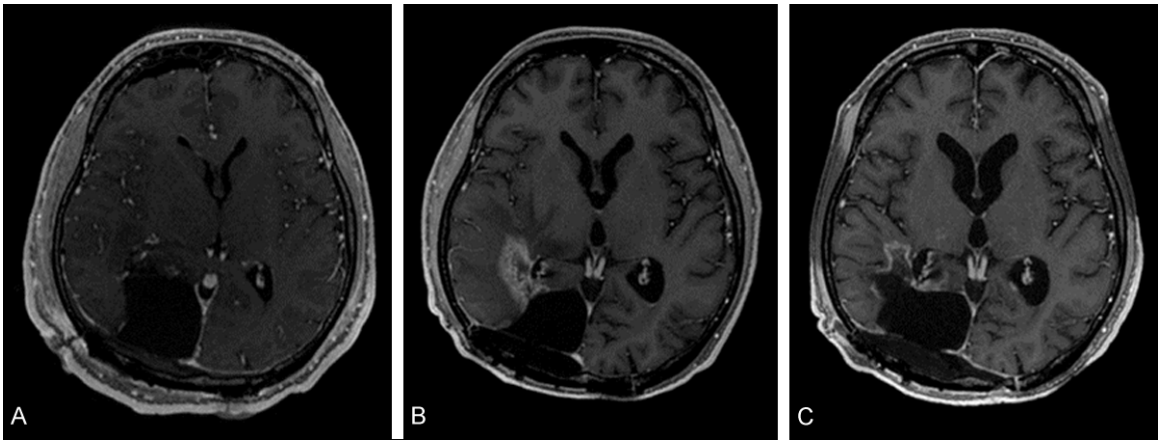

Figure 2. Postoperative MRI (contrast-enhanced T1-weighted images). A. The postoperative partial defect in the right occipital lobe is seen. B. Fifteen months after the operation, a small, enhancing nodular lesion has appeared at the operation site. C. Three and a half years after the operation, multiple, small enhancing lesions have emerged on the lateral ventricular wall.

necrosis or hemorrhage was not grossly apparent.

Histopathology

The tumor consisted of two distinct components that were closely admixed with each other in some areas. The major component consisted of a dense proliferation of primitive, small round or short spindle cells having round or elliptical nuclei and scant, palely eosinophilic and fibrillary cytoplasm (**Figure 3A**). Tumor cells mainly exhibited a perivascular pseudorosette-like arrangement resembling ependymoma, but ependymal rosettes/canals were absent. In some areas, pseudopapillary structures reminiscent of PGNT were observed (**Figure 3B**). In these areas, small blood vessels were surrounded by a paucicellular fibrillary zone, in which hypertrophic astrocytic cells having elongated cytoplasmic processes abutted the vascular walls (**Figure 3C**). Primitive small cells were located outside of the perivascular fibrillary zone. The tumor vasculature was well-developed and exhibited fibrous thickening of the walls, but glomeruloid microvascular proliferation was not found. In small areas, tumor cells showed a reticular arrangement on the palely basophilic, myxoid matrix.

The nuclei of small tumor cells had a moderate amount of evenly distributed chromatin and small basophilic nucleoli, and, although mitotic figures were scattered, the nuclear atypia and pleomorphism were mild. In small areas, round tumor cells with clear cytoplasm showed a pavement arrangement partitioned by delicate blood vessels showing a “chicken-wire” feature (**Figure 3D**). Many calcospherites were observed in these areas. Nuclear palisading was also found in a few areas (**Figure 3E**). Neoplastic small cells showed infiltrative growth and invaded the adjacent cerebral cortical tissue. A few large foci of ischemic necrosis were found, but pseudopalisading of tumor cells was not seen around the necrotic foci.

The minor component formed a small nodule showing expansive growth against the surrounding non-neoplastic tissue and showed features of a low-grade glioneuronal tumor. It consisted of diffuse proliferation of astrocytes having slightly pleomorphic, vesicular nuclei and eosinophilic cytoplasm forming thick or slender processes (**Figure 4A**). Its cell density was lower than that of the major component, and a small number of neuronal cells showing an uneven distribution was scattered (**Figure 4B**). A few Rosenthal fibers were found (**Figure 4C**). These histopathological features resembled those of ganglioglioma, but large, dysmorphic or binucleated neurons having distinct Nissl substance were absent. Blood vessels often exhibited marked fibro-hyalinous thickening of the walls, and perivascular deposition of hemosiderin (**Figure 4D**) and lymphocytic infiltration (**Figure 4E**) were also focally seen.

Immunohistochemical findings

Immunohistochemical studies were performed using an automated immunostainer (Leica

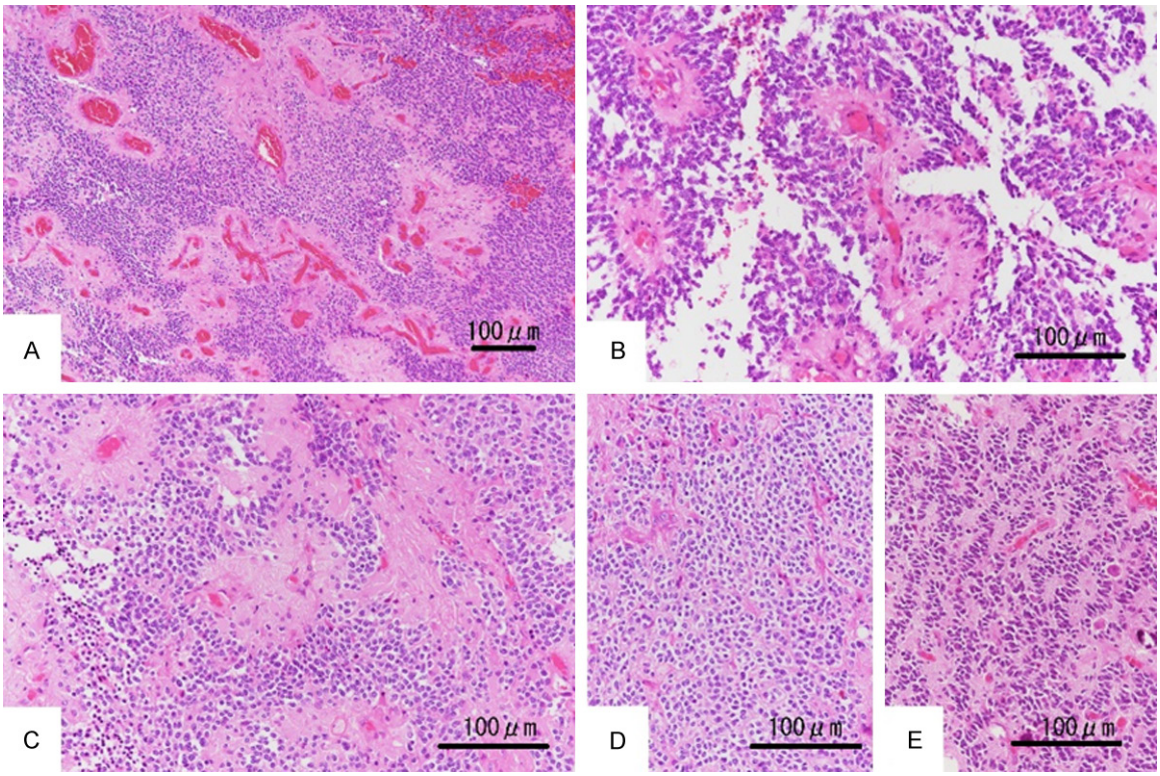

Figure 3. Histopathologic findings of the high-grade component of the tumor (hematoxylin-eosin stain). A. Small round or short spindle cells show dense proliferation around small blood vessels, forming perivascular pseudorosette-like structures (×100). B. Pseudopapillary structures formed by the dehiscence of tumor cells are occasionally observed. Blood vessels show mild mural thickening (×200). C. Tumor cells show astrocytic differentiation in the perivascular paucicellular zone (×200). D. In some areas, compact proliferation of round cells with clear cytoplasm is partitioned by delicate blood vessels, producing an oligodendroglioma-like appearance (×200). E. Nuclear palisading is found in small areas (×200). Scale bars: 100 μm.

Bond-Max, Leica Biosystems, Wetzlar, Germany). Monoclonal or polyclonal primary antibodies against the following substances were used: glial fibrillary acidic protein (GFAP) (mouse monoclonal, clone EP672Y, Roche Diagnostics, Rotkreutz, Switzerland, prediluted), nestin (rabbit polyclonal, Immune-Biological Laboratories (IBL), Takasaki, Japan, 1:100), oligodendrocyte transcription factor 2 (Olig2) (rabbit polyclonal, IBL, 1:200), neuronal nuclear antigen (NeuN) (rabbit polyclonal, Abcam Inc., Cambridge, MA, USA, 1:500), S-100 protein (rabbit polyclonal, Leica Biosystems, 1:500), alpha-thalassemia/mental retardation syndrome X-linked protein (ATRX) (rabbit polyclonal, Sigma Aldrich, St Louis, MO, USA, 1:500), epithelial membrane antigen (EMA) (mouse monoclonal, clone M0613, Dako, Glostrup, Denmark, 1:400), synaptophysin (mouse monoclonal, clone 27G12, Leica Biosystems, 1:200), chromogranin A (mouse monoclonal, clone 5H7, Leica Biosystems, 1:400), CD34 (mouse monoclonal, clone QBEnd/10, Leica Biosystems, 1:400), p53 (mouse monoclonal, clone DO-7, Leica Biosystems, 1:400), isocitrate dehydrogenase 1 (IDH1)-R132H (mouse monoclonal, clone H09, Dianova GmbH, Hamburg, Germany, 1:100), histone 3 (H3)-K27M (mouse monoclonal, clone ABE419, EMD Millipore, Billerica, MA, USA, 1:1,000), trimethylation at lysine 27 of H3 (H3K27me3) (mouse monoclonal, clone C15410195, Diagenode, Seraing, Belgium, 1:1,250), and Ki-67 (mouse monoclonal, clone MIB-1, Dako, 1:100).

In the small cell-predominant component, although small tumor cells uniformly exhibited immunoreactivity for Olig2 (**Figure 5A**), only a small number of them were immunoreactive for GFAP (**Figure 5B**). Most small cells were immunoreactive for synaptophysin (**Figure 5C**), but not for nestin or NeuN. Hypertrophic astrocytic cells abutting blood vessels were immunoreactive for GFAP, S-100 protein, and nestin (**Figure**

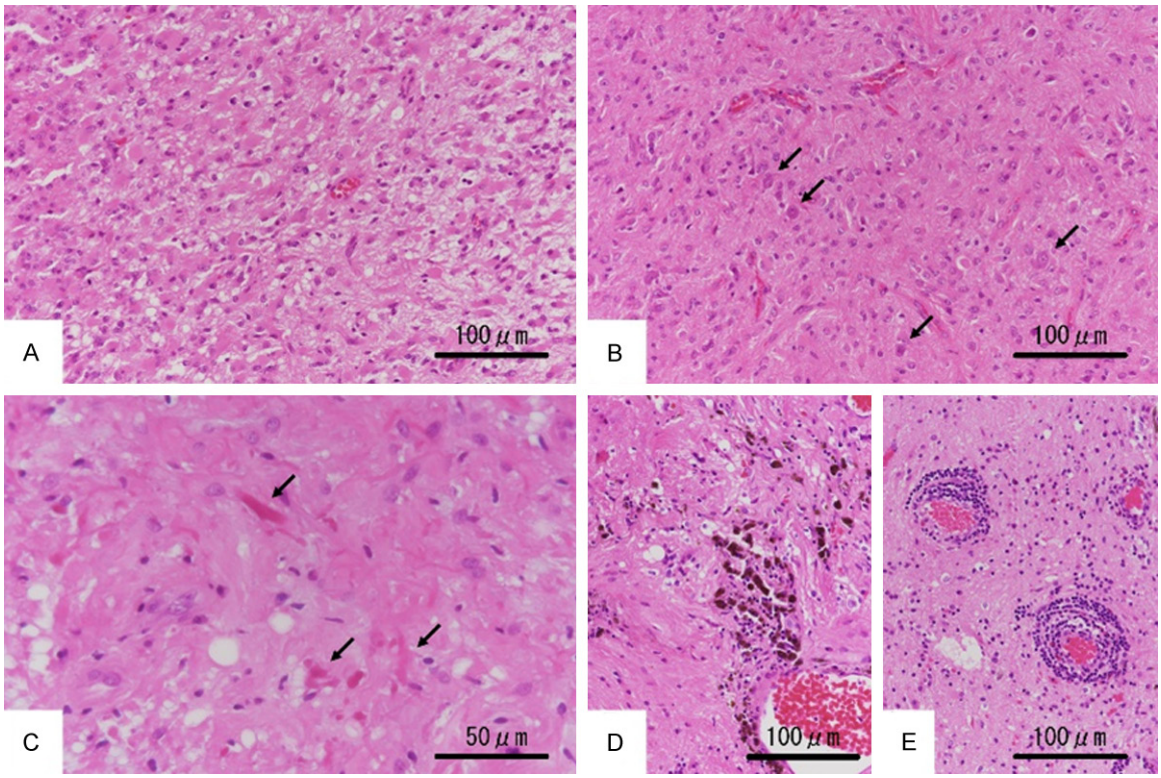

Figure 4. Histopathologic findings of the low-grade glioneuronal component (hematoxylin-eosin stain). (A) Well-differentiated astrocytes having eccentric nuclei and abundant, eosinophilic cytoplasm show diffuse growth (×200). (B) Few neuronal cells showing an irregular distribution (arrows) are found in the neuropil-like matrix (×200). (C) A few Rosenthal fibers are observed (arrows) (×400). (D) Perivascular hemosiderin deposition (×200) and (E) lymphocytic infiltration are seen (×200). Scale bars: 100 μm (A, B, D, E) and 50 μm (C).

5D) but not for Olig2. In the low-grade glioneuronal component, some hypertrophic astrocytes were strongly immunoreactive for nestin (**Figure 5E**), and neuronal cells were positive for NeuN (**Figure 5F**), although the NeuN-immunoreactivity was less intense than that of normal cortical neurons, suggesting that these neurons were not entrapped, but neoplastic [1]. A meshwork of synaptophysin-positive fine fibrils was observed in the background, and the surface of some large neurons was decorated by synaptophysin-positive, coarse granules (**Figure 5G**). Finely arborizing, dendritic cytoplasmic processes ("ramified cells") [1] were focally observed with CD34-immunostaining (**Figure 5H**). Throughout the whole tumor, no cells immunoreactive for EMA, chromogranin A, IDH1-R132H, or H3-K27M were found, and H3K27me3 was wild type. The nuclear expression of ATRX was retained, and p53 showed a wild-type staining pattern. The Ki-67 labeling indices were 23.9% and 7.6% in the high-grade component and low-grade component, respectively.

Molecular genetic findings

For the cytogenetic studies, genomic DNA was extracted from formalin-fixed, paraffin-embedded tumor tissue. The extracted DNA was amplified by polymerase chain reaction (PCR) and sequenced using the primer sets for *IDH1/2*, *H3F3A*, *BRAF*, *FGFR1*, and the *TERT* promoter. PCR products were sequenced using a SeqStudio Genetic Analyzer (Applied Biosystems, Foster City, CA, USA) with a Big Dye Terminator v.1.1 Cycle Sequencing Kit (Applied Biosystems) in accordance with standard procedures. No mutations or rearrangements were observed in the above-mentioned genes, and the hot spots of these genes were wild type.

Targeted next-generation sequencing using an Ampliseq Cancer Hotspot Panel version 2 (Life Technologies, Grand Island, NY, USA) was then performed. The high-grade and low-grade components were examined separately. Although

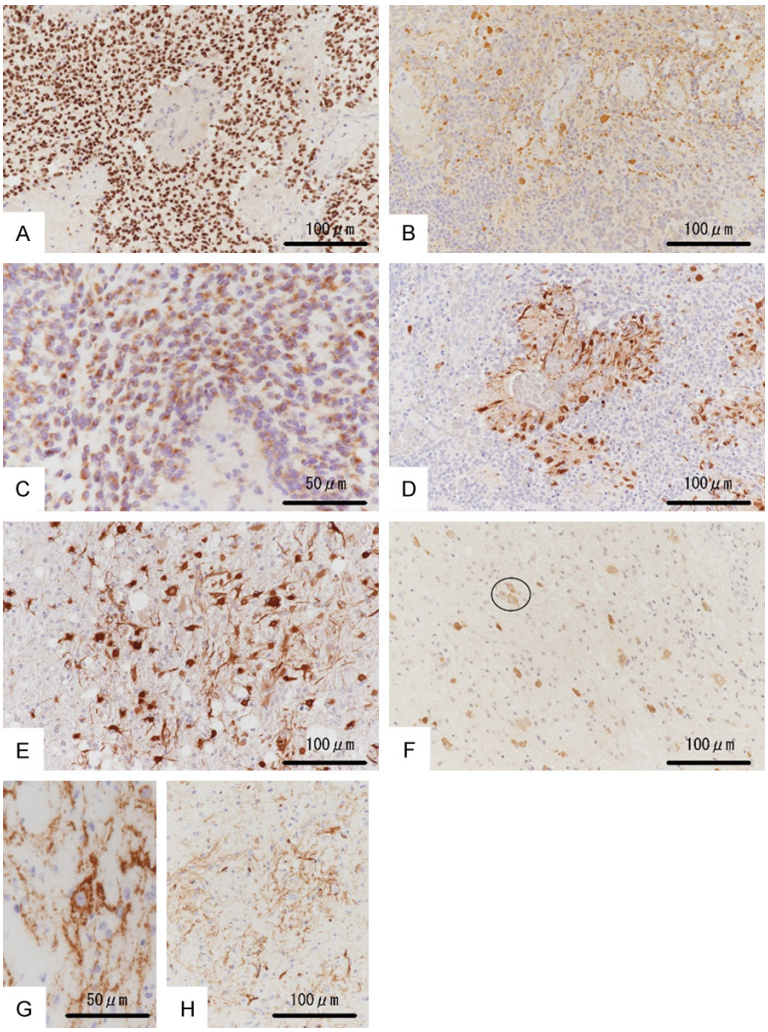

Figure 5. Immunohistochemical findings. (A) In the high-grade component, small tumor cells uniformly show nuclear immunoreactivity for Olig2 (×200). (B) Perivascular hypertrophic astrocytic cells and a few small tumor cells are immunoreactive for GFAP (×200). (C) The majority of small tumor cells are immunoreactive for synaptophysin (×400). (D) Hypertrophic astrocytic cells abutting blood vessels are clearly depicted with immunostaining for nestin (×200). (E) In the low-grade component, neoplastic astrocytes show intense immunoreactivity for nestin (×200). (F) Neuronal cells, some of which show abnormal clustering (encircled), are weakly immunoreactive for NeuN (×200). (G) The surface of some large neurons is decorated by synaptophysin-positive, coarse granules. Mesh-like, finely fibrillary immunoreactivity is found on the background (×400). (H) CD34-immunoreactive, dendritic cytoplasmic processes are focally observed (×200). Scale bars: 100 μm (A, B, D-F, H) and 50 μm (C, G).

point mutations involving a few genes were detected in each component, they were interpreted as false-positive results and could not be considered significant, because the quality of the examined materials was, unfortunately, suboptimal, and only a small number of cells could be analyzed.

Discussion

The cerebral tumor in the present patient consisted of two distinct components: a high-grade component consisting predominantly of primitive small cells that showed bidirectional neuronal and glial differentiation; and a low-grade, mixed glioneuronal component. In the former, which was predominant in amount, a pseudorosette-like arrangement with a perivascular paucicellular zone suggested ependymal differentiation, but true ependymal rosettes/canals were not observed, and tumor cells were completely negative for EMA. On the other hand, although the low-grade component showed features resembling low-grade diffuse astrocytoma, this was ruled out by the cytogenetic studies (no mutations in the *IDH1* or *IDH2* genes) and also by the presence of a small number of neoplastic neuronal cells. The most reasonable interpretation is that the small cell-predominant, high-grade component evolved secondarily from a low-grade glioneuronal tumor (precursor lesion) and overgrew the latter.

The low-grade glioneuronal component resembled gangliglioma in its histopathologic appearance. Gangliglioma is a prototypic glioneuronal tumor arising mostly in the temporal lobe of young adults and contains neoplastic neuronal cells showing a dysmorphic appearance [1, 3-7]. The presence of a large cyst within the tumor is common, and degenerative features such as Rosenthal fibers or eosinophilic granular bodies are frequently observed [1, 3, 4, 6, 7]. The present case shared these findings. Furthermore, the surface of some large neuro-

nal cells was decorated by synaptophysin-positive, coarse granules [8], and finely arborizing, dendritic cytoplasmic processes immunoreactive for CD34, a stem cell marker transiently expressed during early neurulation and also in gangliogliomas [1, 5, 9], were noted. These findings suggest that the low-grade component in the present case was closely akin to gangliogliomas.

However, the present tumor also differed from gangliogliomas in several clinical and pathologic aspects: the patient was middle-aged, there was no clinical history of epileptic seizures, and the occipital lobe is a rare site for the occurrence of gangliogliomas [1]. Dysmorphic and chromogranin A-positive ganglion cells [1, 4] were not observed, and *BRAF* mutation, a genetic abnormality frequently seen in gangliogliomas [1, 7, 10], was absent.

Anaplastic transformation of low-grade glioneuronal tumors occurs either primarily (*de novo*) or, rarely, as a secondary phenomenon mostly after radiation therapy [4, 7, 11-13]. However, the diagnostic criteria for anaplasia in these glioneuronal tumors remain controversial [1, 5]. Anaplastic transformation usually occurs in the glial component [1, 4, 5, 7, 12]. Lucas et al. reported cases of the divergent evolution of the pleomorphic xanthoastrocytoma (PXA) and gangliogliomas components from a common *BRAF* p.V600E-mutant precursor lesion and suggested the possibility that some PXAs may represent tumors that transformed from a gangliogliomas precursor lesion [14]. On the other hand, rare cases in which the anaplastic transformation involved the neuronal component [13, 15] or both neuronal and glial components [11, 16, 17] have been documented.

In the present case, the majority of small cells in the high-grade component were immunoreactive for both Olig2 and synaptophysin. These cells did not express NeuN and were considered primitive or immature neuronal cells. Olig2-positive, small round cells are frequently observed in various glioneuronal tumors and, although they have heterogeneous characteristics, they express both neuronal and glial phenotypes [18]. There are several reports of anaplastic gangliogliomas showing small cell-predominant histopathologic features [13, 15, 19, 20]. On the other hand, hyperplastic astrocytic cells in the perivascular region showed expression of nestin, the primitive neural cytoskeletal protein that is expressed in gangliogliomas [21, 22]. Kawataki et al. reported a case of *de novo* anaplastic gangliogliomas and suggested that the tumor originated from neural stem cells expressing nestin [17]. In their case, tumor dissemination occurred through cerebrospinal fluid (CSF). In the present case as well, astrocytic tumor cells expressed nestin, and multiple periventricular lesions probably formed by CSF dissemination developed after the operation.

One of the intriguing aspects of the present case was the formation of prominent perivascular pseudorosette-like or pseudopapillary structures in the small cell-predominant, high-grade component. Well-differentiated astrocytic cells covered the vascular wall, and the primitive small cells were located outside of them. Similar structures are seldom seen in gangliogliomas [23] or other glioneuronal tumors except PGNT. PGNT is a rare type of low-grade glioneuronal tumor preferentially arising in the cerebrum of adolescents or young adults [1, 24, 25]. It is characterized by a prominent pseudopapillary architecture with hyalinized blood vessels surrounded by astrocytes, associated with sheets of neurocytes mingled with ganglion cells within the interpapillary area [1, 24, 25]. A fusion between *SLC44A1* and *PRKCA* genes is a specific genetic abnormality of this tumor [26]. Tanaka et al. demonstrated that oligodendrocyte-like small cells in PGNT were immunoreactive for Olig2 and perivascular astrocytic cells were immunolabeled for nestin [25]. The neuroepithelial stem cell origin of PGNT has been proposed on the basis of the co-expression of GFAP, synaptophysin, and CD133 in neoplastic cells [27], and PGNT can exhibit atypical morphology that occasionally resembles gangliogliomas [1]. A rare case of gangliogliomas having *PRKAR2B-BRAF* fusion that was recently reported by Oon et al. [23] contained a component featuring PGNT-like pseudopapillary structures in addition to a typical gangliogliomatous component. However, in that case, a small cell-predominant, high-grade component as seen in the present case was absent. Although the histopathological resemblance between the present case and PGNT may be only superficial, rare examples of the occur-

rence of PGNT in middle-aged adults [1], atypical or frankly anaplastic PGNT [28, 29], and recurrent PGNT presenting as a ganglioglioma [30, 31], have been reported. The relationship between ganglioglioma and PGNT therefore needs to be further investigated. The origin and pathogenesis of ganglioglioma or other kinds of supratentorial glioneuronal tumors are not certain, but they most likely originate from multipotent stem cells residing in several regions of the cerebrum, including the subventricular zone and subcortical white matter [2, 22]. These cells can differentiate along neuronal and glial lineages and express CD34 [5, 9] and nestin [22].

In conclusion, the present case cannot be adequately categorized by the current classification of glioneuronal neoplasms, but the low-grade glioneuronal component suggests a close relationship to ganglioglioma. The pseudopapillary architecture with perivascular small cells and hypertrophic astrocytic cells in the high-grade component is a unique feature and may suggest a possible relationship with PGNT.

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Written informed consent to use both clinical data and pathologic material was obtained from the patient and the next of kin.

Disclosure of conflict of interest

None.

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