Combined pleomorphic xanthoastrocytoma-ganglioglioma with *BRAF* V600E mutation: case report

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Combined pleomorphic xanthoastrocytoma (PXA) and ganglioglioma (GG) is an extremely rare tumor, with fewer than 20 cases reported. The authors report a case of combined PXA-GG in an 18-year-old man with a history of seizures. The tumor showed necrosis and the *BRAF* V600E mutation on histological examination, with no evidence of tumor recurrence 1 year after gross-total resection. The *BRAF* V600E mutation was present, which suggests that both cell lineages may share a common cellular origin.

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COMBINED or composite pleomorphic xanthoastrocytoma-ganglioglioma (PXA-GG) is a rare entity within brain tumors that has a relatively favorable prognosis. It affects mainly young patients who present with a history of seizures. The tumor is usually located superficially within the supratentorial region and has a predilection for the temporal lobe.^{1,9,24} However, a cerebellar location was reported by Evans et al.⁸

Microscopically, this mixed tumor is characterized by 2 different cellular components: the PXA component is formed by astrocytes that show marked nuclear pleomorphism, whereas the GG component is formed by ganglion-like cells. This biphasic lesion has received different names, such as combined, composite, or mixed PXA-GG.⁸ Increased mitotic activity, vascular proliferation, and necrosis are rare and normally appear in recurrent lesions.^{19,20}

We report a case of a young patient with a PXA-GG who presented with necrosis at histological examination, with no evidence of tumor recurrence at 1 year after surgery with verified gross-total resection. The *BRAF* V600E gene encodes B-raf protein, a member of the Raf kinase family of growth signal transduction protein kinases. The *BRAF* mutation was present in the histological analysis, which suggests that both cell lineages may share a common cellular origin.

Case Report

History and Examination

An 18-year-old man was admitted with acute onset of generalized seizures. Neurological examination revealed a right homonymous hemianopia without other neurological deficits. A CT scan showed a left parietooccipital lesion with heterogeneous and irregular contrast enhancement and significant mass effect. An MRI sequence revealed a solid parietooccipital tumor with a central area of necrosis, which measured 48 × 74 × 60 mm (in axial, anteroposterior, and craniocaudal axes, respectively). The lesion was hypointense on T1-weighted sequences and hyperintense and highly vascularized on T2-weighted images. Postcontrast T1-weighted images showed an intense and heterogeneous contrast enhancement. Perfusion studies revealed high cerebral blood volume and cerebral blood flow. Perilesional edema with mass effect was noted, with a midline shift of 5 mm evaluated at the level of the septum pellucidum. The initial radiological diagnosis was high-grade glioma (Fig. 1).

Operation and Postoperative Course

The patient underwent surgery in which a left superior parietal lobule approach was performed. The tumor's

ABBREVIATIONS GFAP = glial fibrillary acidic protein; GG = ganglioglioma; PCR = polymerase chain reaction; PXA = pleomorphic xanthoastrocytoma.

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FIG. 1. A and B: Postcontrast T1-weighted MR images showing a parietooccipital voluminous lesion with intense and heterogeneous contrast enhancement. **C and D:** Postoperative MR images with no evidence of tumor recurrence at 1 year after gross-total resection.

macroscopic appearance was of a gray, highly vascularized mass with necrotic areas, and it presented a well-delimited cleavage plane from the adjacent brain parenchyma. A gross-total resection was performed, which was verified on postoperative control MRI. The patient made an uneventful postoperative recovery and has been seizure free on a regimen of antiepileptic drugs for 1 year after surgery. He has no evidence of tumor recurrence after 1 year of follow-up (Fig. 1).

Pathological Findings

In the H & E–stained sections, the lesion was composed of cells with medium-to-large nuclei that had conspicuous nucleoli displaying a neuronal appearance. Dystrophic, binucleated, and overtly atypical neurons were observed. Large, highly pleomorphic nuclei and multinucleated cells with intracytoplasmic microvacuolation were found, suggesting a xanthomatous component. The areas with abundant ganglion-like cells represented approximately one-third of the lesion and were mainly located in the superficial area. The lesion showed different background patterns, with microcystic areas and basophilic, Alcian blue–positive zones. Abundant hyalinized, medium-sized vessels were observed, as well as larger vessels with perivascular lymphocytic infiltrate and signs of vascular thrombosis. Irregular necrotic areas were found, in the absence of mitotic activity. Eosinophilic granular bodies without Rosenthal fibers were abundant and easily seen. In some areas, the reticulin stain highlighted a rich reticulin network.

Immunohistochemical studies showed diffuse glial fibrillary acidic protein (GFAP) and synaptophysin expression in cells with neuronal differentiation. Some cells showed divergent differentiation and expressed both GFAP and synaptophysin (Fig. 2). A patchy expression of neurofilaments and p16 was found, but no CD34 expression could be seen. No IDH1 R132H mutation was found by immunohistochemistry. The proliferative activity of the tumor was evaluated using the Ki 67 proliferation index, which was obtained by immunohistochemical staining with anti-Ki 67/MIB-1 (monoclonal mouse anti-human Ki 67 antigen clone MIB-1, Dako). The Ki 67 index was quantified as the percentage of Ki 67–positive nuclei measured in the area containing the largest number of positive tumor cells at high-power magnification ($\times 40$). The Ki 67 index was low (1%–2%), with isolated foci reaching 10%. The diagnosis of a combined PXA-GG was made.

The *BRAF* V600E mutation was detected using a real-time polymerase chain reaction test on the cobas 4800 System (Roche Molecular Systems) with DNA extracted from formalin-fixed, paraffin-embedded tissue. Furthermore, immunohistochemical staining of the *BRAF* V600E mutation (anti-*BRAF* V600E, VE1, mouse monoclonal primary antibody; Ventana) revealed the presence of the mutation in both cellular components, with strong immunoreactivity in neuronal bodies of the GG component (Fig. 3).

Discussion

Combined PXA-GG was first described in 1992 by Furuta et al. as a cystic tumor in the temporal lobe of a young adult.⁹ Since the original description, only 19 cases (including the present one) have been reported.^{8,9,12,16,18–20,24,25} A PXA-GG is a rare lesion that typically affects young adults with clinical onset of seizures; the median age of the reported cases is 28 years (range 9–82 years). According to reports, PXA-GG shows predilection for cerebral hemispheres, especially the temporal lobe (11 of 19 cases). In general, these are superficial tumors with meningeal involvement.^{1,7,16,18–20,22,24–26} The frontal lobe and cerebellum are the second most common locations, and occipital involvement has not yet been reported.^{8,19,20} Neuroradiologically, most cases present with a large cystic component with enhancing mural nodules. However, in the present case a solid mass with irregular contrast enhancement was found. Homogeneous enhancement in solid lesions has also been reported.⁸ The solid and cystic components usually have increased signal intensity on T2-weighted images, such as in PXAs. Perfusion studies have not yet been described in this kind of tumor. The present case showed an increased cerebral blood volume, as has been reported in low-grade gliomas such as oligodendrogliomas, pilocytic astrocytomas, and pleomorphic xanthoastrocytomas.³

Histologically, these lesions correspond to a tumor with mixed PXA and GG components. The PXA component is characterized by pleomorphic and lipidized cells expressing GFAP, often surrounded by a rich reticulin network, eosinophilic granular bodies, and perivascular lymphocytes.¹⁰ The GG component is composed of ganglion-like neuronal cells in combination with glial cells.^{2,24} Kros et al. were the first to describe neuronal differentiation in

FIG. 2. Photomicrographs showing pathological findings. Tumor sections showing microcystic background with numerous cells with microvacuolated cytoplasm and neuronal-like elements, and with round nuclei and prominent nucleoli (A and B); intense and diffuse GFAP expression (C); and synaptophysin expression in neuronal-like elements (D). H & E, panels A and B; GFAP, panel C; synaptophysin, panel D. Original magnification $\times 200$ (A, C, and D), $\times 400$ (B). In panels A and D, asterisks designate ganglion-like cells. Figure is available in color online only.

PXA.¹⁷ Further immunohistochemical studies found synaptophysin expression in 38% of PXAs¹¹ and ultrastructural neuronal differentiation in 20% of PXAs.¹³ However, the extension of this neuronal differentiation has not yet been quantified.^{17,21} Five years after the initial description of the entity, Perry et al.²⁰ described 2 different types of PXA-GG: Type 1 lesions have separate cell components, with almost no intermingled area (66% of the reported cases belong to this type).²⁴ The present case would fit into the Type 2 group, in which both cell components are mixed and a clear margin between them cannot be found. Some authors interpret Type 1 PXA-GG as a nodule of neuronal differentiation inside a PXA, whereas in Type 2 the lesion would correspond to a GG with a PXA as its glial component. Furuta et al.⁹ proposed that both components of the PXA-GG were the result of a common maldevelopment of neuronal and glial cells. In addition, Lach et al.¹⁸ reported 3 cases with cortical dysplasia in the surrounding brain, suggesting that these lesions could be a secondary neoplastic transformation of residual germi-

nal matrix in the setting of focal cortical maldevelopment. These results suggest that PXA and GG share a common origin and that combined PXA-GG would be positioned along a spectrum between PXA and GG.⁸

The Ki 67/MIB-1 proliferation index was low in the present case, although some regions of the tumor reached 10%. The MIB-1 labeling indices have been reported with a range of 1.7%–5.7% in some PXA-GG, without apparent correlation with clinical outcome.^{8,20} The recent work of Ida et al.¹⁴ on PXA described the significant prognostic impact of the mitotic index (≥ 5 mitoses/10 hpf) and the presence of necrosis, but not as independent factors. Furthermore, these investigators reported that the *BRAF* V600E mutation is a prognostic marker of a better overall survival. Given the similarities between pure PXA and mixed PXA-GG, all of these findings could be applied to the latter. Necrosis and vascular proliferation have previously been reported in recurrent cases of PXA-GG.^{8,19,20} As far as we know, this is the first report of PXA-GG with necrosis at initial resection, but its significance is still unclear.

FIG. 3. Photomicrograph of a tumor section showing intense *BRAF* expression in both cellular components: astrocytes and ganglion-like cells. Asterisks designate strong immunoreactivity in neuronal bodies of the GG component. Original magnification $\times 100$. Figure is available in color online only.

Detecting the *BRAF* mutation in PXA-GG is essential because patients could therefore benefit from *BRAF*-inhibitor therapies like vemurafenib. Total or partial responses of PXAs to these therapies have been reported.⁴ Two independent studies have reported a high frequency of *BRAF* mutation in PXA (60%–66%),^{5,23} and Dougherty et al.⁶ also explored GG and pilocytic astrocytoma, finding 18% and 9% of these lesions, respectively, with *BRAF* mutations. Moreover, a common origin for these 3 tumors has been proposed. They all affect young patients and are well-delimited, slow-growing tumors with a glial component and a possible neuronal differentiation. In this report we have shown that they could also have common molecular alterations. The immunohistochemical study of the *BRAF* V600E mutation in GG has revealed high expression of the mutant protein in neuronal bodies,¹⁵ as was found in our case.

The clinical course of these tumors is generally good after total/subtotal resection, and no differences in clinical behavior have been reported between the 2 histological types described. The role of radiotherapy and chemotherapy is unclear. Radiotherapy has been used in some cases, especially after subtotal resection or in recurrent tumors. Chemotherapy has only been used after tumor recurrence.²⁰ The detection of the *BRAF* mutation is clinically important because it could provide new targeted therapies in the future. In our case, we decided on a watchful waiting approach with MRI follow-up after total resection of the tumor.

Conclusions

Combined PXA-GG is an extremely rare brain tumor with a relatively benign course. It is more frequent in young adults and it is usually located in the temporal lobe. Histological analyses reveal 2 cellular components that could have a common genetic origin: PXA and GG. The

current treatment of choice is total resection of the tumor followed by radiotherapy in case of tumor recurrence. The *BRAF* V600E mutation seems to be an important molecular aberration and therapeutic target that may change the treatment approach in the coming years.

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Disclosures

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

Author Contributions

Conception and design: Cicuendez. Acquisition of data: Cicuendez. Analysis and interpretation of data: Cicuendez, Martinez-Saez. Drafting the article: all authors. Critically revising the article: all authors. Reviewed submitted version of manuscript: Cicuendez, Martinez-Saez, Sahuquillo. Approved the final version of the manuscript on behalf of all authors: Cicuendez.

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