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CASE REPORT

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# Pleomorphic xanthoastrocytoma as a component of a temporal lobe cystic ganglioglioma: a case report

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**Abstract** We report a case of pleomorphic xanthoastrocytoma (PXA) as a component of a ganglioglioma in a 13-year-old Japanese boy. Magnetic resonance imaging showed a large cystic lesion with an enhanced mural nodule of the left temporal lobe. Microscopic examination of the tumor showed that it was composed of two distinct neoplastic components: dysplastic ganglion cells and a PXA. There were gradual transitions between the two neoplastic components, and the PXA constituted the gliomatous component of the ganglioglioma. The PXA component showed spindle-shaped and pleomorphic large cells with lipidized cytoplasm. The tumor cells were surrounded by numerous reticulin fibers. Immunohistochemically, the ganglion cells were negative for glial fibrillary acidic protein (GFAP), but showed positive staining for a 70-kDa neurofilament protein, synaptophysin, and NeuN. In contrast, PXA cells were positive for GFAP but negative for neuronal markers. Our case is therefore histologically classified as ganglioglioma with PXA as the glial component. These results suggested that PXA and ganglioglioma share a common origin and that the combination of PXA–ganglioglioma would be positioned along the spectrum between PXA and ganglioglioma. Alternatively, these results may support the hypothesis that PXA originates from glioneuronal progenitor cells capable of generating astrocytic and neuronal cell types.

**Key words** Pleomorphic xanthoastrocytoma · Ganglioglioma · Combined tumor · Glioneuronal tumor

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## Introduction

The pleomorphic xanthoastrocytoma (PXA) was first described by Kepes et al. in 1979.[1] It is characterized as a distinctive meningocerebral glioma that occurs in young subjects and has a relatively favorable prognosis. Subsequently, many additional cases have been reported worldwide, and most patients have had a long, symptom-free postoperative survival.[2] PXAs have also been shown to be immunoreactive for glial fibrillary acidic protein (GFAP), establishing their astrocytic lineage. However, over the past 20 years, there have been increasing reports of PXA with neuronal elements or composite PXA and ganglioglioma.[2–13]

Recently, we treated a patient with a PXA as a component of a temporal lobe cystic ganglioglioma. In the present study, we discuss the clinicopathological features of this unusual composite PXA and ganglioglioma.

## Materials and methods

### Case report

A 13-year-old Japanese boy visited the Department of Neurosurgery of our hospital, complaining of head injury. The boy had no events during his peri- or postnatal periods and no previous neurological disease. He was right-handed and had no neurological deficits such as hemiparesis or visual abnormality. Magnetic resonance imaging (MRI) showed a large cystic lesion with a mural nodule of the left temporal lobe on $T_1$-weighted images. On $T_1$-weighted images with gadolinium enhancement, the mural nodule was markedly enhanced (Fig. 1A). On $T_2$-weighted images, perifocal edema of the lesion was not apparent (Fig. 1B).

The patient was initially followed as an outpatient because he had no clinical symptoms. However, 1 month after the first medical examination, he showed an

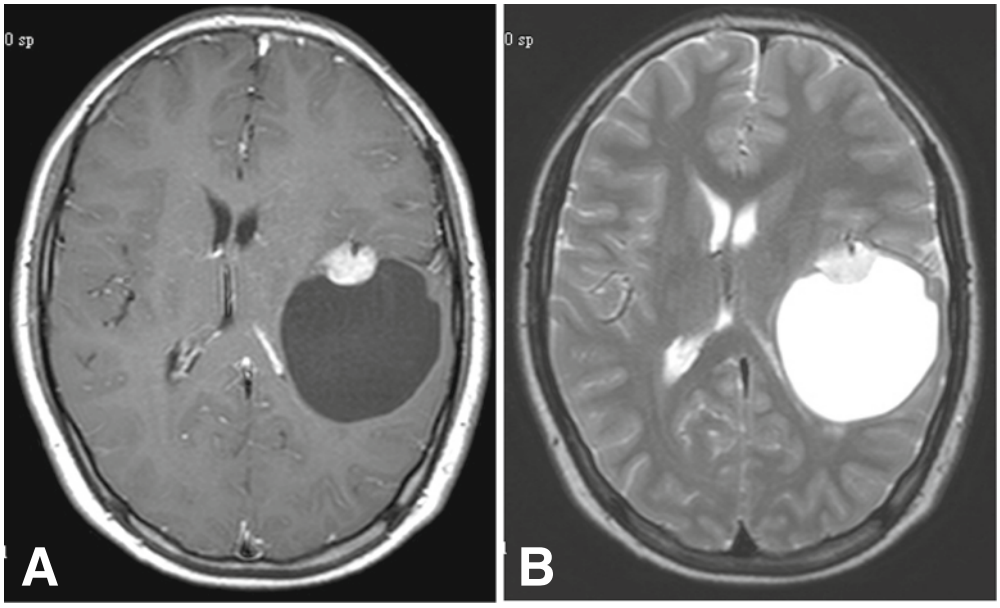


**Fig. 1.** **A** Magnetic resonance imaging (MRI) showed a large cystic lesion with a mural nodule of the left temporal lobe on $T_1$-weighted images. With gadolinium enhancement, the mural nodule was markedly enhanced. **B** MRI showed no apparent perifocal edema around the cystic lesion on $T_2$-weighted images

acceleration of intracranial pressure, as evidenced by such symptoms as bilateral abducens nerve palsy, nausea, and vomiting. Accordingly, surgical removal of the tumor was scheduled.

At surgery, a yellowish tumor was found to be localized in the cystic wall as a mural nodule. An intraoperative frozen section showed neoplastic components of the tumor in the mural nodule but no neoplastic components in another cyst wall. Therefore, resection of the mural nodule was performed, except for the part of the tumor attached to the left middle cerebral artery and the other cyst wall. The postoperative course was uneventful. The patient showed no evidence of tumor recurrence in the 7-month follow-up period.

### Histological and immunohistochemical studies

Tissue samples were fixed in 10% buffered formalin, embedded in paraffin, and processed conventionally for histology and immunohistochemistry. Sections (5 μm thick) were stained using hematoxylin and eosin (H&E) for histological evaluation. The remaining serial unstained sections were used for immunohistochemistry. Immunohistochemical studies were performed using peroxidase avidin–biotin methods (LSAB kit; DakoCytomation, Carpinteria, CA, USA) on paraffin sections following heat-induced antigen retrieval. Primary antibodies were directed toward glial fibrillary acidic protein (GFAP, prediluted; DakoCytomation), Neu N (dilution 1:50; DakoCytomation), synaptophysin(dilution 1:50; DakoCytomation), neurofilament protein (2F11, dilution 1:10; DakoCytomation), and MIB-1 (dilution 1:100; Immunotech, Marseille, France). The MIB-1 labeling index was determined by counting 1000 cells at 400× magnification in three different fields in the region of highest density of positively stained cells.

## Results

### Histological findings

Microscopic examination of the tumor showed moderate cellularity but great variation in the size and shape of the tumor cells with desmoplasia. Lymphocytic infiltration of the perivascular space was present at the periphery of the tumor (Fig. 2A). The dysplastic neurons showed large round nucleated cells with vesicular nuclei and prominent nucleoli (Fig. 2B). The high-power view showed binucleated neuronal cells (Fig. 3A). The tumor consisted of neuronal cells and astrocytic cells which, in several areas, blended with each other to create a transitional appearance. The tumor also contained nuclear pseudoinclusions in the spindle astrocytic components and numerous eosinophilic granular bodies (Fig. 3B,D). Pleomorphic astrocytic cells showed multiple lipid droplets within the cytoplasm (Fig. 3C,D).

No mitosis or necrosis was identified. Reticulin staining in the PXA-predominant area demonstrated staining around individual tumor cells (Fig. 4A). Immunohistochemically, the pleomorphic xanthic cells showed cytoplasmic immunoreactivity with GFAP (Fig. 4B), whereas dysplastic ganglion cells were negative for GFAP (Fig. 4B). In contrast, the ganglionic tumor cells showed immunoreactivity with synaptophysin, neurofilaments (Fig. 4C), and Neu-N (Fig. 4D). The tumor showed a comparatively low MIB-1 labeling index (2%).

## Discussion

PXAs are characterized as astrocytic neoplasms with relatively favorable prognosis, and are typically encountered in children and young adults, with superficial location in the cerebral hemispheres and involvement of the meninges.

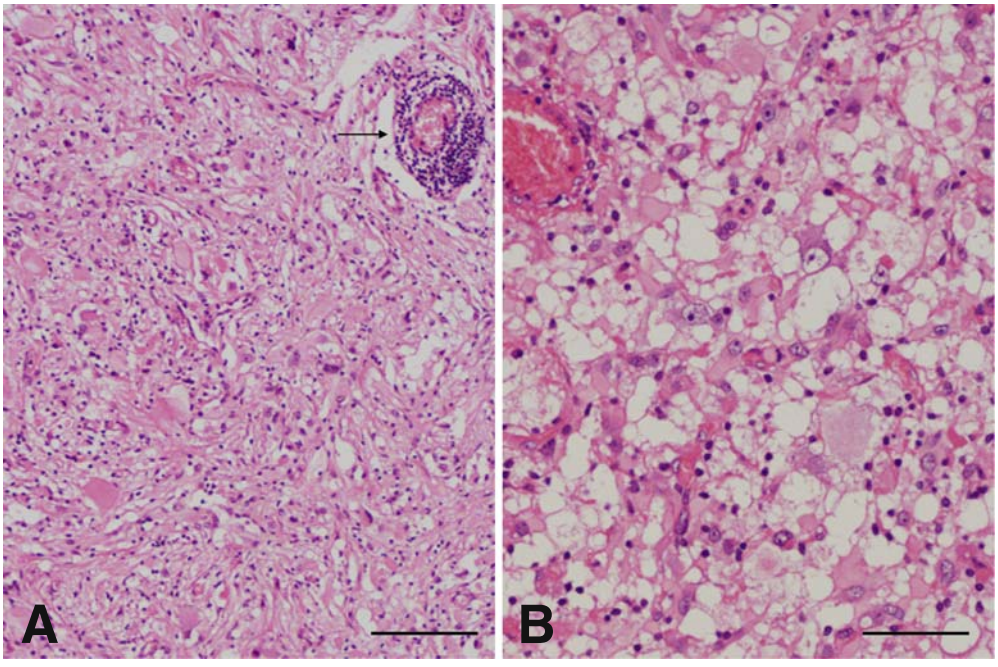


**Fig. 2.** **A** Low-power micrograph shows infiltration of the tumor with moderate cellularity but great variation in size and shape of the tumor cells. Lymphocytic infiltration of the perivascular space is present at the periphery of the tumor (*arrow*). Hematoxylin and eosin (H&E) staining. **B** Micrograph shows many large round nucleated cells with vesicular nuclei and prominent nucleoli diffusely. H&E. *Bars* **A** 130 μm; **B** 70 μm

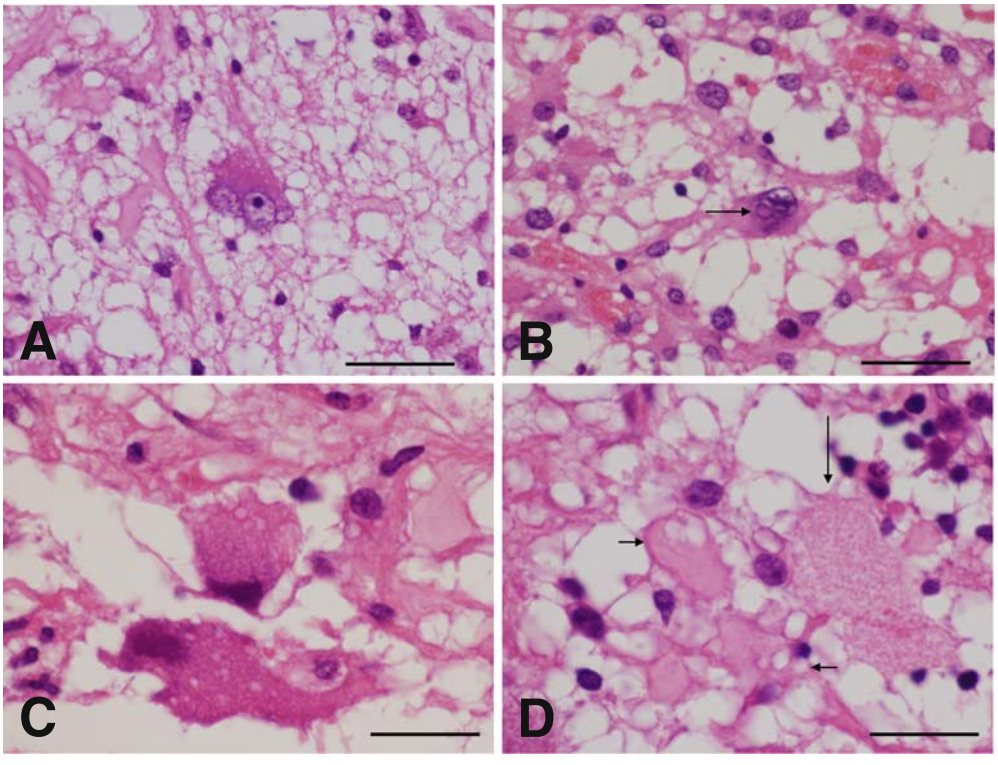


**Fig. 3.** **A** High-power view shows binucleated neuronal cells. H&E. **B** A spindle astrocytic tumor cell shows nuclear pseudoinclusions (*arrow*). H&E. **C** Pleomorphic astrocytic cells showing multiple lipid droplets within the cytoplasm. H&E. **D** Eosinophilic granular bodies are evident (*long arrow*). H&E. Lipid-filled astrocytic tumor cells are seen (*short arrow*). *Bars* **A**, **B** 40 μm; **C**, **D** 20 μm

The characteristic histological features of PXA include pleomorphic and lipidized cells expressing GFAP, and the tumors are often surrounded by a reticulin network as well as eosinophilic granular bodies.[2,14] Focal collections of small lymphocytes are also frequent.[2,14] On the other hand, gangliogliomas are characterized as well-differentiated, slowly growing neuroepithelial tumors, composed of neoplastic, mature ganglion cells alone (gangliocytoma) or in combination with neoplastic glial cells (ganglioglioma).[15,16]

A case of PXA with neoplastic neural elements was first described by Kros et al. in 1991.[3] Subsequently, many additional cases have been reported as combined or composite PXA–ganglioglioma.[3–13] The clinicopathological characteristics of the reported cases of combined or composite PXA–ganglioglioma are very similar to those of pure PXA or ganglioglioma (Table 1). These patients are generally young, and the lesions show a predilection for the temporal lobe; 12 of the 17 reported tumors have had cystic components.

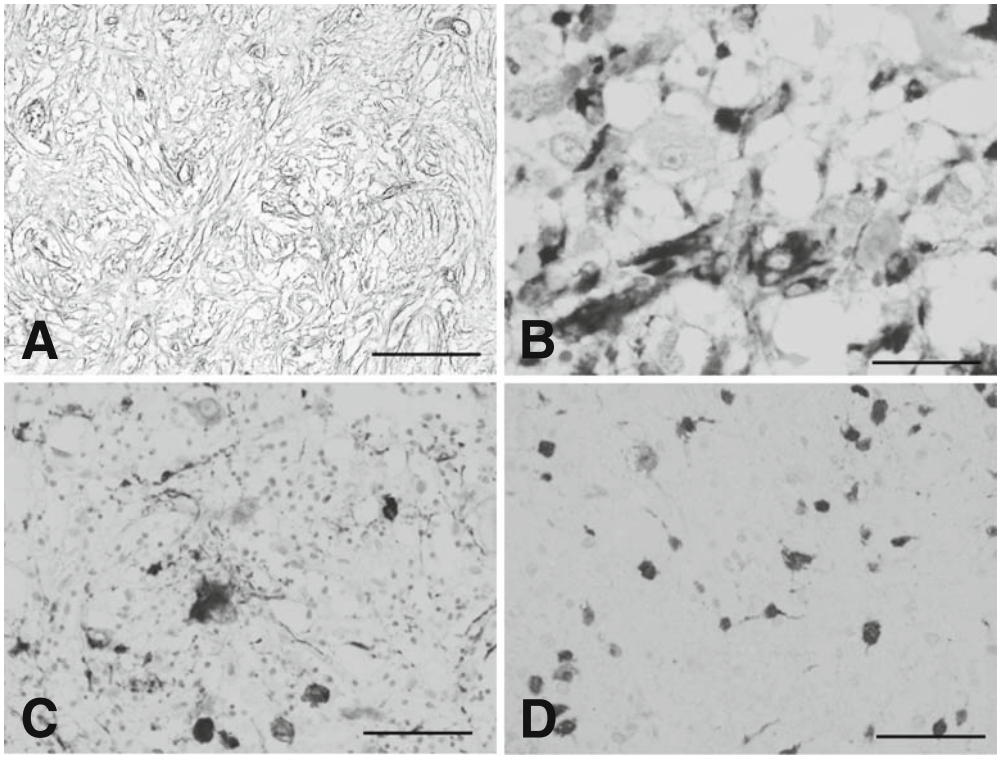


**Fig. 4.** **A** Reticulin staining in the pleomorphic xanthoastrocytoma (PXA) area demonstrates staining around individual tumor cells. **B** Glial fibrillary acidic protein (GFAP) staining is present in pleomorphic and xanthic cells. **C** Ganglionic cells show intense cytoplasmic immunoreactivity with neurofilaments. **D** Ganglionic cells show intense cytoplasmic immunoreactivity with Neu-N. *Bars* **A**, **C**, **D** 70 μm; **B** 40 μm

The clinical course of these cases has generally been characterized as low-grade malignancy. With respect to treatment of the 17 reported cases, total, subtotal, and partial resection have been performed in 8, 6, and 3 cases, respectively; 2 of 8 total resection cases and 2 of 6 subtotal resection cases, respectively, recurred.

Radiation therapy was done in 2 of 8 total resection cases and 3 of 6 subtotal resection cases, respectively. One patient with subtotal resection of the anaplastic form has been reported to have died after multiple recurrence, with a final histopathological diagnosis of glioblastoma (Table 1, case 9). In the present case, we left a small amount of tissue around the mural nodule in the operation because it was adherent to the left cerebral artery. We adopted a "wait-and-see" approach after the operation because the existence of residual tumor in the attachment to the left cerebral artery remains obscure and the role of adjuvant radiotherapy and/or chemotherapy remains uncertain.

Histologically, Perry et al. classified two types of composite PXA–ganglioglioma.[8] The first form consists of PXA and ganglioglioma elements coexisting with minimal intermingling (type 1) and the second form consists of the finding of dystrophic mono- or binucleate ganglion cells distributed individually within the substance of a PXA (type 2). Including previous publications, 11 and 6 cases have been categorized as type 1 and type 2, respectively (Table 1).

These results suggest that the finding of type 1 is indicative of ganglionic differentiation of the PXA: similarly, an acceptable explanation of type 2 is that such neoplasms represent ganglioglioma with PXA as its glial component. Actually, the spectrum of glial elements in gangliogliomas is broad and includes cell types resembling fibrillary astrocytoma, oligodendroglioma, or pilocytic astrocytoma. Some investigators have added PXA as a glial element in gangliogliomas.[5,10,11] In our case, the tumor was composed of two distinct neoplastic components – dysplastic ganglion cells and a PXA – with gradual transitions between them. Therefore, our case is best histologically classified as a ganglioglioma with a PXA as the glial component.

It is actually difficult to strictly differentiate these two types. However, considering the condition of the components of the tumor, the classification of composite PXA–ganglioglioma by Perry et al. is certainly pertinent at the present time. The histogenesis of combined or composite PXA–ganglioglioma is obscure. Powell et al. reported the detection of cytoplasmic immunoreactivity for neuronal/neuroendocrine antigens in a subpopulation of tumor cells within PXAs.[17] They concluded that abortive neuronal differentiation might occur in PXAs, suggesting a relationship between PXA and other developmental neoplasms that have a more overt neurophenotype, such as a ganglioglioma, dysembryoplastic neuroepithelial tumor, or desmoplastic ganglioglioma, and with tumors expressing ambiguous glial/neuronal lineages, such as the subependymal giant cell astrocytoma.

Hirose et al. investigated the ultrastructural features of PXA and reported that 20% of PXAs contained cells with neuronal features, as evidenced by the presence of dense-core granules, microtubules, and clear vesicles.[18] Thus, they speculated that PXA may be derived from neuroepithelial stem cells, despite the fact that PXAs were derived from subpial astrocytes in the original paper by Kepes et al.[1] Interestingly, Lach et al. described three cases of combined PXA–ganglioglioma that were associated with cortical dys-

**Table 1.** Reported cases of combined pleomorphic xanthoastrocytoma–ganglioglioma

| Patient no. | Authors | Age (years)/ gender | Tumor site and characteristics | Histopathology | Treatment and follow-up results |
|---|---|---|---|---|---|
| 1 | Kros et al. (1991)[1] | 9/F | Temporal-thalamus<br>Cystic and solid mass | Type 1 | PR<br>No recurrence at 4 years |
| 2 | Furuta et al. (1992)[4] | 16/M | Left temporal<br>Calcified, solid mass | Type 1 | TR and RT<br>No recurrence at 16 months |
| 3 | Lindboe et al. (1992)[5] | 27/M | Midline cerebellum<br>Cystic mass | Type 2 | TR<br>Recurrence at 12 years; resected, clear at 11 months |
| 4 | Kordek et al. (1995)[6] | 24/F | Left temporal<br>Cyst with mural nodule | Type 2 | TR and RT<br>No recurrence at 4 years |
| 5 | Lach et al. (1996)[7] | 50/F | Right temporal<br>Solid mass | Type 1 | TR<br>No recurrence at 18 months |
| 6 | Lach et al. (1996)[7] | 47/M | Left temporal<br>Cyst with mural nodule | Type 1 | TR<br>No recurrence at 5 months |
| 7 | Lach et al. (1996)[7] | 17/M | Right temporal<br>Cystic mass | Type 2 | TR<br>No recurrence at 12 years |
| 8 | Perry et al. (1997)[8] | 24/F | Cerebellum<br>Solid mass with calcification and multiple cysts | Type 1 | PR<br>Stable in residual tumor at 7 months |
| 9 | Perry et al. (1997)[8] | 22/M | Right temporal-parietal<br>Calcified solid mass | Type 1 | SR, CT, and RT<br>Three recurrences in 4 years |
| 10 | Perry et al. (1997)[8] | 82/M | Left frontal<br>Solid mass | Type 1 | PR<br>Unknown |
| 11 | Perry et al. (1997)[8] | 14/F | Cerebellum<br>Cystic mass | Type 1 | SR, RT, and CT<br>Recurrence at 12 months; resected, clear at 18 months |
| 12 | Vajatai et al. (1997)[9] | 32/M | Left temporal<br>Solid and cystic mass | Type 1 | TR<br>No recurrence at 12 years |
| 13 | Hessler et al. (1999)[10] | 27/M | Right frontal<br>Solid and cystic mass | Type 2 | SR<br>Stable in residual tumor at 12 months |
| 14 | Evans et al. (2000)[11] | 60/M | Cerebellum<br>Solid mass | Type 2 | SR and RT<br>No recurrence at 16 months |
| 15 | Ebato et al. (2002)[12] | 9/F | Right frontal<br>Cystic and solid mass | Type 1 | TR<br>Recurrence at 14 months; resected |
| 16 | Yeh et al. (2003)[13] | 12/M | Suprasellar<br>Solid and cystic mass | Type 1 | SR<br>Unknown |
| 17 | Present case (2008) | 13/M | Left frontal-temporal<br>Cyst with mural nodule | Type 2 | SR<br>No recurrence at 7 months |

Type 1, a tumor consisting of pleomorphic xanthoastrocytoma (PXA) and ganglioglioma elements coexisting with minimal intermingling; type 2, a tumor consisting of the finding of dystrophic mono- or binucleate ganglion cells distributed individually within the substance of a PXA; PR, partial resection; SR, subtotal resection; TR, total resection; CT, chemotherapy; RT, radiation therapy

plasia in the surrounding brain, suggesting that these lesions may represent neoplastic transformation of the residual germinal matrix in the setting of focal cortical maldevelopment.[7] Vajtai et al. have experienced a composite glioneuronal tumor comprising PXA and ganglioglioma, and they considered that PXA is a likely candidate to be included in the broad spectrum of desmoplastic supratentorial neuroepithelial tumors, with the histogenetic concept of subpial astrocytes to be redefined accordingly.[9]

Interestingly, Reifenberger et al. demonstrated that the frequency of CD 34 immunoreactivity in PXAs was within a range similar to that reported for ganglioglioma, providing further evidence of a phenotypic relationship between PXAs and gangliogliomas.[19] Evans et al. pointed out that the existence of combined PXA–ganglioglioma has been interpreted by some as evidence that PXA and ganglioglioma share a common origin and that combined PXA–ganglioglioma would be positioned along a spectrum between PXA and ganglioglioma.[11] Alternatively, these results may support the hypothesis that PXA originates from glioneuronal progenitor cells capable of generating astrocytic and neuronal cell types.

With regard to the frequency of occurrence, combined or composite PXA–ganglioglioma appear to represent only a small portion of PXAs. However, Lach et al. found that each case for which peritumoral brain tissue was available in their relatively modest collection of PXAs demonstrated some neuronal abnormalities, often detected only after multiple-level recuts of the original biopsy specimens.[7] Thus, they demonstrated that the neuronal pattern of differentiation in PXAs is substantially underestimated at the present time. Accordingly, a large study will be needed to confirm the clinicopathological features and histogenesis of combined or composite PXA–ganglioglioma.

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