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Case Report

Epilepsy due to a temporal ganglioglioma and its subsequent malignant transformation into a primitive neuroectodermal tumor

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Abstract

Background: Gangliogliomas (GGs) are rare brain tumors, and their malignant changes are still less frequent. In these cases, almost always the malignant component is the glial one. However, there are few cases in which the neuronal component exhibits malignant transformation.

Case Description: We described a case of a 14-year-old male patient who started with seizures and 5 years later, its frequency was almost daily despite being treated with several antiepileptic drugs. Magnetic resonance imaging showed a nonenhancing lesion located at the right inferior temporal gyri. He underwent surgery, and the tumor was completely removed. Histological diagnosis was GG. He had no seizures anymore, but 3 years later, the tumor recurred as a giant heterogeneously enhancing space-occupying mass within the right temporal lobe. A second surgical resection was performed. Histological diagnosis was a primitive neuroectodermal tumor (PNET). One month and a half later, the tumor has recurred again. He and his family decided not to undergo another operation, so he was referred to the radiotherapy department.

Conclusion: As in this patient, GGs may recur as a primitive neuroectodermal tumor, likely because both types of neoplasm form part of the same heterogeneous group of brain tumors which contains neuronal components, but on the other side of the malignancy spectrum.

Key Words: Ganglioglioma, glioneural tumors, malignant transformation, supratentorial primitive neuroectodermal tumor, tumoral epilepsy

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INTRODUCTION

Gangliogliomas (GGs) are rare brain tumors, accounting for approximately 0.4–2% of all intracranial neoplasms, but in fact it is more common in children.[2,5,6,8,11,12,15,16,20,21,25,26] Its malignant changes are still less frequent, and if these happen, almost always the malignant component is the glial one, evolving toward glioblastoma.[2,5,6,8,10,11,12,15-18,20,21] There are only few cases in which the neuronal component exhibits malignant

transformation.[2,3,5,6,10,12,19,25] We present a case of a temporal GG and its malignant recurrence as a primitive neuroectodermal tumor (PNET).

CASE REPORT

A 14-year-old male patient started with automotor seizures without loss of consciousness, which included oroalimentary and distal portions of the extremity automatisms, preceded by an abdominal aura. Initially he had persistent seizures, approximately three attacks per month. He was treated with antiepileptic drugs, which reduced their frequency to one attack per month. When he was 19 years old, seizures frequency was almost daily despite being treated with several antiepileptic drugs such as topiramate, carbamazepine, valproate, and clobazam. Also, automotor seizures evolved to secondary generalized tonic–clonic ones, three times during that year. He had two seizures during the video-electroencephalography monitoring, which showed an epileptiform activity compatible with acute temporal waves. Magnetic resonance imaging (MRI) showed a nonenhancing lesion located at the right inferior temporal gyri, which was hypointense and hyperintense in T1- and T2-weighted images, respectively. There were only few linear enhancing images near the lesion after contrast administration, which were thought as vessels. Furthermore, MRI revealed cortical retraction in the right temporal lobe, in which both subarachnoid spaces within the sulcus and the sylvian cistern were wider than left side ones [Figure 1]. Presurgical evaluation included the placement of five deep brain electrodes in his right temporal and frontal lobes to confirm if it was the epileptogenic zone. Invasive monitoring confirmed that seizures originated in the right temporal lobe, thus, a right anterior temporal lobe resection was performed. Histological diagnosis of the resected tumor was GG. There were dysplastic neuronal cells, atypical low grade glial cells, and microcalcifications. Glial component was positive for glial fibrillary acidic protein (GFAP) whereas the neuronal component was immunoreactive for neuronal nuclei (NeuN), synaptophysin, and neurofilament protein. The Ki-67 proliferation index was very low: 1% [Figure 2]. It was reported by the pathologist as a grade I lesion according to the World Health Organization (WHO) classification of tumors of the central nervous system.[15]

Thereafter, the patient continued with antiepileptic drugs, and he had no seizures anymore. Three years later, he started with headache, nausea, and vomiting. New MRI demonstrated a giant heterogeneously enhancing space-occupying mass within the right temporal lobe. It had cystic areas mainly in its upper parts. There was brainstem compression, and the midline shift was evident. The middle cerebral artery was displaced; it was just above and beyond the superomedial aspect of the lesion [Figure 3a–d]. Thus, a second resection was performed and the entire tumor was removed [Figure 3e]. Histological examination of the resected specimen report was PNET. It was a small-cell and high grade tumor with abrupt borders, which included areas of necrosis and rosettes formation as the typical pattern formed by cells in neuroblastoma. The majority of its cells were small, with hyperchromatic nuclei, increased nuclear:cytoplasm ratio, and immunoreactive for synaptophysin and negative for NeuN. It exhibited only focal positivity for GFAP. The Ki-67 proliferation index was 50% [Figure 4].

Immediate postoperative recovery was uneventful. One month and a half after the last operation, he was admitted

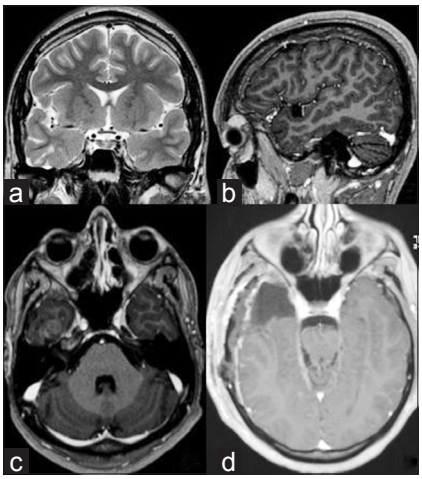

Figure 1: (a) Coronal T2-weighted image showing a hyperintense lesion located at the right inferior temporal gyri. Right subarachnoid spaces within the sulcus and the sylvian cistern are wider than left side ones. (b and c) Sagittal and axial T1-weighted scans following gadolinium administration. (d) Postoperative axial T1-weighted sequence showing complete resection

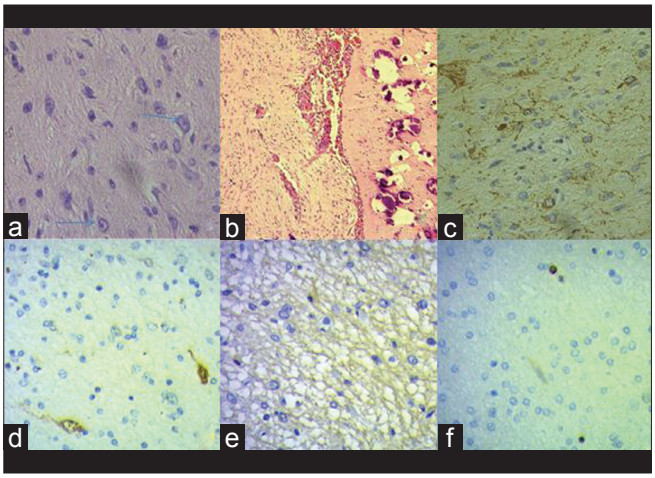

Figure 2: (a) Some neuronal dysplastic elements (arrows) between glial neoplastic cells in a H and E, ×40. (b) Microcalcifications in a H and E, ×10. (c and d) Neuronal component was immunoreactive for neurofilament protein (c) and NeuN (d). (e) Glial component was positive for GFAP. (f) The Ki-67 (MIB-1) proliferation index was 1%

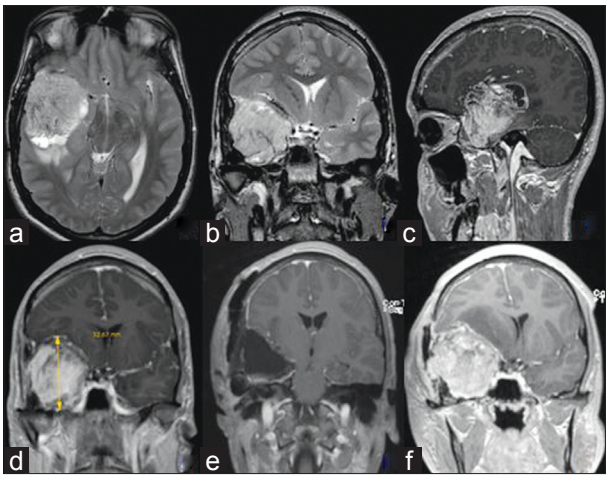

Figure 3: (a) Axial T2-weighted image showing a giant mass within the right temporal lobe which presents cystic areas and causes brainstem compression. (b) Coronal T2-weighted sequence revealing the middle cerebral artery displacement. (c, d) Heterogeneous contrast enhancement after gadolinium administration on sagittal (c) and coronal (d) T1-weighted image. (e) Postoperative coronal T1-weighted scan. (f) Coronal T1-weighted image demonstrating a recurrent tumor 1 month and a half after the second surgical resection

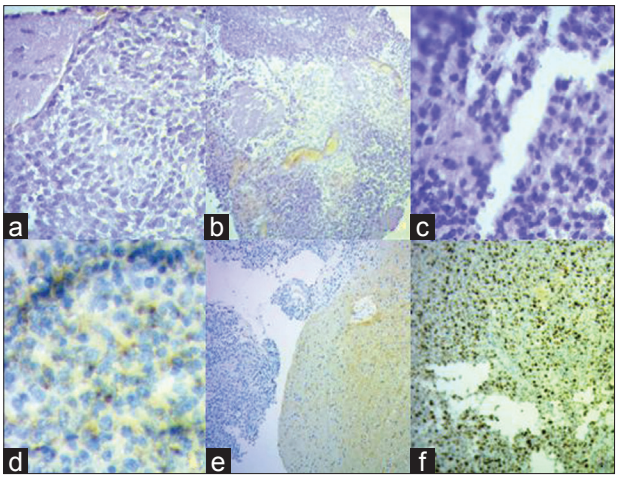

Figure 4: (a) High grade tumor with abrupt borders formed by monomorphic cells; H and E, ×10. (b) Areas of necrosis within the tumor in a H and E, ×4. (c) Neuroblastic rosette formation, H and E, ×10. (d) Positive immunoreactivity for synaptophysin. (e) Focal positive immunoreactivity for GFAP at the right side of the histological section. (f) The Ki-67 (MIB-1) proliferation index was 50%, magnification 4×

again because of headaches and left hemiparesis. MRI showed a giant right temporal tumor again [Figure 3f]. He and his family decided not to undergo another operation, so he was referred to the radiotherapy department. At the moment when this article was written, he has started craniospinal radiotherapy and he will start chemotherapy depending on his clinical condition. His neurological state did not improve so far.

DISCUSSION

GGs are mixed tumors, formed by both neuronal and glial elements, which are usually classified as WHO grade I lesions, although there are some cases of atypical (WHO grade II) and anaplastic (WHO grade III) GGs described in the literature. Thus, GGs form part of the heterogeneous group of brain tumors which contains neuronal components such as dysembryoplastic neuroepithelial tumors, medulloblastomas, supratentorial PNETs, and medulloepitheliomas. If there are neuronal cells alone, it is named gangliocytoma. The glial component is ordinarily astrocytic, but rarely, it may have oligodendroglial differentiation.[7,15-19,21,25,26] Its most frequent location is the temporal lobe, followed by frontal and parietal lobes, but it can develop elsewhere in the central nervous system, including diencephalic, brainstem, cerebellar, and spinal cord locations.[8,15,16,25] Immunohistochemical demonstration of GFAP is used to identify glial cells, which are usually negative to MAP-2 in GGs, whereas several neuronal markers like neurofilament protein, synaptophysin, NeuN, neuron specific enolase and MAP-2 are helpful in visualizing the neuronal portion. Also, S-100 protein and vimentin may be used to demonstrate glial elements. Despite being useful, these markers cannot differentiate between normal and neoplastic cells.[8,10,11,15,16,25]

GGs are a bit more frequent in males than females. It is more common in children; however, it may develop at any age. Therefore, mean age at diagnosis varies widely in the literature from 8.5 to 26.4 years.[8,11,15-17,21,25,26] GGs usually present with seizures and it is the major cause of refractory temporal lobe epilepsy caused by tumor in young people, because of its predilection for this brain lobe.[7,8,11,17,18,21,25,26] GGs are generally hypodense on computed tomography scans, but in up to 15% they may be hyperdense. Calcifications can be found within the tumor. Most often, GGs are hypo or isointense in T1-weighted images and hyperintense in the T2-weighted MRI sequence. In general, although not as a rule, heterogeneous or at least some degree of contrast enhancement is seen in imaging studies.[8,18,25]

The recommended treatment for GGs is surgical excision. Epilepsy caused by GG may be cured after tumor resection. Postoperative seizure control is associated with gross total resection of the mass, shorter duration of epilepsy, younger age at surgery, and the absence of generalized seizures.[1,8,11,25] Most of the times, patients with GG have good prognosis.[8,11,16,17] In a long series of 184 patients who underwent surgery for supratentorial GGs, there was a 7.5-year survival rate of 98%. Furthermore, they found that temporal tumor location and long-term epilepsy were associated with an improved outcome in their patients, whereas residual tumor masses after

resection were associated with higher recurrence rates.[16] Thus, if it is allowed by the tumor features, a gross total resection should be done, since malignant transformation was associated with incomplete resections too.[1,8,11,16,17,25] Although the results of radiotherapy for GGs are not well established, it is generally used for patients with postoperative residual tumor, in GGs with malignant degeneration and in case of recurrence, principally if another surgical resection is not possible.[8,9,22,25] The benefit of using chemotherapy in these patients is uncertain.[8]

Supratentorial PNET is a very rare and aggressive embryonal tumor, which corresponds to WHO grade IV and is composed of neuroepithelial cells which are able to differentiate along neuronal, astrocytic, muscular, or melanocytic lines. Usually, the proliferation index is high, as in our patient, who, moreover, had a very early recurrence even after complete resection.[15,24] Supratentorial PNETs on MRI are hypo and hyperintense on T1 and T2-weighted sequences, respectively, and in most of the cases there is heterogeneous contrast enhancement after gadolinium administration. Some areas of decreased diffusion within the lesion are common findings, due to the high cell density. Also, there may be intratumoral hemorrhage, cysts, calcification, surrounding brain edema, and necrosis.[13,15,23,24] In adults, these tumors are treated by surgical resection and craniospinal irradiation, based on the tumor features, although the best treatment has not been established yet. Chemotherapy may be useful too.[4,13,14,24]

Although being almost always benign lesions, some GGs may develop malignant transformation.[8,16,17] In those cases, typically, malignant changes occur in the glial cells. However, despite being extremely uncommon, there are some cases reported in which the malignant component was the neuronal one, with or without malignant transformation of the glial elements.[2,3,5,6,10,12,19,25] The first report we found in the literature was in 1979 by Bevilacqua and Sarnelli, who described a spinal cord GG that appeared to have anaplastic features in both components.[2] Kawataki *et al.* reported a case of a recurrent temporal GG, which had malignant features in both components too.[12] Tarnaris *et al.* presented a GG with neuroblastomatous transformation following radiotherapy.[25] Jay *et al* described a well-differentiated GG with evolution to a malignant tumor formed by a unique cell type, which showed positive markers for neuronal and glial cells.[10] David *et al.* presented a case of a frontal GG with purely neuroblastomatous malignant transformation.[6] Biernat *et al.* described a brain tumor formed by three portions: one part containing a mixture of a GG with adipocytic-like cells and chondroid metaplasia, other portion with neurocytic differentiation, and a third part of supratentorial PNET. It was thought as a probable teratoma.[3] Mittelbronn *et al.* reported a case similar to our patient, in which a benign GG recurred as a tumor with malignant transformation in both components and assigned to WHO grade IV.[19]

GGs are thought to originate from glioneural precursor cells, like neural stem cells.[12,17,21,26] Nestin is a neural stem cell cytoskeletal protein and its expression was found in cells in transition from the stem cell to becoming neuronal and glial cells too. This protein was found in both neural and glial components of a GG, suggesting that both cell types developed from the same stem cell lineage, which would be able to differentiate toward both cell lines.[12] Other study, which investigated the clonality of eight GGs, concluded that most GGs are monoclonal in origin and derive from a common precursor cell that subsequently differentiates into both cell types.[26] Thus, this common origin may be the physiopathological basis of the malignant transformation of both components together as have occurred in this case.

CONCLUSION

Despite being infrequent, it must be taken in mind that GGs may become aggressive tumors with malignant transformation in either or both neuronal and glial components, probably due to the existence of a common glioneural precursor cell. As in this patient, it may recur as a PNET, likely because both types of neoplasm form part of the same heterogeneous group of brain tumors which contains neuronal components, but on the other side of the malignancy spectrum.

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