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Case Report

A Case of Diffuse Multicentric Metachronous Astrocytoma of Temporoinular and Intramedullary Location

Jorge Linares Torres*, Guillermo Ibáñez Botella, Antonio Selfa Rodríguez, Laura Cerro Larrazábal, Julia Casado Ruiz and Miguel Ángel Arráez Sánchez

Neurosurgery Department, Regional University Hospital of Málaga, University of Málaga, Málaga, Spain

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ABSTRACT

Multiple gliomas are rare glial tumors with a histology that is typically consistent with high-grade gliomas. A distinction is made between multifocal and multicentric gliomas according to criteria of anatomical continuity, as well as between synchronous and metachronous gliomas according to chronological time of onset. We present the case of a professional saxophonist with a left temporoinular lesion who underwent awake craniotomy with monitoring of verbal and musical ability as well as primary sensory and motor cortices. Histopathological study revealed an isocitrate dehydrogenase 1 (*IDH*)-mutant diffuse astrocytoma. After 4 years of complete oncological remission, the patient developed impaired proprioception in all four extremities. An intramedullary lesion was detected at the level of C4 consistent with an *IDH* wild-type diffuse astrocytoma. We highlight the singularity of this case as it involved two low-grade glial lesions, separated in time (metachronous) and location (multicentric), as well as genetic differences between both lesions (*IDH* mutant and wild type).

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Introduction

Multiple gliomas are a relatively rare heterogeneous entity with histology consistent with high-grade gliomas in most cases. Among these, we can differentiate between multifocal glioma and multicentric glioma. In 1963, Batzdorf and Malamud proposed the criteria for making this distinction. In addition, according to the time of presentation, multiple gliomas can be defined as synchronous when they are simultaneously present on the first radiological examination and metachronous when months or years elapse between the diagnosis of both lesions. We present the case of a patient treated for a diffuse left temporoinular astrocytoma with oncological criteria of complete remission who, three years later, underwent surgery for a low-grade cervical intramedullary astrocytoma.

Case Report

A 27-year-old male saxophonist with no significant medical history presented with absence seizures lasting seconds. He was examined in the Neurology Department and referred to Neurosurgery after the detection of a left temporoinular space-occupying lesion. Examination showed no focal neurological deficits. Macroscopically complete resection was achieved through awake craniotomy with monitoring of verbal and musical abilities (the patient played the saxophone in the operating room during the mapping and resection phase) as well as motor and sensory cortices. Figure 1 shows pre and postsurgical MRI of temporoinular lesion. Pathological study identified a diffuse astrocytoma (World Health Organization [WHO] grade II) with an isocitrate dehydrogenase 1 (*IDH1*) R132H mutation, *MGMT* methylated and *ATRX* loss. Immediate postoperative magnetic resonance imaging (MRI) revealed

*Correspondence to: Jorge Linares Torres, Neurosurgery Department, Regional University Hospital of Málaga, University of Málaga, Av. Carlos Haya, s/n 29010, Málaga, Spain; Tel: +034662566258; ORCID: 0000-0002-1333-5251; E-mail: jorgelt@me.com

apparently complete resection. However, follow-up MRI one month after surgery showed possible residual tumor of the insular and external capsule region, shown to be neoplastic on methionine positron emission tomography. Adjuvant treatment with fractionated stereotactic

radiotherapy and sequential PCV chemotherapy was therefore given. Subsequent follow-up MRIs performed every 6 months showed the remaining millimetric tumor remnant to be stable according to RANO criteria and response was considered to be oncologically complete.

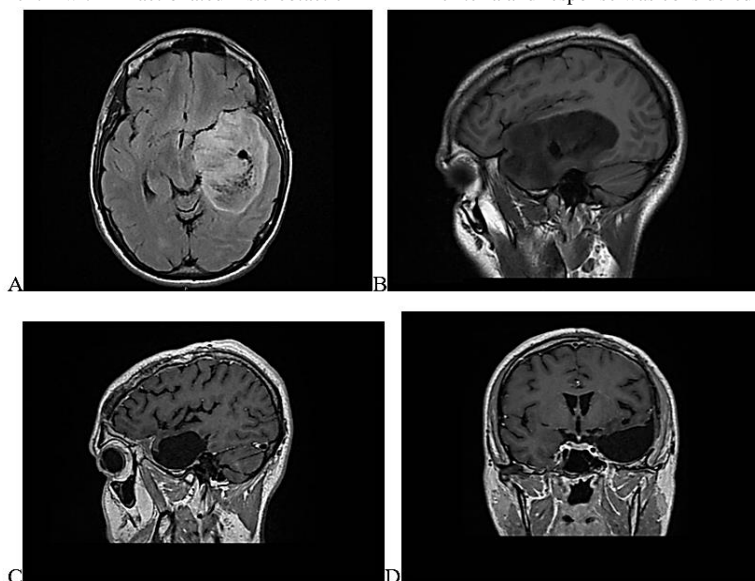


Figure 1: Pre- and post-surgical MRIs showing apparently complete resection of temporoinular lesion. **A)** Presurgical axial FLAIR images **B)** Presurgical sagittal T1-weighted images. **C)** Postsurgical sagittal T1-weighted postcontrast images. **D)** Postsurgical coronal T1-weighted postcontrast images.

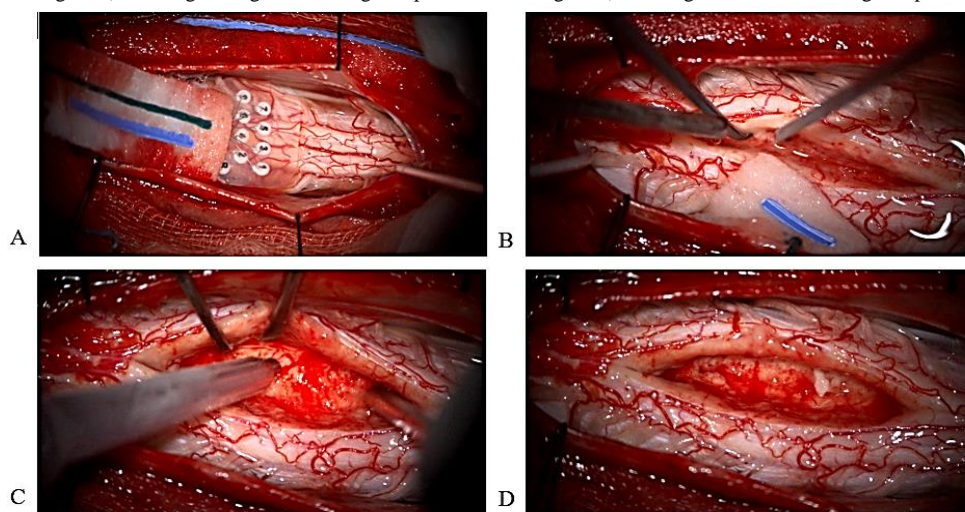


Figure 2: Operative images of intramedullary cervical lesion. **A)** Intraoperative dorsal column monitoring is used for finding location of midline myelotomy. **B)** Interface between the tumor and the cord is searched to determine the feasibility of resection. **C)** Ultrasonic aspirator gives soft tumor decompression. **D)** Apparently gross total resection is reached.

Four years after the initial surgery, the patient was seen due to the onset of numbness in the fingers and toes, with impaired proprioceptive sensitivity (unable to play the saxophone or tie his shoes) with neurological examination revealing hyperreflexia in all four extremities. Cervical and thoracic MRI showed a ring-enhancing, intramedullary, space-occupying lesion at C4. The patient was admitted and underwent laminoplasty and resection of the lesion. Intraoperative images are shown in (Figure 2). Complete resection was confirmed on post-surgical control MRI. Figure 3 shows presurgical and post-surgical MRI images

of cervical lesion. The patient developed slight left hemiparesis (4/5) from which he recovered in the postoperative period. After several months, he continued to experience a slight alteration in proprioceptive sensitivity in all four extremities, which did not prevent him from carrying out his activities as a musician. Pathological analysis revealed an *IDH* wild-type diffuse astrocytoma (WHO grade II), preserved *ATRX*, *MGMT* methylated and *BRAF* negative. Cervical MRI 6 months after surgery confirmed complete tumor resection.

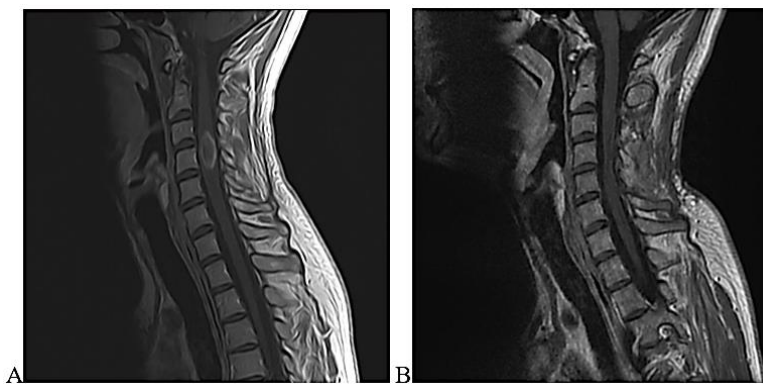


Figure 3: Pre- and post-surgical images of cervical lesion. **A)** Presurgical sagittal T1-weighted postcontrast images. **B)** Postsurgical sagittal T1-weighted postcontrast images show complete resection 6 months after surgery.

Discussion

Diffuse astrocytoma, classified as grade II according to the WHO classification of tumors of the central nervous system, is characterized by diffuse infiltration of the brain parenchyma, causing swelling and distortion (but not destruction) of the anatomical structures affected [1]. They represent 11-15% of all astrocytic brain tumors and usually affect adults, with a mean age of 36 years [2]. In adulthood, a disease-free rate of 34% is achieved at 10 years [3]. The standard of care continues to be maximal possible resection without causing neurological deficits [4]. Notable among the factors of poor prognosis is multicentricity, although most multifocal and multicentric gliomas are associated with more aggressive histologies such as glioblastomas (WHO grade IV) and/or anaplastic astrocytomas (WHO grade III) [5].

The difference between multifocal and multicentric glioma was defined by Batzdorf and Malamud: Multifocal glioma is a multiple glioma resulting from the spread or growth of the tumor along a known anatomical pathway [6]. These include white matter tracts or commissures (corpus callosum, fornix, internal capsule or massa intermedia), cerebrospinal fluid (CSF) channels or satellite or local metastases. In contrast, multicentric gliomas are multiple gliomas the components of which appear in different lobes or hemispheres with no known connecting anatomical pathway. These also include metachronous gliomas, which occur at different time points during the course of treatment [7]. Literature on multiple low-grade gliomas is very limited [8, 9]. The case we describe is even more atypical given the wide separation between the lesions - supratentorial intracranial and intramedullary. One of the largest series in the literature describes 25 cases of multicentric gliomas, in which the most frequent histology was glioblastoma multiforme (GBM, 48%), followed by anaplastic astrocytoma (20%), and simultaneous GBM and anaplastic astrocytoma (20%) [10]. In this series, only one case of diffuse glioma coexisting with GBM was found. No multicentric glioma with a medullary component is described. Only 4 of the 25 cases were metachronous, with a time interval of 2, 3 and 9 months and 6 years between both lesions, respectively. In our case, 4 years elapsed between the two lesions.

In the article by Inoue *et al.*, which reports a case of supratentorial and infratentorial multicentric gliomas, the authors state that after reviewing the literature they found only 11 cases of these multicentric gliomas, and each presented a different histology [11-19]. In our case, although the

histological grade was similar, the genetic profile was different. The temporoinular astrocytoma was consistent with an *IDH*-mutant (R132H) grade II diffuse astrocytoma with loss of *ATRX*, *p53* of 80% and *Ki67* of 25% on immunohistochemistry. The intramedullary astrocytoma was classified as *IDH* wild type (negative molecular biology for *IDH1* and *IDH2* mutations), preserved *ATRX*, *Ki67* of 1%, negative *BRAF* and weak *p53* on immunohistochemistry. Methylation was present in both samples and telomerase reverse transcriptase immunoexpression analysis was negative. Diffuse astrocytomas in adulthood without *IDH* mutations, regardless of their histological grade, tend to be more aggressive [20].

The pathogenesis of multicentric tumors is yet to be elucidated. It is attributed to the ability of tumor cells to invade and migrate over long distances [5]. Willis *et al.* suggest that multicentric lesions arise as a result of a two-step process [21]. First, initiation occurs, a process by which a large area of the parenchymal brain or the entire brain undergoes a neoplastic transformation, making it more susceptible to uncontrolled neoplastic growth. Second, promotion takes place, by which neoplastic proliferation begins in different areas of the central nervous system after receiving different types of stimuli: biochemical, hormonal, mechanical or viral. Several cases of glial cell tumor metastasis have also been described in the literature, specifically, forms of CSF metastasis in patients with GBM. In autopsy studies, CSF dissemination of GBM is found in 15-25% of supratentorial sites and up to 60% of infratentorial sites [22]. Metastases are most commonly found in the leptomeningeal space and have a predilection for the upper lumbar or lumbosacral area [23]. In our case, the lesion was entirely intramedullary in nature, and the study of the rest of the neuronal axis found no other lesions, making the possibility of dissemination through the CSF very unlikely.

Conclusion

The singularity of the case presented lies in the appearance of two tumor lesions separated in time (metachronous) and spatial location (multicentric). Similarly, although multicentricity is most frequently associated with high-grade astrocytomas, our case had a low histological grade. In addition, there were differences in the genetics of both lesions: the intracerebral tumor was *IDH* mutant, and the intramedullary tumor was *IDH* wild type. The low prevalence of cases of this type makes it unfeasible from a cost-benefit perspective to routinely perform neural axis screening that could detect possible multicentricity before

symptoms occur. However, we consider that careful clinical follow-up is essential. The patient being followed should be examined and queried about other possible clinical signs or symptoms that could lead to the appearance of this phenomenon.

Author Contributions

Not applicable.

Consent

Consent to participate was not required, as it is a retrospective case report.

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Conflicts of Interest

None.

Availability of Data and Materials

Not applicable.

Code Availability

Not applicable.

Ethical Approval

Not applicable.

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